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EDITORIAL

Our dear readers,

We are proud to publish the new issue of JOMPAC.As you know, from now on, our journal will be published 6 times per a year. When we look reverse to last three years, it is clearly understood that our journal has come a long way in a successfully way. We are getting closer to our scientific goals day by day. In near future, we want to contribute to international literature at an increasing level and to increase the success bar of our journal by entering valuable international indexes such as SCI-Expanded and Pubmed. We would like to thank all authors for submitting articles contributing to both domestic and international literature with their comprehensive scientific content for publication in our journal.

Sincerely yours

Alpaslan TANOGLU, MD, PhD
Associate Professor
Editor in Chief

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Outcomes of pancreaticoduodenectomy with venous resection: a single center experience with 11 cases

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ABSTRACT

Aim: To perform a retrospective evaluation of the morbidity and mortality rates and reliability of venous resection with pancreaticoduodenectomy (PD) procedures in our clinic.

Material and Method: The records of 11 patients who underwent PD with venous resection between May 2016 and May 2021 in the Eskişehir Osmangazi University Faculty of Medicine Department of General Surgery were analyzed retrospectively.

Results: Eleven patients (five women and six men) were included. The patients' mean age was 64.09±9.27 years (range 47-78). Four (36.36%) patients underwent type 1 reconstruction, one (9.09%) type 2 reconstruction, five (45.45%) type 3 reconstruction and one (9.09%) type 4 reconstruction. Eight (72.73%) patients experienced venous invasion according to the histopathology reports. Mean time between diagnosis and surgery was 14.91±11.33 days, and the mean follow-up time was 17.64±13.31 months. Grade C pancreatic fistula was observed in one (9.09%) patient, who died on the 17th postoperative day. No patients experienced recurrence or metastasis during surveillance.

Conclusion: Pancreaticoduodenectomy with venous resection-reconstruction is safe and the only curative option in patients with pancreatic cancer and venous invasion.

Keywords: Pancreaticoduodenectomy with venous resection, portal vein resection, pancreaticoduodenectomy

INTRODUCTION

Pancreaticoduodenectomy (PD) is a complex, high-risk surgical procedure. The best operative mortality rates and long-term outcomes are reported from high-volume centers (1, 2). The mean operative time for the PD procedure is 5.5 hours, mean blood loss is 350 mL, and operative mortality is less than 4% in experienced centers (3).

Venous resection is not performed in most PD procedures. Venous involvement was at one time a relative contraindication for curative resection. However, experience with vein resection in hepatobiliary surgery began to emerge a few decades ago. Results following the perioperative period results were similar in PDs with venous resection, and venous resection procedures became more practicable (4).

One of the leading case reports concerning PD with venous resection was published in 1951 (5). Those surgeons observed invasion of the tumor to the lateral wall of the superior mesenteric vein (SMV) during surgery and performed segmental SMV resection end-to-end anastomosis. Numerous resection-reconstruction methods were subsequently described, and various inferences were drawn. These include the arguments for different reconstruction techniques, and the potential benefit of superior mesenteric artery (SMA) clamping, splenic vein (SV) preservation or ligation, and intraoperative heparin and postoperative anticoagulant use.

In the 1970s, Fortner drew greater attention to vascular resection during pancreatic surgery. (6). During those years, however, the method was not widely

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accepted due to the high morbidity and mortality of PD with vascular resection. However, as advances were made in preoperative evaluation, surgical technique, postoperative management, and anesthesia an extensive body of literature has emerged on this topic over the past three decades. PD with venous resection is now recognized as a frequently applied approach in high-volume centers.

The purpose of this study is to evaluate the results of PD with venous resection performed in our clinic and to compare our surgical results with other series in the literature in terms of mortality, morbidity, and safety.

MATERIAL AND METHOD

The study was carried out with the permission of the Eskişehir Osmangazi University Faculty of Medicine Ethical Committee (Date: 01.06.2021, Decision no: 02). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The data for 11 patients who underwent PD with venous resection between 01.05.2016 and 01.05.2021 in the Osmangazi Medicine Faculty General Surgery Department, Turkey, were subjected to analysis. Demographic characteristics, date of diagnosis, date of recurrence, follow-up period, histopathological features of the specimen, tumor localization, preoperative imaging reports, resectability status (6), neoadjuvant therapy status, preoperative clinical TNM stage (7), characteristics of surgical intervention, vascular resection type (8), and postoperative complications were recorded for all patients (**Table**).

Table. Summary of patients' and tumor characteristics

Age	64.09±9.27 (47-78)
Gender	
Female	5 (45.45%)
Male	6 (54.55%)
Type of reconstruction	
Type 1	4 (36.36%)
Type 2	1 (9.09%)
Type 3	5 (45.45%)
Type 4	1 (9.09%)
Invasion (histopathology)	8 (72.73%)
Follow-up time, months	17.64±13.31 (1-40)
Status	
Exitus	1 (9.09%)
Alive	10 (90.91%)
Recurrence	0 (0.00%)
Metastasis	0 (0.00%)
Diagnosis	
Exocrine pancreas adenocarcinoma	11 (100.00%)
Differentiation	
Poor	2 (18.18%)
Moderate	6 (54.55%)
Good	3 (27.27%)
Stage	
Stage IA	0 (0.00%)
Stage IB	4 (36.36%)
Stage IIA	0 (0.00%)
Stage IIB	5 (45.45%)
Stage III	2 (18.18%)
Stage IV	0 (0.00%)
Location	
Head	11 (100.00%)
Tumor size, mm	32.27±9.67 (22-50)
Number of lymph nodes	23.18±14.52 (9-61)
Number of metastatic lymph nodes	3.82±5.08 (0-17)
Extracapsular invasion	3 (27.27%)
Resectability	
Resectable	2 (18.18%)
Borderline	9 (81.82%)
Unresectable	0 (0.00%)
Perineural invasion	9 (81.82%)
Lymphovascular invasion	9 (81.82%)
Resection margin	
R0	9 (81.82%)
R1	2 (18.18%)
R2	0 (0.00%)
Surgical margin type	
Negative	9 (81.82%)
Pancreatic parenchyma	0 (0.00%)
Choledocal	0 (0.00%)
Retropancreatic	2 (18.18%)
Choledocal and pancreatic parenchyma	0 (0.00%)
Pancreaticojejunostomy type	
Ducto-jejunostomy	11 (100.00%)
Gastrojejunostomy type	
Simple gastrojejunostomy + Braun anastomosis	11 (100.00%)
Pylorus	
Not-preserved	11 (100.00%)
Preserved	0 (0.00%)
Neoadjuvant chemotherapy	2 (18.18%)
Neoadjuvant radiotherapy	0 (0.00%)
Adjuvant chemotherapy	9 (81.82%)
Adjuvant radiotherapy	7 (63.64%)
Length of stay in hospital, days	12.18±5.25 (4-21)
Leakage	
None	10 (90.91%)
Biochemical	0 (0.00%)
Macroscopic	1 (9.09%)
Fistula	
None	10 (90.91%)
Grade A	0 (0.00%)
Grade B	0 (0.00%)
Grade C	1 (9.09%)
Surgical site infection	2 (18.18%)
DGE	2 (18.18%)
Clavien-Dindo classification	
No complication	7 (63.64%)
Grade I	0 (0.00%)
Grade II	3 (27.27%)
Grade III	0 (0.00%)
Grade IV	0 (0.00%)
Grade V	1 (9.09%)
Preoperative endoscopic retrograde cholangiopancreatography	1 (9.09%)
Preoperative stenting	1 (9.09%)
Intraoperative blood loss	322.73±90.45 (200-450)

Data are presented as mean±standard deviation (minimum-maximum) for continuous variables and as frequency (percentage) for categorical variables

Statistical Analysis

Statistical analysis of this study were performed on SPSS version 25.0 software (SPSS Inc., Chicago, IL, USA). Data are presented as mean±standard deviation, and as frequency values for categorical variables. Data concerning surgical treatment results are presented in tables in percentage form.

Technical Details

Computed tomography (CT) was used for staging in the preoperative period. Magnetic resonance imaging (MRI) and positron emission tomography (PET) were also applied in some cases with suspected metastasis on CT images.

No patient underwent pylorus-sparing surgery. Regional lymph nodes, hepatoduodenal ligament, celiac axis (CA), and SMA were routinely dissected. The para-aortic area was dissected in cases with suspected metastasis at imaging. En-bloc resection and reconstruction were performed in cases with obvious portomesenteric venous invasion at preoperative imaging and in the intraoperative period. However, tangential resection-venorrhaphy or reconstruction with a patch was performed for tumors invading the right axis of the portal vein (PV) or the SMV. Primary anastomosis was employed in cases in which segmental venous resection was performed due to invasion. However, reconstruction was performed with a cadaveric iliac vein graft in one case in which tension-free anastomosis was not possible despite maximum mobilization.

Postoperative complications were classified according to the Clavien-Dindo system. Patients with suitable performance status received adjuvant chemoradiotherapy after the operation. CA.199 levels and abdominal CT scans for recurrence/distant metastasis were employed during follow-up.

RESULTS

Eleven patients (five female and six male) with a mean age of 64.09±9.27 years (range 47-78) were included in the study. Four (36.36%) patients underwent type 1 reconstruction, one (9.09%) type 2 reconstruction, five (45.45%) type 3 reconstruction, and one (9.09%) type 4 reconstruction. Pathology reports identified venous invasion in eight (72.73%) patients. Mean time between diagnosis and surgery was 14.91±11.33 (range 2-36) days, and the mean follow-up time was 17.64±13.31 (1-40) months. One (9.09%) patient died on the 17th postoperative day due to grade C pancreaticojejunostomy leak. No recurrence or metastasis were observed during surveillance.

Exocrine pancreas ductal adenocarcinoma (PDAC) was diagnosed in all patients. The most common tumor stage was IIB (45.45%). The tumor was in the head of the pancreas in all cases. Mean tumor size was 32.27±9.67 (range 22-50) mm. Three (27.27%) patients exhibited extracapsular invasion, and nine (81.82%) perineural and lymphovascular invasion. The resection margin was R1 in two (18.18%) cases, both of which were retropancreatic. Ducto-jejunostomy and simple gastrojejunostomy + Braun anastomosis were performed on all patients. The pylorus was not preserved in any patient.

Two (18.18%) patients received neoadjuvant chemotherapy, nine (81.82%) received adjuvant chemotherapy, and seven (63.64%) received adjuvant radiotherapy. Macroscopic leakage and grade C fistula were present in one (9.09%) case (this patient was exitus). Two (18.18%) patients experienced postoperative surgical site infection and two (18.18%) delayed gastric emptying (DGE). Three (27.27%) patients had grade II complications. One (9.09%) patient underwent preoperative endoscopic retrograde cholangiopancreatography (ERCP) and stent. Mean intraoperative blood loss was 322.73±90.45 (range 200-450) ml.

DISCUSSION

The purpose of this study was to conduct a retrospective evaluation of the morbidity-mortality rates and reliability of venous resection with PD procedures performed in our clinic. PDAC has a very poor prognosis, and the only curative therapeutic option is currently surgical resection. The addition of venous resection in addition to standard PD in some cases with venous involvement provides R0 resection with advanced dissection of the peripancreatic vessels and peripancreatic fatty tissue.

Recent reports have shown that venous resection is safe as a therapeutic option in borderline resectable pancreatic cancer (9-11). Xie et al. (11) showed that patients undergoing radical resection of PDAC and PV resection exhibited significantly improved survival compared to those undergoing chemotherapy or palliative surgical procedures alone..

Resection margin is one of the most important prognostic factors in surgically treated PDAC. (12). The aim of PV-SMV resection is to achieve negative resection margins in patients with suspected PV-SMV invasion. The reported R0 resection rate ranges from 49% to 87.5% (13, 14). The R0 rate in the present study was 81.8%. The residual tumor was in the retropancreatic area in all our patients with a positive resection margin (18.2%).

The reported rate of venous invasion detected at pathological examination after venous resection in the literature is between 3% and 80%. (15-24). The figure in the present study was 72.7%.

There are two types of venous resection, partial and segmental, involving various reconstruction techniques, including venorrhaphy, patch repair, end-to-end anastomosis, and autologous or prosthetic interposition graft (8). All exhibit similar results in terms of patency (14, 25). We performed partial vein resection on five of our patients and segmental vein resection on six. Similarly to the majority of previously published series, we performed four types of venous resection (13, 26, 27). However, our segmental resection rate was higher (45.4%) than that in previous series. This is probably attributable to the experience and orientation of the surgical team.

In our study, intraoperative blood loss was calculated as 322.73±90.45 ml. Intraoperative transfusion was not employed in any case.

Long-term postoperative anticoagulation is recommended only for patients with prosthetic grafts and those with PV thrombosis (13). No prosthetic graft was employed in any patient in the present study, and oral anticoagulant use was not required.

All patients in our study underwent wirsungojejunostomy. The pylorus sparing method was not employed in any case.

The patients were followed-up for an average of 17.64±13.31 months, during which no recurrence was detected. One (9.09%) patient died on the 17th postoperative day due to grade C pancreaticojejunostomy leak. No other mortality was observed during follow-up.

CONCLUSION

In conclusion, the results of this study show that venous resection with PD is associated with acceptable morbidity and mortality rates. PD with venous resection/reconstruction is safe and the only available option for curative treatment in patients with pancreatic cancer and venous invasion.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Osmangazi University Non-interventional Clinical Research Ethics Committee (Date: 01.06.2021, Decision No: 02).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients**.**

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

MEDICINE PALLIATIVE CARE

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Mediastinal adipose tissue and aortic measurements in thoracic CT: is it related to atherosclerosis?

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ABSTRACT

Aim: We aimed to investigate whether the mediastinal adipose tissue plays a role in thoracic aortic atherosclerosis with thoracic Computed Tomography (CT) imaging. We aimed to elucidate the relationship between the amount and density of mediastinal adipose tissue, age, sex, and the presence of atherosclerotic plaque in the aorta.

Material and Method: In this retrospective study, the thoracic computed tomography (CT) images of 45 patients (21 men and 24 women) were examined in two groups. There were 23 patients aged >60 years in group 1 and 22 patients aged <60 years in group 2. The measurements were manually performed from the image where the mediastinal fat tissue, located anterior compartment of the aorta and the pulmonary artery, is viewed widest. The area and density of mediastinal fat tissue, the diameter of the aorta and the distance from the anterior of the aorta to the sternum were measured. The narrowest distance between the aorta and the pulmonary artery, and the subcutaneous fat tissue thickness from the anterior of the sternum in the same section were measured. The presence and absence of atherosclerotic plaque in the aorta were also recorded.

Results: We found no significant differences in demographic and clinical data between the groups. Among the patients aged >60 years (group 1) and <60 years (group 2), statistically significant differences in fat density, sternal fat thickness, and aortic diameter were found. Age was associated with the presence of atherosclerotic plaque. A statistically significant relationship was observed between sternal fat thickness and atherosclerotic plaque. The sternal fat thickness was greater in those with than in those without atherosclerotic plaques. The presence of atherosclerotic plaque was associated with aortic diameter. No statistically significant relationships were observed between the presence of atherosclerotic plaque and the amount and density of mediastinal fat, the aortosternal distance, and the aortopulmonary artery distance.

Conclusion: The risk of atherosclerosis increases not only with excess adipose tissue but also depending on many other parameters. While evaluating atherosclerotic risk and plaque development, patient age, sex, fat distribution, and other diseases should also be evaluated. It should be kept in mind that atherosclerosis is still an unexplained multifactorial parameter in development.

Keywords: Atherosclerosis, aorta plaque, mediastinal fat tissue, thoracic CT

INTRODUCTION

Atherosclerosis is the most important cause of cardiovascular diseases such as myocardial infarction and stroke (1). According to the World Health Organization report, atherosclerosis is the main cause of death, accounting for 32% of all deaths (2). In the etiology of atherosclerosis, inflammatory risk factors such as hypercholesterolemia, diabetes, obesity, smoking, and hypertension are believed to initiate vascular chronic inflammation by affecting arterial wall cells (3).

Obesity is a preventable cause of disease and death in Western societies (4). Although general body fat excess increases the incidence of cardiovascular diseases, recent studies have shown that fat distribution is more important (5). The role of the perivascular adipose tissue in the formation of cardiovascular diseases has been revealed (6). The perivascular adipose tissue is thought to have local effects on blood vessels (7,8). Adipose tissue is considered to be the source of proinflammatory secretions. The perivascular adipose tissue activates macrophages, T cells, and proinflammatory cytokines (9). All these trigger inflammation, atherosclerosis, restenosis, and vascular smooth muscle cell proliferation (10).

On the basis of these findings, we aimed to question whether the mediastinal adipose tissue is also involved in thoracic aortic atherosclerosis. We aimed to elucidate the relationship between the amount and density of mediastinal adipose tissue, age, sex, and the presence of atherosclerotic plaque in the aorta.

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MATERIAL AND METHOD

This retrospective study was conducted at Kırıkkale University, Faculty of Medicine, Radiology Department according to the principles of the Declaration of Helsinki. Thoracic computed tomography (CT) scans were retrieved from the digital database of the Radiology Department of Kırıkkale University, Faculty of Medicine. Ethics committee approval was obtained from Kırıkkale University Non-invasive Researches Ethics Committee (Date: 11.01.2023, Decision No: 2023.01.11). There was no need to obtain informed consent because the data were evaluated retrospectively.

Subjects

This study was conducted retrospectively. The thoracic computed tomography (CT) images of 45 patients (21 men and 24 women) were retrieved from the hospital's Picture Archiving and Communication System (PACS) between January 2023 and November 2022. The patients were examined in two groups. There were 23 patients aged >60 years in group 1 and 22 patients aged <60 years in group 2. The patients' mean age was 71.78±6.24 years in group 1 and 44.77±10.43 years in group 2. The mean ages of the male and female patients were 59.67±15.33 years (range, 20–75 years) and 57.63±17 years (range, 24–89 years), respectively. Patients with histories of malignancy and thoracic surgery were not included in the present study.

Thoracic CT Imaging and Analysis

All CT scans were obtained using routine thoracic CT imaging in the supine position. Contrast was used for the procedures. The images were acquired using a 64-slice CT scanner (Brilliance 64, Philips Medical System, Best, the Netherlands). All scans were obtained using the following parameters: tube voltage, 120 kV; effective tube mAs, 180; slice thickness, 1.25 mm; field of view (FOV), 350 mm; and image matrix, 972 × 972. The images were transferred to a workstation, and the raw data were reconstructed using bone algorithms. After scanning, the coronal, axial, and sagittal images were reconstructed with a slice thickness of 1.25 mm. The axial plane was often preferred. All cases included in this study were evaluated by the same radiology expert (P.Z.B.S.) on a high-resolution monitor.

Measurements

The axial plane is often preferred for measurements. The measurements were manually performed from the image where the mediastinal fat tissue, located anterior compartment of the aorta and the pulmonary artery, is viewed widest. The anterior mediastinal fat tissue area was measured manually and recorded in millimeter squared (mm2). The density of the mediastinal fat tissue in Hounsfield units (HU) was measured by placing a 1-cm2 diameter of a region of interest (ROI) in the middle of the measured fat area. The diameter of the aorta and the distance from the anterior of the aorta to the sternum were measured. Moreover, the narrowest distance between the aorta and the pulmonary artery, and the subcutaneous fat tissue thickness from the anterior of the sternum in the same section were measured and recorded in millimeters. The presence and absence of atherosclerotic plaque in the aorta were also recorded.

Statistical Analysis

The SPSS 21.0 software (IBM Inc., Chicago, IL) was used for the statistical analysis. The conformity of the data to the normal distribution was tested using the Shapiro-Wilk test. An independent-sample T test was used to compare normally distributed data. A chi-square test was also used. A p value of <0.05 was considered statistically significant.

RESULTS

We found no significant differences in demographic and clinical data between the groups ($p > 0.01$). Among the patients aged >60 years (group 1) and <60 years (group 2), statistically significant differences in fat density ($p=0.023$), sternal fat thickness ($p=0.021$), and aortic diameter ($p=0.001$) were found. No statistically significant differences in aorta sternum distance ($p=0.143$), mediastinal fat area ($p=0.745$), and distance between the aorta and pulmonary artery ($p=0.861$) were found.

When the relationship between sex and age and the presence of atherosclerotic plaque was investigated, no relationship was found between sex and the presence of atherosclerotic plaque ($p=0.423$). However, age was associated with the presence of atherosclerotic plaque ($p=0.001$). A statistically significant relationship was observed between sternal fat thickness and atherosclerotic plaque ($p=0.044$). The sternal fat thickness was greater in those with than in those without atherosclerotic plaques, with a mean sternal fat thicknesses of 13.01 and 17.53 mm, respectively. A statistically significant relationship was observed between the presence of atherosclerotic plaque and aortic diameter ($p=0.001$), which was 33.78 mm in those with atherosclerotic plaque and 26.84 mm in those without atherosclerotic plaque. The presence of atherosclerotic plaque was associated with aortic diameter. No statistically significant relationships were observed between the presence of atherosclerotic plaque and the amount ($p=0.483$) and density of mediastinal fat ($p=0.108$) , the aortosternal distance ($p=0.977$), and the aortopulmonary artery distance ($p=0.796$).

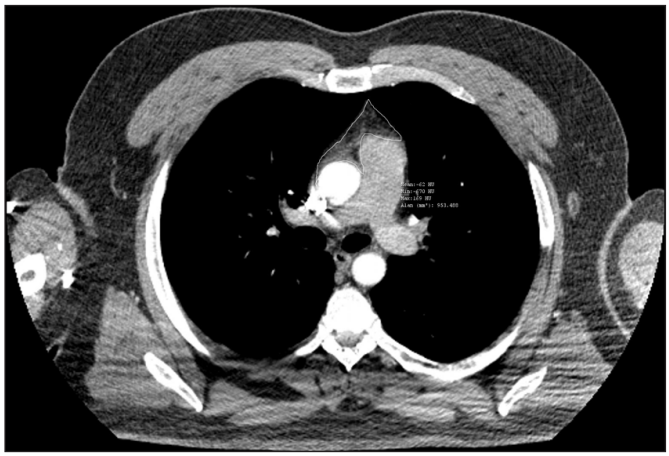

Figure 1. The figure shows the area of mediastinal fat tissue.

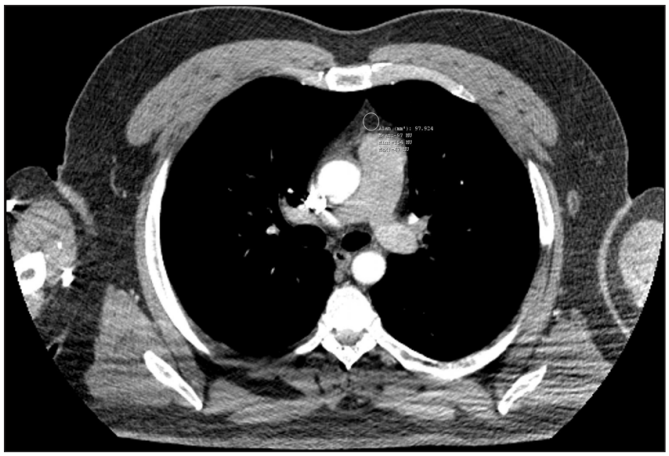

Figure 2. The measurement of fat dansity is shown.

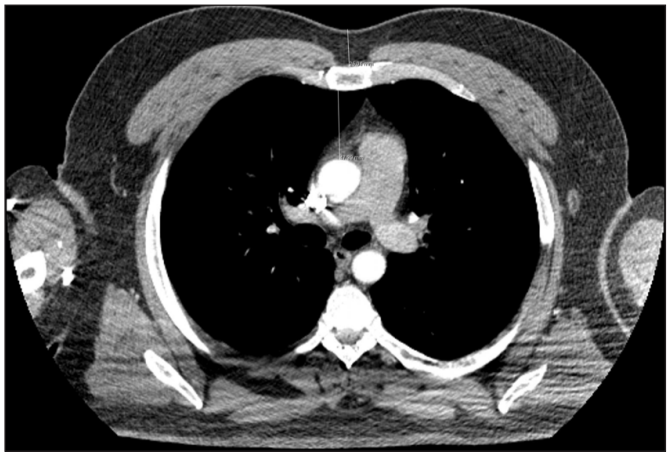

Figure 3. The measurements of the distance from the anterior of the aorta to the sternum and the subcutaneous fat tissue thickness from the anterior of the sternum in the same section are shown.

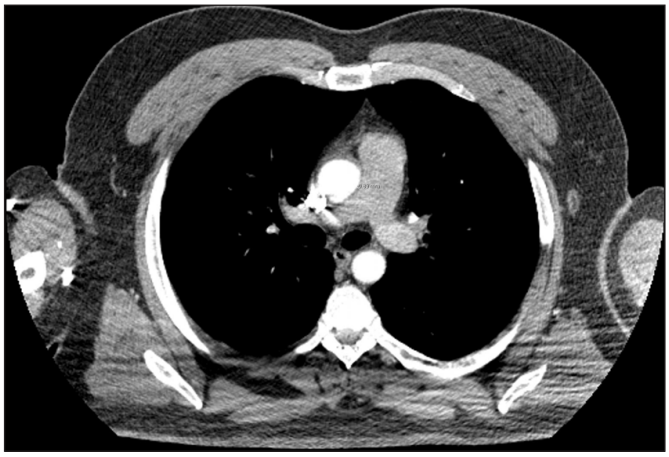

Figure 4. The figure shows the narrowest distance between the aorta and the pulmonary artery.

DISCUSSION

Obesity is a state of abnormal accumulation of fat in the body. Obesity and accompanying metabolic conditions are known to be risk factors of cardiovascular diseases (11). However, this has not yet been clarified. Some studies have shown that the epicardial and perivascular fat areas can directly contribute to the development of cardiovascular complications with a local effect (12,13). Systemic inflammation and adipokine production from adipose tissue have been pointed out to be responsible for the negative effects of adipose tissue on the vessel wall (14). In addition, metabolites, cytokines, and hormones secreted into the environment by the adipose tissue may affect the liver and cause changes in lipoproteins. This causes coagulation and inflammatory factors to prepare the vessel wall for its atherogenic environment (15). In addition, adipose tissue-derived factors have been shown to affect the gene expression and cell function in endothelial cells, arterial smooth muscle cells, and macrophages (13). Therefore, the adipose tissue is an endocrine and metabolic organ that influences the systemic inflammatory state and affects metabolism (16,17). In light of this information, we aimed to determine whether an interaction exists between the presence of aortic artery plaque and the fat ratio and density in the anterior mediastinum. In our study, when the relationships of the presence of atherosclerotic plaque with the amount of mediastinal fat, fat density, and aortosternal distance were examined, no statistically significant differences were observed between those with and without atherosclerotic plaques. We found no correlation between the presence of atherosclerotic plaque and the amount of mediastinal fat. We did not find a similar study in the literature that investigated the relationship between the mediastinal adipose tissue and the aorta. However, examination of the literature provided the understanding that not only the presence of adipose tissue but also the distribution of adipose tissue in the body differs in the development of atherosclerosis, and different mediators are released from adipose tissue in different places (14,18-20). Our results may be related to mediastinal adipose tissue properties or can be explained by the fact that many other factors influence the development of aortic atherosclerosis. This may be a new finding, as the mediastinal adipose tissue and its mediators have not yet been studied. Further studies are needed on this subject.

According to our study, the sternal fat thickness was lower, the aortic diameter was larger, and the presence of atherosclerotic plaque was more pronounced in the patients aged >60 years. We found that the aortic diameter was larger in those with atherosclerotic plaques. In our study, we observed that the sternal fat thickness was greater in those without atherosclerotic plaques. Aging, decreased endothelial cell function, increased collagen deposition, fibrosis, and hardening of the arteries reshape the arterial walls and facilitates the development of atherosclerosis before (21,22). Our results on aging are consistent with the reports in the literature, but the relationship between adipose tissue thickness in the sternum and atherosclerosis is interesting. This condition can occur with age-related dysregulation of lipid metabolism in subcutaneous adipocytes that occurs with aging and a decrease in the ability of subcutaneous adipocytes to act as lipid stores (23,24). Further research is needed on age-related changes in mediastinal fat tissue and thoracic subcutaneous fat distribution.

This study has several limitations. One of these is the small number of patients. Larger case series are needed for better results. If biochemical blood inflammation parameters and lipid profiles are added to the comparison, more detailed research results can be obtained. In addition, pathologies such as the presence of diabetes and hypertension could not be excluded in our study. A clearer contribution to the literature can be made by excluding other pathologies that cause systemic inflammation.

CONCLUSION

Atherosclerosis is one of the most common inflammatory diseases. Obesity and perivascular fat trigger inflammatory mediators. Increases in the mediators and inflammatory cells in the body can cause atherosclerosis. However, the risk of atherosclerosis increases not only with excess adipose tissue but also depending on many other parameters. While evaluating atherosclerotic risk and plaque development, patient age, sex, fat distribution, and other diseases should also be evaluated. It should be kept in mind that atherosclerosis is still an unexplained multifactorial parameter in development.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kırıkkale University Non-invasive Researches Ethics Committee (Date: 11.01.2023, Decision No: 2023.01.11).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients**.**

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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Diagnostic efficacy of computed tomography histogram analysis for the differentiation of histopathological low- and high-grade tumors in colorectal carcinoma

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ABSTRACT

Aim: Colorectal adenocarcinoma (CA) is the most common type of cancer worldwide and the third leading cause of cancer-related deaths. Primary pathological grade bears importance in the course of the disease. The possibility of non-invasive grading through radiology modalities is still an important issue. The present study aims to reveal whether a non-invasive grading similar to pathological grading can be performed using histogram analysis on computed tomography (CT) scan images.

Material and Method: 58 patients operated and diagnosed with CA pathologically were included in the present study. As for medical protocol, abdominal intravenous contrast CT scan images obtained from TOSHIBA Alexion and TOSHIBA Aquilion ONE (Toshiba Medical Systems, Nasu, Japan) devices with 120 kVp tube voltage were set to a window width of 400 and a window level of 40. Patient images from retrospective scanning were evaluated on a workstation. For the evalution of mass, intraluminal air, necrotic areas, pericolonic fat tissue or intra-mass large feeding vessels were not included in the measurement range. Mass size was measured on the largest axis according to the longest axis. For histogram analysis, regions of interest were positioned. Parameters included in the histogram analysis were pixels, mean, standard deviation, minimum, maximum, median, variance, entropy, size L%, size U%, size M%, kurtosis, skewness, uniformity, percent01, percent03, percent05, percent10, percent25, percent75, percent90, percent95, percent97 and percentile 99.

Results: Histogram analysis results obtained from three different measurements for each of 58 patients were not found to be statistically significant in the differentation of pathologically defined histological grading system.

Conclusion: Although the use of a non-invasive method instead of an invasive one may offer an advantage, was not statistically significant in the prediction of histological grade.

Keywords: Colorectal adenocarcinoma, histogram analysis, computed tomography, histological grade, texture analysis

INTRODUCTION

Colorectal cancer (CC) is the most common type of cancer worldwide (1). Grading in CC is closely related with tumor aggressiveness, survival and prognosis (2).

American Joint Committee on Cancer (AJCC) proposed a two-stage classification system, i.e. high and low grade, in order to standardize any potential subjectivity, reduce variations among different observers and increase its prognostic importance (3).

Tumor heterogeneity has been analyzed in many recent studies. It can be categorized into two groups as intertumor and intratumor heterogeneity (4).

Cellular heterogeneity observed in computed tomography (CT) scans often results from photon noise and obscures biological heterogeneity. Although routine CT scans may detect some distinguishing features of well or poorly differentitated tumors in preoperative staging in CC patients, they are still qualitative and subjective features, which may vary from one observer to another (5). A quantitative analysis of CT scans, however, is likely to reveal new promising biomarkers in the form of numerical parameters. If the clinical importance of these parameters is verified, they may significantly contribute to the redefinition of the role of diagnostic imaging and improvement of CC management.

Texture Analysis (histogram) analyzes the spatial distribution and relationship of pixels with different gray level values in an image for a more objective

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evaluation of tumor heterogeneity, thus offering a more unbiased interpretation of visual data in a gray region. Texture analysis includes statistical, model-based and transform-based methods. Arithmetic mean, standard deviation, variance and kurtosis are some histogram values that can be obtained from pixel values in a texture analysis (6). Texture analysis has been used in many individual treatment programs as an assisting method for patient management (7).

In today's world, the role of texture analysis in the diagnosis, treatment and monitoring of tumoral lesions has been analyzed, as manifested by some studies on its significance in lung cancer (8). As for CC, it was reported in the existing literature that measured values from primary lesion were independent predictors of 5-year survival and response to treatment (9). A pretreatment texture analysis in the presence of hepatic metastasis is correlated with pathological and clinical results (10). It was also reported that texture analysis was a potential biomarker for the evaluation of KRAS mutation (11) and a useful non-invasive method for rectal neuroendocrine tumor grading (12).

However, no studies have been so far carried out to analyze the relationship between texture analysis and histological grading of primary CC. The present study aims to analyze the potential diagnostic efficacy of CT histogram analysis for the differentiation of histopathological low- and high-grade tumors.

MATERIAL AND METHOD

The study was carried out with the permission of Kahramanmaraş Sütçü İmam University, Clinical Researches Ethics Committee (Date 2021/01 Decision No:12). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study design

The study was initiated with 154 patients who underwent colectomy between January 2009 and August 2019. 58 patients diagnosed with pathological colorectal carcinoma were included in the study. The patients who underwent preoperative chemo/radiotherapy were not included in the present study due to potential changes in their lesions. In addition, the patients without preoperative CT scans or a suitable CT scan protocol were also excluded from the study. Finally, the patients whose pathology in CT scans could not be optimally observed were also excluded. Their imaging archive records were analyzed in the study group. Demographical data such as sex and age and clinicopathological prognostic data were obtained from hospital records.

Pathological Diagnosis

Microscopic slides representing cancer tissue samples of the selected cases were analyzed by a pathologist again using NiKon Eclipse Ni light microscope. Histological grading was performed via a binary grading system suggested by WHO for colorectal tumor classification (Source: "WHO Classification of Tumors Editorial Board. WHO classification of tumors: digestive system tumours. 5th ed. Geneva: World Health Organization, 2019.") Cancer stage was determined using 8th edition of American Joint Committee on Cancer.

Accepted CT Scan Protocol, Image Processing and Analysis

Abdominal intravenous contrast CT scan images were obtained from TOSHIBA Alexion and TOSHIBA Aquilion ONE (Toshiba Medical Systems, Nasu, Japan) devices with 120 kVp tube voltage. Patient images were evaluated on a workstation on a 27-inch iMac computer (Apple Inc. Cupertino, California, USA), including the analysis of sagittal and coronal reformat images when necessary. Measurements for histogram analysis were made on the same computer with the Osirix program. Mass size was measured on the largest axis (axial, sagittal or coronal). Intraluminal air, necrotic areas, pericolonic fat tissue or intra-mass large feeding vessels were not included in the measurement range for the evalution of primary mass.

Regions of interest (ROI) were positioned and drawn manually for the histogram analysis. A circle corresponding to a diameter of 10 mm was taken as reference region for a standardized measurement. When the standardized circle was larger than the segment itself, an equal area (ellipsoid region) was taken as reference. Three measurements were performed on each lesion: proximal of small intestine, anal canal (distal end) and a medial point between these two ends. As a result, a total of 174 measurements (58 proximal, 58 medial and 58 distal) was obtained from 58 different patients. Histogram parameters were evaluated for three different measurements on each lesion to analyze their performances in the prediction of histological grade. Hounsfield unit (HU) value of each pixel in a ROI was transferred to an XML (eXtensible Markum Language) file. MATLAB version 2009b (MATrix LABoratory, Mathworks Inc., USA) was used to perform histogram analysis on XML files. The following parameters were used for histogram analysis: mean, standard deviation, minimum, maximum, median, variance, entropy, size L%, size U%, size M%, kurtosis, skewness, uniformity, percent01, percent03, percent05, percent10, percent25, percent75, percent90, percent95, percent97 and percentile99.

Statistical Analysis

The obtained results were analyzed using SPSS program ver. 22 (IBM corporation, Armonk, NY, USA). All values are presented in mean±SD. The normality distribution of the obtained data was analyzed using "Kolmogorov-Smirov Test". Normally distributed data were compared using Student T and ANOVA tests, while non-normally distributed data were compared using Mann-Whitney U and Kruskal-Wallis tests. The categorical values were given in % for descriptive data analysis. $p<0.05$ was accepted as the level of statistical significance.

RESULTS

While 17 patients (29.3%) were female, 41 patients (70.7%) were male. The age groups varied between 29 and 86. 22 patients (37.9%) were 65 or younger, whereas 36 patients (62%) were over 65.

The lesion was in the right colon in 24 patients (41.3%), left colon in 19 patients (32.7%) and in the rectum in 15 patients (25.8%). While the lesions were shorter than 5 cm in 26 patients (44.8%), they were 5 cm or longer in 32 patients (55.1%). The number of patients in T1, T2, T3 and T4 stages was 1 (1.7%), 7 (12%), 44 (75.8%) and 6 (10.3%), respectively. The number of patients in N0, N1 and N2 stages was 38 (65.5%), 13 (22.4%) and 7 (12%), respectively. 51 patients (%) were in M0 stage, while 7 patients (%) were M1a stage. The number of patients with conventional adenocarcinoma, mucinous carcinoma and signet ring cell carcinoma was 51 (87.9%), 5 (8.6%) and 2 (3.4%), respectively. In terms of histological grade, 44 patients (75.9%) had low-grade tumors, while 14 patients (24.1%) had high grade tumors. In all patients, the number of proximal, medial and distal lesion samples was 58 (33.3%), 58 (33.3%) and 58 (33.3%), respectively, reaching a total of 174 (%100) samples. None of 174 measured values from proximal (**Table 1**), medial (**Table 2**) and distal (**Table 3**) lesions of the patients were significantly correlated with 24 different histogram parameters.

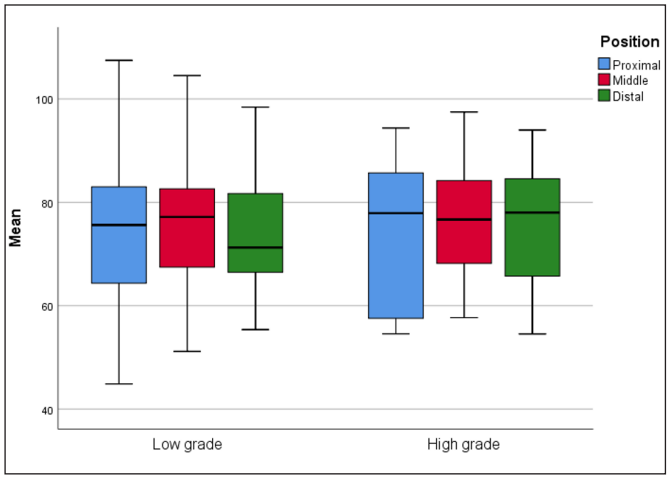

Figure 1. Distribution of histogram analysis

Table 1: Histogram analysis of the patients' primary proximal lesion measurements and their levels of statistical significance ($p<0.005$)

Histogram parameters	Low grade	High grade	p value
Mean	73.8235	74.204	0.929*
Standard deviation	32.05	21.5	0.042†
Minimum	28.68	32.07	0.513†
Maximum	126.36	117.14	0.504*
Median	74.102	74.214	0.979*
Variance	32.05	21.5	0.042†
Entropy	5.672	5.5828	0.286*
Size L%	29.39	29.81	0.928†
Size U%	15.7463	16.4517	0.303*
Size M%	30.66	25.86	0.304†
Kurtosis	29.57	29.29	0.957†
Skewness	29.93	28.14	0.73†
Uniformity	28.93	31.29	0.65†
Percent 01	28.56	32.71	0.451†
Percent 03	28.61	32.29	0.479†
Percent 05	41.9864	45.45	0.523*
Percent 10	48.7477	51.1357	0.621*
Percent 25	60.5114	62.0714	0.724*
Percent 75	87.1136	81.0714	0.812*
Percent 90	98.8273	96.6	0.644*
Percent 95	105.5057	102.7179	0.599*
Percent 97	109.4259	106.3593	0.581*
Percent 99	117.2755	112.752	0.441*

* Student T, †Mann-Whitney U

Table 2: Histogram analysis of the patients' primary medial lesion measurements and their levels of statistical significance ($p<0.005$)

Histogram parameters	Low grade	High grade	p value
Mean	75.6643	75.003	0.882*
Standard deviation	31.11	24.43	0.197†
Minimum	28.74	31.89	0.542†
Maximum	122.34	118.79	0.59*
Median	76.205	75.714	0.914*
Variance	31.11	24.43	0.197†
Entropy	5.6326	5.6167	0.837*
Size L%	29.42	29.75	0.949†
Size U%	15.7127	15.9178	0.82*
Size M%	29.72	28.82	0.863†
Kurtosis	29.28	30.18	0.863†
Skewness	29.68	28.93	0.884†
Uniformity	28.97	31.18	0.669†
Percent 01	28.41	32.93	0.383†
Percent 03	28.17	33.68	0.288†
Percent 05	42.6852	44.7	0.708*
Percent 10	50.4159	51.2714	0.87*
Percent 25	63.483	62.8036	0.879*
Percent 75	88.6364	87.2143	0.757*
Percent 90	99.3614	99.0857	0.957*
Percent 95	106.4193	104.075	0.666*
Percent 97	110.4441	107.8857	0.646*
Percent 99	118.2075	114.5857	0.554*

* Student T, †Mann-Whitney U

Table 3: Histogram analysis of the patients' primary distal lesion measurements and their levels of statistical significance (p<0.005)

Histogram parameters	Low grade	High grade	p value
Mean	74.1606	75.6012	0.716*
Standart deviation	30.39	26.71	0.479†
Minimum	28.41	32.93	0.383†
Maximum	119.34	116.14	0.572*
Median	74.909	75.75	0.837*
Variance	30.39	26.79	0.479†
Entropy	5.6416	5.6086	0.703*
Size L%	29.2	30.43	0.813†
Size U%	15.3822	16.1426	0.363*
Size M%	30.06	27.75	0.656†
Kurtosis	30.16	28.43	0.589†
Skewness	30.48	26.43	0.435†
Uniformity	28.28	32.71	0.414†
Percent 01	28.16	33.71	0.284†
Percent 03	28.18	33.64	0.292†
Percent 05	42.8318	46.0643	0.434*
Percent 10	49.8318	52.7643	0.505*
Percent 25	61.3409	63.5179	0.607*
Percent 75	86.9318	87.9643	0.799*
Percent 90	98.5455	98.4857	0.989*
Percent 95	105.0102	103.7679	0.793*
Percent 97	108.9134	107.2664	0.737*
Percent 99	116.03	112.7621	0.537*

* Student T, †Mann-Whitney U

DISCUSSION

The obtained data demonstrated that CT scan texture analysis results of primary CC were not correlated with histopathological grading. It can be clearly stated that homogenous or heterogeneous tumors did not correspond to high or low grade tumors from a histopathological perspective.

Blood flow heterogeneity in a tumor causes the formation of hypoxic zones, which may result in oxidative stress and genomic instability (13-15). Similarly, heterogeneous blood flow will deteriorate treatment response due to a low amount of chemotherapeutic agents transferred into areas with low vascularity.

Few studies have so far directly dealt with primary CC heterogeneity in the existing literature. Ganeshan et al. (16), which is one of these studies, suggested that primary tumors with a higher heterogeneity were correlated with a poor prognosis and survival and that such an inversely proportional correlation was likely to be related with high cellular density and vascular permeability (8). It was also argued in the same study that contrast CT scan results were likely to be correlated with vascular permeability of a tumor and, as a result, tumors with a higher vascular permeability would lead to a lower contrast resolution and less heterogeneity in texture analysis. This argument is based on the idea that aggressive high-grade tumors display a more homogeneous structure. Another study on the histogram analysis of non-contrast CT scans in 17 patients with small cell lung cancer indicated a negative correlation between homogeneity and tumor stage (16).

Previous studies have underlined the importance of heterogeneity and homogeneity for tumor structure. However, there are multi-centered and multiple variables in such studies which result from differences in the analysis environment (histological type and grade of primary pathology), pathogenesis (hypoxia, vascularity etc.) and obtained results (prognosis, stage, survival etc.). Although the present study paid utmost attention to the selection of patients and image analysis, the above-mentioned differences and various limitations led to analysis results which contradict with those reported in the current literature, thus requiring a multi-dimensional analysis method for the research topic in question. The specification of these difference in future studies on this topic and emphasis on the limitations listed below will yield more reliable and valid results.

Reaching satisfactory historical grading results using a preoperative non-invasive method in CC patients will contribute to the diagnosis of potentially risky stage 2 cancer patients who can benefit from additional adjuvant and neoadjuvant treatments. In addition, it will also guide post-treatment process and facilitate the optimization of cancer treatment based on prognostic factors during a period with variable and unpredictable prognosis.

Since histological grading is an invasive procedure with inconsistent results for different observers, similar to the present study, future studies on the prediction of tumor grade using texture analysis are likely to replace virtual biopsy and eliminate contradicting observation results.

Given that CC patients usually suffer from moderately differentitated adenocarcinoma, texture analysis may increase existing characterization and emerge as a promising and additional prognostic biomarker for tumor staging.

Limitations

Firstly, limited sampling from certain areas on tumoral tissues, uncertainties regarding the similarity of texture analysis regions on these tissues and insufficient size of ROI can be considered as various histopathological limitations in the present study. Secondly, the results of this retrospective study were obtained from a single patient population. Thirdly, although our CT scan images were obtained in portal venous phase in order to minimize contrast differences, it cannot be

said to eliminate heterogeneity in imaging parameters completely. Fourthly, ROI positioning was carried out by a single user, which makes it difficult to make multi-centered and variable generalizations based on the obtained results. In order to reduce observer bias and variability caused by ROI positioning in texture analysis, further studies are needed for the analysis of multiple readers and test-retest reliability. Fifthly, the characteristic ratio of (nearly 3/1) low grade and high grade patients in our analysis is likely to have affected our results negatively. A study on a group of patients in similar numbers may yield more reliable results.

CONCLUSION

The view that CT scan tissue analysis can be applied to individualized treatment plans as a non-invasive and quantitative method for preoperatively distinguishing low-grade and high-grade CA patients is still only a possibility. Further studies are required to improve texture analysis for neoadjuvant treatment in rectal cancer patients with a high risk of local recurrence and for adjuvant treatment in high risk stage 2 colon cancer patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kahramanmaraş Sütçü İmam University, Clinical Researches Ethics Committee (Date 2021/01 Decision No:12)

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients**.**

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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The pregnancy results were not affected from the administration day of Depot GnRH agonists in artificial cycle frozen-thawed embryo transfers

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ABSTRACT

Aim: In frozen-thawed embryo transfers (FET), Gonadotropin-Releasing Hormone (GnRH) agonists have recently been used to improve implantation results. It is preferred to administer it in the luteal phase of the previous cycle. The objective was to compare the effects of different administration days of depot GnRH agonists on implantation and pregnancy rates in the artificial cycle of FET.

Material and Method: A retrospective case-control study was conducted in an in vitro fertilization (IVF) center in a university hospital, including all women starting an artificial cycle of FET. One thousand two hundred and twenty-seven (n:1227) FET cycles were scanned from the files from October 2014 to December 2021. Depot agonists (Lucrin depot 3.75 mg sc Abbott USA.-leuprolide acetate) were used in 219 patients with endometriosis. In 58 patients, it was administered on day 21 of the previous cycle (Group 1), and in 161 patients, it was administered on day 2 of the same cycle (Group 2).

Results: This study showed no statistically significant difference between the two groups in laboratory parameters and endometrial thickness ($p>0.05$). There was no statistically significant association between the abort rate and transfer day ($p>0.05$). There was no statistically significant association between the pregnancy results and transfer day ($p>0.05$). The ongoing pregnancy rate (OPR) rate was relatively high in the second group compared to the twenty-first day of the previous cycle (87/161(54%) vs. 30/58 (51.7%)). The biochemical pregnancy was relatively high in the second-day group compared to the twenty-first day of the previous cycle (62/161(38.5%) vs. 21/58 (36.2%)). The abort rate was relatively high in the twenty-first-day group compared to the second day of the cycle (25/87(28.75%) vs. 9/30(30%)).

Conclusion: In conclusion, the impacts of various administration days of depot Gonadotropin-releasing hormone (GnRH) agonists on implantation and pregnancy rates were not statistically significant.

Keywords: Assisted reproduction technology, FET cycle, GnRH agonist, implantation

INTRODUCTION

Infertility and the inability to reproduce have always been problems humans face, leading to several psychological and social outcomes for the individuals and families involved (1,2). With the progress of science and technology, doctors and researchers have recently investigated the efficiency of in vitro fertilization methods, which are generally known as assisted reproduction technology (ART) today, giving desirable and promising results (3). Since the publication of the first successful reports regarding frozen-thawed embryo transfer cycle (FET) in the 80s, cryopreservation has become a very important procedure for the treatment of infertile couples (4). Human implantation is a complicated and multifactorial procedure (5). Implantation needs a receptive endometrium, a healthy embryo, and a synchronized molecular dialogue (6). The factors that affect the success of implantation and FET methods have been reviewed in many articles. Many researchers seek to investigate the effect or the extent of the effect of different factors on the success of ART methods. In recent years, the role of timing in FET has received the attention of researchers, and the effect of progesterone administration on pregnancy results in HRT cycles is being studied (7).

Cryopreservation of human embryos significantly improved in the last decade with the introduction of

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vitrification protocols (8-10). Embryo vitrification has been routinely applied for the "freeze-all" (FA) strategy, based on ovarian stimulation segmentation, the ovulation triggering, vitrified-warmed embryo transfer in subsequent natural or artificial cycles, and all viable embryos' elective cryopreservation (11). There have been popular FA policies in recent years.

Compared to other protocols related to the growth stimulation of different follicles, FET protocols are simpler. Their primary and foremost purpose is limited to preparing the endometrium for embryo reception(12). Some authors believe that FA strategy increased pregnancy outcomes and decreased the risks of ovarian hyperstimulation syndrome (OHSS) (13).

The simplest method is the natural cycle FET (NC-FET) needed for preparation of endometrium, but the disadvantages are the risk of unexpected ovulation and difficulties of transferring the embryo at the proper time (14). Induction of ovulation is usually applied for patients with irregular menstruation, and unexpected ovulation is the disadvantage of this approach (15). In artificial cycle FET (AC-FET), progesterone and estrogen are applied to imitate the endometrium's endocrine surroundings. Still, these hormones' administration does not fully guarantee pituitary suppression, leading to unexpected ovulation. For this reason, one can use the gonadotropin-releasing hormone (GnRH) agonist (GnRH-a) (16). GnRH agonists in FET have recently been used to improve implantation results. It should be administered in the previous cycle's luteal phase (17).

In the present study, the effects of the administration day of Depot GnRH-a in artificial cycle of FET on ongoing pregnancy rate (OPR), biochemical pregnancy results, and abortion rate in the women included in the research were investigated. The results of this study are valuable for patients and health centers for more accurate planning and reducing patient waiting time. Based on our knowledge, no study in the literature shows that Depot GnRH agonists are made on different days in FET cycles. Since this study is the first in the literature, it is important.

MATERIAL AND METHOD

This retrospective, cross-sectional study conducted in Bahcesehir University Göztepe MedicalPark Hospital IVF Clinic. The study was carried out with the permission of Ordu University Clinical Researches Ethics Committee (Date 22.07.2022, Decision No:170). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

A retrospective case-control study was performed in an IVF center in a university hospital, including all women starting an artificial cycle of FET. One thousand two hundred and twenty-seven (n:1227) FET cycles were observed from the files from October 2014 to December 2021. Depot agonists (Lucrin depot 3.75 mg sc Abbott USA.-leuprolide acetate) were used in 219 patients with endometriosis. In 58 patients, it was administered on day 21 in the previous cycle (Group:1), and in 161 patients, it was administered on day 2 of the same cycle (Group:2).

Women between the ages of 25 and 39 were included in this study. The exclusion criteria were as follows: 1) known chronic disease, 2) over 39 years of age, 3) history of recurrent miscarriage, 4) known chromosomal disorder, and 5) history of fetus with anomaly.

The detection made the diagnosis of endometriosis-adenomyosis of endometrioma or adenomyotic focus by ultrasonography. The analog application was made on the 2nd or 21st day, according to the patient's admission day. Blood values are checked on the 2nd or 3rd day of menstruation when the fresh cycle starts. All cases were transferred within 3 months after the fresh cycle. A single dose of analog was used in all patients. 2 mg estradiol (E2) hemihydrate (17beta-estradiol) treatment was started orally three times a day and was continued at the same dose for at least seven days. The dose was increased (2 x 2 per oral per day) in cases of a thin endometrium (< 7mm) or serum E2 did not reach 300 pg/ml. Intramuscular progesterone injection of 1x100mg per day was started when the endometrial thickness was more than 7mm. These medications were used until a βhCG test. Controlled ovarian stimulation was done by recombinant follicle-stimulating hormone (r-FSH; Gonal-F®, Serono, Geneva, Switzerland), and suppression for LH surge was done by a gonadotropin-releasing hormone (GnRH) antagonist, cetrorelix acetate (Cetrotide®), Merck KGaA, Serono, Geneva, Switzerland). Final follicular maturation has been completed by the analog trigger, Leuprolide acetate (Lupron; TAP Pharmaceuticals, North Chicago, IL, USA). Finally, ovum pick-up is performed after 35-36 hours with transvaginal ultrasound. The fertilization process is done with Intracytoplasmic sperm injection (ICSI) for all patients.

The estradiol levels and endometrial thickness measured on a triggering day in the case group of the study were 1578.25±989.7 and 9.93±1.05, respectively. The estradiol levels and endometrial thickness measured on a triggering day in the case group of the study were 1611.09±973.71 and 9.98±1.73, respectively.

Statistical Analysis

The Kolmogorov-Smirnov test was performed to check the normality, and the nonparametric tests were performed given the non-normality of the groups before the statistical analyses. Mean and standard deviations (SD) were measured to check each continuous variable, including age, BMI, Total oocytes, MII oocytes, PN, AMH, Prolactin, FT4, TSH, FSH, LH, E2, and Endometrial thickness. The Mann-Whitney U test was performed to study the difference between the two groups. SPSS v22 was used for statistical analyses. A value of $p< 0.05$ was accepted as statistically significant. We employed the GPower 3.1 program to estimate the sample size. The two groups' total mean was measured based on the Mann-Whitney test with a power of 90%, effect size of 40%, and 0.05 type 1 error for at least 226 patients (18).

RESULTS

This study included two hundred nineteen (n:219) age-matched (30.75±3.39) and body mass index (BMI)-matched (23.78±2.28) women. The majority of study participants try IVF for the first time(71.7%). **Table 1** shows descriptive statistics of study parameters.

Table 2 compares case and control groups on the laboratory values. As stated in **Table 2**, a Mann-Whitney test did not find a statistically significant association between the case and control in regard to total oocytes ($p>0.05$). There was no statistically significant difference between groups in terms of MII oocytes and PN ($p>0.05$).

AMH of the second-day group (Mean=1.68) was comparable to the 21st-day group (Mean=1.67). A Mann-Whitney test indicated that this difference was not statistically significant ($p>0.05$).

Table 1. Descriptive statistics of study parameters in women (n=242).

Study parameters	median (range) mean±SD
Maternal characteristics	
Age	32(20-35)30.75±3.39
BMI	23.8(19-29.8)23.78±2.28
Laboratory values	
Total oocytes	9(7-14)8.87±1.23
MII oocytes	8(6-11)7.84±0.98
PN	7(6-10)7.48±0.85
AMH	1.8(1-3.64)1.67±0.44
Prolactin	17.6(8.2-25)17.54±4.97
FT4	1.02(0.31-1.62)1.02±0.28
TSH	1.62(0.63-2.46)1.58±0.53
FSH	7(2.3-9.86)6.88±1.47
LH	7.23(3.52-15.2)7.52±1.71
E2	42(29-51.2)39.89±6.57
Endometrial thickness	9(9-12)9.82±1.04

SD, standard deviation.

There was no statistically significant difference between groups in terms of Prolactin (p=0. 981), FT4 (p=0.955), TSH (p=0.440), FSH (p=0.534), LH (p=0.704) and E2 (p=0.853).

The endometrial thickness of the second-day group (Mean=9.82) was comparable to the 21st-day group (Mean=9.83). A Mann-Whitney test indicated that this difference was not statistically significant ($p>0.05$).

As stated in **Table 3**, a chi-square test found no statistically significant association between the pregnancy results and transfer day ($p>0.05$).

As stated in **Table 4**, a chi-square test found no statistically significant association between the abort rate and transfer day ($p>0.05$).

Table 2. Comparison of case and control groups

Study parameters	Second day Case (n=161) median (range) mean±SD	21st day Control(n=58) median (range) mean±SD	p
Laboratory values			
Total oocytes	9(7-14)8.88±1.27	9(7-12)8.84±1.14	0.968
MII oocytes	8(6-11)7.84±1	8(6-10)7.83±0.94	0.887
PN	7(6-10)7.51±0.85	7(6-10)7.41±0.84	0.422
AMH	1.92(1-3)1.68±0.41	1.51(1-3.64)1.67±0.52	0.951
Prolactin	17.78(8.2-25)17.56±4.81	17.2(8.48-25)17.48±5.45	0.981
FT4	1.02(0.31-1.62)1.02±0.28	1.02(0.31-1.62)1.04±0.29	0.955
TSH	1.54(0.63-2.46)1.57±0.52	1.76(0.63-2.46)1.6±0.56	0.440
FSH	7(3.96-9.86)6.87±1.51	7(2.3-9.86)6.92±1.36	0.534
LH	7.2(4.72-12.6)7.51±1.17	7.27(3.52-15.2)7.54±2.7	0.704
E2	42(29-50)39.86±6.64	40.5(30-51.2)39.97±6.41	0.853
Endometrial thickness	9(9-12)9.82±1.04	9(9-12)9.83±1.05	0.923

M, Mean; N, number of subjects; AMH, Anti-Mullerian hormone; PN, multi-pronuclei; FT4, Free T4; TSH, thyroid-stimulating hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; E2, ; All variables tested by a Mann-Whitney U test.

Table 3. The relationship between pregnancy results and transfer day

Variables	Second day Case (n=161) n (%)	21st day Control (n=58) n (%)	p
Pregnancy results Bhcg(+)(%)			0.762*
Yes	87 (54)	30 (51.7)	
No	74 (46)	28 (48.3)	
Ongoing pregnancy rate(%)			0.582*
Yes	62 (38.5)	21 (36.2)	
No	99(61.5)	37(63.8)	

*A Chi-square test.

Table 4. The relationship between abort rate and transfer day

Variable	Second day Case (n=87) n (%)	21st day Control (n=30) n (%)	p-value
Abort rate (%)			0.159*
Yes	25 (28.75)	9 (30)	
No	62 (71.25)	21 (70)	

*A Chi-square test.

DISCUSSION

In the present study, different administration days (The 21st day of the previous cycle and the second day) were compared in regard to laboratory parameters, endometrial thickness, and pregnancy results.

The effect of endometrial thickness on the reproductive outcome is apparent (19). The interaction between the receptive endometrium and the embryo is a complicated molecular process that results in effective implantation (20). When the level of P4 reaches a critical threshold, it drives an orderly and timely secretory transformation of the endometrium, leading to receptivity (21). The present study reported the same endometrial thickness transition in two groups. No significant effect was observed between days 2 and 21.

This study showed no statistically significant difference between the two groups in laboratory parameters. In some parameters such as Total oocytes, MII oocytes, PN, AMH, and Prolactin, the second-day values were relatively higher than 21st day. In other parameters such as FT4, TSH, FSH, LH, and E2, that was vice versa.

In the current study, the OPR rate was relatively high in the second group compared to the twenty-first day of the previous cycle (87/161(54%) vs. 30/58 (51.7%)). The biochemical pregnancy was relatively high in the second group compared to the twenty-first day of the previous cycle (62/161(38.5%) vs. 21/58 (36.2%)). The abort rate was relatively high in the twenty-first group compared to the second day of the previous cycle (25/87(28.75%) vs. 9/30(30%)). However, the differences did not achieve statistical significance in terms of OPR, biochemical pregnancy, and abort rate ($p>0.05$).

The effects of the endometrial preparation protocol artificial cycle (with/without GnRH-a suppression) vs. natural cycle (true/modified) vs. stimulated cycle on the risk of live birth rate, OPR, and early pregnancy loss after FET was the topic of many reports (22-25). Different results about the benefits and disadvantages of protocols were reported (26,27). Conversely, it needs to be more studies regarding the effects of timing on the success of protocols. To the best of our knowledge, this study is the first research that addresses the administration day of depot GnRH-a in artificial cycle FET outcomes. GnRH-a suppresses ovarian steroidogenesis by a downregulation of pituitary GnRH receptors that affects gonadotropin secretion. Pituitary GnRH receptors are downregulated to suppress ovarian steroidogenesis, with GnRH-a affecting gonadotropin secretion. One can administer GnRH -a through different routes, but since the sc way can be easily used, it is preferred. Successful medical management of endometriosis has been done using GnRH-a for many years. Endometrial implants are found to be affected by lower estrogen production or counteract E action at a peripheral level. Deep suppression of luteinizing hormone is done while FSH levels significantly decrease only in the 1st month of therapy, before a constant increase. Suppression of the pituitary gonadotropin secretion in COH caused to prevent premature luteinization of LH and surge, reducing the cancellation rate and improving the assisted reproduction's routine organization (28,29). GnRH-a formulations were used to increase the patients' and clinicians' convenience (3). The difference in the administration of depot GnRH-a and the possible effects of various versions on the pregnancy results was the motivation for this research. Because of the lack of similar study in the literature, the issue was raised as a fundamental question for the authors of this article. The pregnancy results administered on day 2 of the previous cycle were more successful than those in another group. However, there was no statistically significant. It is recommended to conduct the protocol on the second day.

The imbalance between the two groups is one of the most critical limitations of this study (Group 1:58 vs. Group 2:161). However, a sufficient number of patients have compensated for this weakness. Another limitation of this study is its single center. Using data from several centers in future studies is recommended to create a sample.

CONCLUSION

As a result, the effects of different administration days of depot GnRH-a on implantation and pregnancy rates were not statistically significant. Medical centers and hospitals can determine the day of transfer based on the patient's condition and the center's facilities. What

is clear is that the day does not significantly affect the reproductive system's success. The second day for transfer is recommended because the patient will wait less in this condition, and the treatment period will be shorter.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ordu University Clinical Researches Ethics Committee (Date 22.07.2022, Decision No:170)

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients**.**

Referee Evaluation Process: Externally peer-reviewed.

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Original Article

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The role of vagal-neuroimmunomodulation index in patients with pulmonary arterial hypertension

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ABSTRACT

Aim: The vagal neuroimmunomodulation (NIM) index is reflective of the cholinergic inflammatory tone in many clinical circumstances as well as in healthy individuals. We aimed to investigate the relationship of NIM-index on the clinical course patients with PAH.

Material and Method: A total of 31 patients diagnosed with pulmonary arterial hypertension (PAH) were included in this study. Data on electrocardiography (ECG) and C-reactive protein (CRP) were retrospectively obtained from patients' electronic files retrospectively. The vagal NIM index was calculated as heart rate variability (HRV) to CRP ratio (HRV/CRP).

Results: During clinical follow-up, most patients required hospitalization at least once (21 vs. 10 patients). Consistent with the current literature and as expected, there was a significant difference between the groups in BNP values (394 ng/L vs 55 ng/L, p=0.005). HRV, CRP, and NIM-index values were not found to be significant between the groups.

Conclusion: NIM-index values were not associated with the need for hospitalization in patients with PAH.

Keywords: Heart rate variability, pulmonary arterial hypertension, C-reactive protein (CRP), neuroimmunomodulation

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a rare disease that affects young people and women relatively more frequently (1). Idiopathic PAH (IPAH) is the most common type of PAH (1). Echocardiography (ECHO) provides the basic evaluation and right heart catheterization (RHC) ensures a definitive diagnosis. Therapeutic strategies can be summarized as specific PAH drugs, calcium channel blockers (CCBs) in responders, and finally lung transplantation.

Many clinical indicators and variables are used to predict the prognosis in patients with PAH (2). However, risk assessment in PAH patients remains unsatisfactory. Risk-stratification assessment needs to be further validated through outcome studies and optimized for patients with PAH.

The vagal-neuroimmunomodulation index (NIM-index), calculated as a ratio of vagally-mediated heart rate variability (vmHRV) and C-reactive protein (CRP), reflects the cholinergic activity and inflammatory status, and is associated with survival in the general population (3). In the current literature, no study addresses the relationship between the NIM-index and the prognosis of patients with PAH. Our aim in this study was to investigate the role of NIM-index in PAH patients.

MATERIAL AND METHOD

The study was carried out with the permission of Ankara City Hospital No:1 Clinical Researches Ethics Committee (Date: 07/09/2022, Decision No: E1-22-2807). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. With the ethics committee approval, the data were scanned retrospectively between 01.03.2019 and 01.07.2022.

A total of 196 patients were identified as pulmonary hypertension (PH). Of these, 32 patients in the pediatric age group (<18 years) were excluded. Of the remaining's, only 76 were in group 1 according to the Dana Point Classification of PH (4). After excluding patients whose heart rate variability (HRV) could not be calculated and whose ECG and C-reactive protein (CRP) values not available, finally 31 patients were included in the study.

HRV was calculated from baseline ECG at the time of diagnosis. For this purpose, root mean square of the successive differences (RMSSD) was used. Patients with atrial fibrillation (AF), extreme bradycardia/AV block and paced rhythm were excluded. CRP values were obtained from the local laboratory database. The baseline CRP values were recorded to coincide in terms

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of timing with ECGs. The NIM-index was calculated as a ratio of HRV (rMSSD) to CRP values (5). Finally, study patients was compared in terms of need for hospitalization (**Table 1**).

Table 1. Baseline demographic and clinical characteristics

	Hospitalization (-) n=10	Hospitalization (+) n=21	p value
Age (y), mean±SD	40.8±9.8	37.2±14.0	0.477
Sex (female), n (%)	5 (50.0)	15 (71.4)	0.244
CHF, n (%)	1 (10.0)	1 (4.8)	0.579
LVEF, %	60 [30-64]	60 [40-76]	0.696
sPAP (ECHO), mmHg	77.3±23.3	89.3±26.5	0.230
mPAP (RHC), mmHg	45.0±15.8	52.9±20.8	0.301
Laboratory			
NT-pro BNP (ng/L)	55 [39-887]	394 [43-11684]	0.006
Glucose (mg/dL)	90.60±10.11	92.38±21.09	0.803
Creatinine (mg/dL)	0.77±0.21	0.74±0.16	0.624
eGFR (ml/min/1.73m2)	107.90±16.63	109.95±18.03	0.756
WBC	6.29±1.40	7.35±2.73	0.164
HGB (g/dL)	14.71±3.51	15.50±3.88	0.592
HCT	44.62±11.23	48.48±12.32	0.409
PLT	238.6±67.4	214.6±124.5	0.574
NLR	2.51±1.04	2.94±1.61	0.381
vmHRV (RMSSD)	15.14 [7.75-43.59]	14.14 [0-116.19]	0.719
CRP (mg/L)	1.25 [0.5-23.4]	3.13 [0.5-162.3]	0.367
NIM-index	13.56 [0.82-34.64]	1.64 [0-232.38]	0.300
Drugs, n (%)			
ERAs	4 (40.0)	13 (61.9)	0.252
PDE5i	4 (40.0)	16 (76.2)	0.049
CCBs	2 (20.0)	0 (0)	0.034
PCA/PRA	1 (10.0)	9 (42.9)	0.067
sGCs	0 (0)	1 (4.8)	0.483

CHF: congestive heart failure; LVEF: left ventricular ejection fraction; sPAP: systolic pulmonary artery pressure; mPAP: mean pulmonary artery pressure; HRV: heart rate variability; NIM-index: the neuroimmunomodulation index; ERAs: endothelin receptor antagonists; PDE5i: phosphodiesterase 5 inhibitor; CCBs: calcium channel blockers; PCA: prostacyclin analogue; PRA: prostacyclin receptor agonist; sGCs: soluble guanylate cyclase stimulator.

Statistical analyses were performed with IBM SPSS Statistics software (ver. 25). The distribution of data was determined by Shapiro-Wilk test. Continuous variables were expressed as mean ± standard deviation or median (minimum-maximum) and categorical variables as frequency and percent. Categorical variables were compared using Pearson chi-square test. Continuous variables were compared with the independent sample t-test or the Mann-Whitney U test for two groups. The variables of age, gender, LVEF, sPAP, mPAP, glucose, creatinine, eGFR, NT-pro BNP, hemoglobin (HGB), hematocrit (HCT), neutrophil-lymphocyte ratio (NLR), CRP, HRV and NIM-index were used in Univariate Binary logistic regression analysis with the Enter method to determine risk factors according to the presence of hospitalization. p value of less than 0.05 was considered as statistically significant for all tests.

RESULTS

A total of 31 patients were included to final analyses. The mean follow-up period for the whole study population was 31±10 months. The patients were divided into 2 groups in terms of the need for hospitalization (**Table 1**). While ten patients were not hospitalized during the follow-up period, 21 patients were hospitalized at least once.

The groups were similar in terms of age and sex. Alike, there are no differences about presence of CHF and mean LVEF values. However, mean NT-pro BNP values were significantly higher in the hospitalization group (394 ng/L vs. 55 ng/L, p=0.006).

When the groups were compared in terms of PAH-specific drug therapy, only the use of PDE5i and CCBs was found to be different (p values are 0.049 and 0.034, respectively).

Both mean sPAP and mean mPAP values of patients were higher in the hospitalization group, but the difference was not statistically significant (**Table 1**).

There was no statistically significant difference between the groups in terms of HRV (14.14 vs 15.14, p=0.719) and CRP (3.13 vs. 1.25, p=0.367). Although the median NIM-index was found to be lower in the hospitalization group, this difference was not statistically significant (1.64 vs 13.56, p=0.300).

When univariate logistic regression analysis was performed, no variable was associated with hospitalization (**Table 2**).

Table 2. Univariate logistic regression analysis of the need for hospitalization

	Odds Ratio	CI (95%)	p value
Age	0.978	0.921-1.038	0.463
Sex	2.500	0.525-11.894	0.250
LVEF	1.034	0.937-1.142	0.503
sPAP	1.020	0.988-1.052	0.224
mPAP	1.025	0.981-1.070	0.275
Glucose	1.006	0.963-1.051	0.795
Creatinine	0.326	0.004-24.581	0.611
eGFR	1.007	0.963-1.054	0.747
NT-pro BNP	1.002	0.999-1.004	0.172
HGB	1.063	0.856-1.320	0.579
HCT	1.031	0.960-1.107	0.399
NLR	1.257	0.704-2.244	0.440
CRP	1.001	0.999-1.002	0.322
HRV	1.010	0.975-1.047	0.567
NIM-index	1.009	0.985-1.033	0.467

LVEF: left ventricular ejection fraction; sPAP: systolic pulmonary artery pressure; mPAP: mean pulmonary artery pressure; HRV: heart rate variability; NIM-index: the neuroimmunomodulation index.

DISCUSSION

Many clinical risk assessment tools researched in patients with PAH. WHO-Functional class, 6-minutes walking distance (6MWD, m) and BNP or NT-pro BNP values are the most valuable and suggested routinely for each patient on clinical follow-up (2). Of these, the WHO-FC is one of the strongest predictors of survival, whether newly or previously diagnosed (6). As expected, NT-pro BNP values were significantly different between the groups in our study.

ECG abnormalities may be useful for the diagnosis of PAH. ECG changes, mostly right axis deviation, combined with other non-invasive tools (e.g. NT-pro BNP) can be used to rule out of PAH diagnosis (7). Bonderman et al. (8) reported a method with 100% sensitivity to exclude pre-capillary PH by combination of ECG and NT-pro BNP on top of ECHO findings. Henkens et al. (9) showed that the combined use of ECG parameters in PAH patients is useful in detecting chronic RV overload. In this study, RV loading was determined by cardiac MRI. Although ECG parameters can be used to rule out or rule in PAH, ECG-based prognostic assessment remains unclear.

CRP, as an inflammatory marker, is associated with poor outcomes in PAH (10). CRP elevation is among the predictors of worse outcomes, including mortality, in adult CHD-related PAH (11,12). Surprisingly, we were not detecting any difference in terms of CRP levels.

HRV is a predictor of worse outcome in children with PAH (13). Yi et al. (14) showed that decreased HRV is associated with PAP and ventricular arrhythmia in patients with idiopathic PAH. Naturally, the need to evaluate the relationship between HRV and PAH treatment arose. Can et al. (15) seek for an answer to exactly this question. As a result, no change was found in HRV with PAH treatment in this study. However, the authors suggest that there is a need for better therapeutic options. In line with the mentioned study, Yoshida et al. (16) designed a preclinical study. They found that electrical vagal nerve stimulation decreased mPAP and improved the survival rate in rats. Although Holter ECG recordings are the preferred method for calculating HRV in the aforementioned studies, short ECG recordings can also be used to calculate HRV (17,18). Hence, we used the standard 12-lead ECGs to calculate HRV.

The parasympathetic system is seeming in closing relationship with inflammatory processes. Previous studies showed that the existence of an "cholinergic anti-inflammatory pathway" and HRV can be used to monitor this activity (19,20). In a recent study, a strong inverse relationship between HRV and CRP was revealed (21).

As a novel indicator, the NIM-index was developed. The first study of the NIM-index was performed on the pancreatic cancer and lung cancer patients (5). In conclusion, authors declared that NIM-index, as a novel marker, associated with prognosis in two fatal cancers. Jarczok et al. (3) tested this index in the general population for overall survival rates. They showed that a lower NIM-index is associated with all-cause mortality in the general population.

There are some limitations to our study. Firstly, this study had a retrospective design and relatively small sample size. Furthermore, this is a single-center study and PAH is a rare disease. Therefore, the sample size in our study can be explained by these. Second, HRV was calculated from short-term ECGs records. Most of the study patients did not have Holter ECG records. Third, this study was planned before the publication of the most recent ESC guideline with a newly changed definition of pulmonary hypertension. Therefore, the mPAP limit in RHC was taken as 25 mmHg for a certain diagnosis. This may also have contributed to the small sample size. Fourth, due to the retrospective study design, 6MWD and WHO-FC data of the patients could not be accessed. Finally, survival analysis could not be performed because the whole study population was alive due of short follow-up period. In lieu of, study patients were compared in terms of hospitalization need.

CONCLUSION

As a result, NIM-index values were not associated with hospitalization in PAH patients. Multicenter, large-scale and long-term studies with Holter ECG monitorization should be designed to display this relevance.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara City Hospital No:1 Clinical Researches Ethics Committee (Date: 07/09/2022, Decision No: E1-22-2807).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients**.**

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Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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Long-term outcome of permanent hemodialysis catheters: a single center experience

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ABSTRACT

Aim: Tunneled dialysis catheters are generally not used as a primary dialysis access but as bridging therapy until a permanent dialysis access is available. However, it has been stated that long-term use may be appropriate if needed. In our study, we aimed to reveal the long-term patency rates of tunneled dialysis catheters and the frequency of catheter-related diseases in a large patient group.

Material and Method: Patients who referred to our center for tunneled dialysis catheter insertion procedure between 2017 and 2022 were retrospectively analyzed with respect of catheter patency durations. The duration between the patients' repetitive admissions to our center due to catheter dysfunction, the cause of the dysfunction and the procedure applied to achieve the patency were noted. Kaplan- Meier survival analysis was used to calculate patency rates of catheters.

Results: 1010 procedures were performed on 464 patients who applied to our center for tunneled dialysis catheter creation or dysfunction. 309 patients were excluded from the study due to short-term follow-up or lack of data. Of the remaining 155 patients with 211 catheter sites included to the study and 467 interventional procedures data analyzed. The mean primary patency duration of the tunneled dialysis catheters was 10.50±10.25 months and the secondary patency duration was 18.00±13.77 months. The 6, 12, and 24-month patency rates of the overall tunneled dialysis catheters were 91.1 %, 83.9 % and 77.9% respectively

Conclusion: Although permanent dialysis catheters, which should not be the first choice for arteriovenous access, have associated comorbidities, they are a method with satisfactory patency rates when other access types are not suitable.

Keywords: Dialysis, tunneled catheter, arteriovenous fistula, complications

INTRODUCTION

Tunneled dialysis catheters are generally not used as the primary dialysis access method, but as bridging therapy until a permanent dialysis access is reached (1). However, tunneled dialysis catheters may be the patient's only dialysis access option in some cases. It is stated that long-term use of tunneled dialysis catheters may be the only way in cases where there is no suitable vascular access, the patient's rejection of other treatment options, the patient's life expectancy is short, and there is a history of multiple unsuccessful arteriovenous fistula creation (2).

One of the factors that determine the type of dialysis access is whether pre-dialysis planning is made by a clinician. An inverse correlation was found between nephrology follow-up and tunneled dialysis catheter placement rate for the first dialysis session of patients (3). It is possible to start dialysis directly through a permanent arteriovenous fistula by planning the dialysis access route in the pre-dialysis phase before the patients start the dialysis process.

Although tunneled dialysis catheters are easier to create than surgical methods, they cause some associated comorbidities in long-term use (4-6). These include catheter site infection, central stenosis, thrombosis, and sepsis. Although it increases morbidity and hospitalization, there is not enough data about mortality (7).

In our study, we aimed to reveal the long-term patency rates of tunneled dialysis catheters and the frequency of catheter-related comorbidities in a large patient group.

MATERIAL AND METHOD

Population

The retrospective study was carried out with the permission of Bolu Abant İzzet Baysal University Hospital, Local Ethics Committee (Date: 2023/01, Decision No: 41) All procedures were carried out in accordance with the Declaration of Helsinki.

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Patients who referred to our center for tunneled dialysis catheter insertion procedure between 2017 and 2022 included to the study. In order to analyze the results of long-term use, patients with a follow-up period of less than 180 days were excluded from the study.

The duration between the of the patients' repetitive admissions to our center due to catheter dysfunction, the cause of the dysfunction and the procedure applied to achieve the patency were noted.

Primary patency was defined as the time between the catheter creation and the first catheter failure.

Secondary patency was defined as the time from the creation of the catheter to the moment that the catheter patency could no longer be achieved with interventional procedures.

Procedure

After the local anesthesia injection, the central vein, whose patency was confirmed by ultrasound, was entered with a 17 G venous needle and the guide wire was extended into the vein. After measuring the distance between the atriocaval junction and the puncture cite, the tunnel was created. The catheter was first passed through the tunnel, then passed through the properly dilated tract and placed at the level of the atriocaval junction. It was tested that the catheter would provide sufficient flow for the dialysis with a syringe. During the replacement of the dysfunctional catheter, an angiogram was obtained by first injecting opaque material through the catheter lumen. After the pathology was detected and treated appropriately, the new catheter was advanced to its proper position via the guide wire (**Figure 1**). In patients with rapid and frequent fibrin sleeve formation, 2 mg/hour t-PA infusion was performed from both lumens of the catheter regularly once a month.

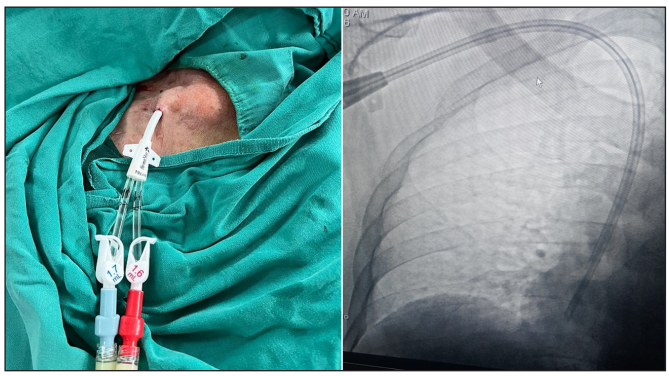

Figure 1. Tunneled catheter inserted via right internal jugular vein is seen (A), Angiographic image of the same tunneled catheter, the tip of the catheter placed at the level of atriocaval junction (B)

Statistical Analysis

Age, gender and catheter cite data analyzed with descriptive statistic methods. Mean patency durations of the dialysis catheters with different locations calculated with student's t test. The primary and secondary patency rates were calculated by the Kaplan-Meier survival analysis. SPSS ver. 26 program was used (IBM corp., Armonk, NY, USA) for statistical analysis.

RESULTS

1010 procedures were performed on 464 patients who applied to our center for tunneled dialysis catheter creation or dysfunction. 309 patients were excluded from the study due to short-term follow-up or lack of data. Of the remaining 155 patients with 211 catheter sites included to the study and 467 interventional procedures data analyzed. The demographic characteristics of the patients and their catheter locations are summarized in **Table 1**. The mean primary patency duration of the tunneled dialysis catheters was 10.50±10.25 months and the secondary patency duration was 18.00±13.77 months. The mean primary and secondary patency durations and patency rates with the aspect of the catheter locations are shown in **Table 2**. There was a significant difference in patency rates of tunneled dialysis catheters between inserted via right jugular vein and left jugular vein (p= 0.002). The 6, 12, and 24-month patency rates of the overall tunneled dialysis catheters were 91.1 %, 83.9 % and 77.9 % respectively (**Figure 2**).

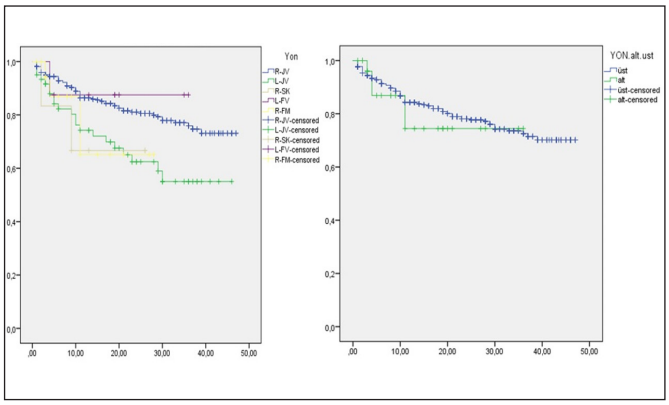

Figure 2. Kaplan–Meier survival curve presenting the patency results of catheters. There is a significant difference in access survival between right jugular and left jugular site catheters (p = 0.002) (A), Kaplan–Meier survival curve presenting the patency results of upper and lower extremity catheters (p=0.648) (B).

Table 1. Patients' characteristics and catheter locations

	Catheter Location						Overall
	RJV	LJV	RSV	LSV	LFV	RFV	
Number of Patients	142	9	2	-	1	1	155
Age	63.12	55.77	54.50	-	58.00	56.00	62,50 (20-93)
Gender (M/F)	81/61	1/8	1/1	-	1/-	1/-	85 (54.8 %)/ 70 (45.2 %)

RJV: Right Jugular Vein; LJV: Left Jugular Vein; RSV: Right Subclavian Vein; LSV: Left Subclavian Vein; LFV: Left Femoral Vein; RFV: Right Femoral Vein; M: Male; F: Female

Table 2. The mean primary and secondary patency durations and patency rates

	Primary Patency	Secondary Patency	6 Months Patency	12 Months Patency	24 Months Patency	P value
RJV	10.48±10.29	20.34±13.99	92.9 %	86.0 %	80.7 %	0.002
LJV	11.65±10.70	18.48±13.29	82.3 %	73.1 %	60.5 %	
RSV	14.16±9.82	14.16±9.82	83.3 %	66.7 %	61.3 %	
LFV	12.12±11.84	18.87±11.96	87.5 %	70.4 %	65.7 %	
RFV	5.65±6.01	9.70±8.24	86.9 %	65.2 %	60.7 %	
Upper extremity	10.69±10.33	20.00±13.86	91.3 %	84.3 %	77.7 %	0.648
Lower extremity	7.50±8.41	12.32±10.13	86.9 %	74.4	69.7 %	
Overall	10.50±10.25	18.00±13.77	91.1 %	83.9 %	77.9 %	

RJV: Right Jugular Vein; LJV: Left Jugular Vein; RSV: Right Subclavian Vein; LSV: Left Subclavian Vein; LFV: Left Femoral Vein; RFV: Right Femoral Vein

Fibrin sleeve developed in 31 (20%) patients, central venous stenosis developed in 22 (14.1%) patients, and central venous thrombosis in 20 (12.9%) patients as the causes of catheter dysfunction. t-PA injection or balloon dilatation was applied to the fibrin sleeve to assess the patency of the catheter. Balloon dilatation was performed for central venous stenosis. No complications were observed procedural and within the 24 hours post procedural period, except in 56 procedures with catheter tract bleeding as leakage. No major complications or mortality related to the procedure were observed.

DISCUSSION

Tunneled dialysis catheters are life-saving equipment when there is no alternative for dialysis access. However, complications such as thrombosis, infection and central stenosis are among its biggest disadvantages. For this reason, it should not be preferred in the first place for long-term use, but should be preferred when other options are not possible.

Despite all efforts to ensure that the permanent dialysis access method is native arteriovenous fistulas, the rate of performing the first dialysis session with a catheter was 65% (8). This condition is observed in fewer patients who receive nephrology treatment and is referred by a nephrologist before dialysis, and it is more advantageous in terms of cost-effectiveness (9). For this reason, the permanent dialysis access made before the dialysis period has a great contribution to the patient during the chronic dialysis decision-making phase.

Despite all efforts, tunneled dialysis catheters may be the only option in cases where there is no suitable arteriovenous fistulae creation site or surgery cannot be performed. In this case, tunneled dialysis catheters can achieve satisfactory patency rates by performing appropriate interventional procedures (10,11). In our study, the average primary patency duration was 10.50±10.25 and secondary patency rate was 18.00±13.77 determined as months. In addition, patency rates of 6, 12 and 24 months were determined 91.1 %, 83.9 % and 77.9 % respectively.

In our study, the rate of catheter-related infection was 12.9% and the number of procedures per patient was 3.01, which emphasizes the importance of creating a native AV fistula. Over time, the catheter causes a complication such as stenosis, especially in the central veins, apart from its own dysfunction. It limits the use of the central catheters and causes comorbidities such as swelling in the face and arms (12-15). In our study, central stenosis developed in 20 patients (14.1%) and balloon dilatation was performed to achieve optimal patency. In cases with central stenosis, stenosis not only disrupts the flow of the catheter, but also causes loss of access in the future and may necessitate insertion of a new catheter from another access site.

In our study, no significant difference was found between the catheters placed in the lower extremity and the catheters placed in the upper extremity in terms of patency rates. It has been reported in the literature that lower extremity catheters have poorer outcomes compared to upper extremity catheters (16, 17). In our study, only 28 patients were followed with lower extremity catheter and different result with the literature might be due to the low number of patients. However, for patients who have access problems in the upper extremity veins, lower extremity veins can be used for catheterization.

Fibrin sleeve formation, described by Motin et al. (18) in 1964, is another cause of catheter dysfunction. In our study, the incidence of fibrin sleeve was found to be 14.1%. In the literature, catheter dysfunction due to the fibrin sleeve is seen with a frequency reaching 76% (11). The reason for the relatively low incidence of fibrin sleeves in our study may be that we regularly inject tissue plasminogen activator through the catheter once a month in patients with catheter dysfunction due to rapid and frequent fibrin formation around the catheter.

The retrospective nature of the study, low number of catheters placed in the lower extremity veins, the inability to analyze the results with the aspect of tunneled catheter types, and lack of data obtained from patients' records might be stated among the limitations of the study.

CONCLUSION

Although permanent dialysis catheters, which should not be the first choice for arteriovenous access, have associated comorbidities, they are a method with satisfactory patency rates when other access types are not suitable.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Bolu Abant İzzet Baysal University Hospital, Local Ethics Committee (Date: 2023/01, Decision No: 41)

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients**.**

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Original Article

MEDICINE PALLIATIVE CARE

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The effects of different anesthetic approaches on recurrence in the surgical treatment of ganglion cysts

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ABSTRACT

Aim: The surgical treatment of ganglion cysts usually involves local anesthesia (LA), regional anesthesia (RA), and axillary block applications. We aimed to show the effects of these anesthesia types on recurrence in surgically treated ganglion cysts.

Material and Method: Between 2017-2019,142 patients were operated on in our clinic due to the dorsal ganglion cyst of the wrist. Cysts outside the dorsal region and patients who did not regularly attend their follow-up visits for at least 12 months were excluded. One hundred and thirty-five patients, with a mean age of 39.3 (15-73) years, were included in the study. LA (Group I) was applied to the patients who stated that they could tolerate the pain, and RA was used on those who stated that they could not (Group II) after preoperative anesthesia consultations. The files of the patients in both groups were reviewed retrospectively, and the effect of anesthesia type on recurrence was investigated.

Results: Recurrence rates were significantly lower in the RA group compared to those in the LA group (p=0.049). The risk of recurrence in the LA group was 2.80 (0.95-8.28) times higher than in the RA group. The mean operation time of the RA group was significantly lower than that of the local anesthesia group (p=0.0001).

Conclusion: The fact that RA allows tourniquet applications with deeper and longer-lasting anesthesia compared to LA increases surgical comfort and makes way for the comfortable dissection of the cyst and total excision of all components within a short operative time.

Keywords: Benign tumors, ganglionic cysts, surgical treatment, local anesthesia, recurrence

Our research's data was presented in 31st National Orthopedics and Traumatology Congress as ''Poster Presentation'' on October 2022.

INTRODUCTION

Ganglion cysts are the most common benign soft tissue tumors encountered in orthopedic surgery. Although common among every age group, it peaks between 20-40 years of age. The incidences in males and females are 25/105, and 43/105, respectively (1-3). Around 60-70% is localized on the dorsal aspect of the wrist. Wrist ganglia are usually 1–2 cm in diameter, cystic, hard structures associated with the underlying joint capsule or tendon sheath (2-4).

Although the etiology is not fully elucidated, long-term microtrauma and stress, especially resulting in mucinous degeneration of the connective tissue, are considered causative factors (4,5). Ganglion cysts typically originate from the connective tissue such as the joint capsule and tendon sheaths, and less frequently from the bone (5).

Most ganglion cysts are asymptomatic(5,6). Anamnesis and examination are usually sufficient for diagnosis. Some patients may present with symptoms such as pain aggravated by wrist movements, tenderness, weakness, and decreased range of motion (7-9). Despite all these clinical findings, the most common complaint is a painless mass. Patients usually visit the physician for cosmetic reasons and sometimes out of fear that the swelling may be a malignant growth. The recurrence rate of conservative treatments is quite high. The aim of surgical treatment is the total excision of the cyst with its sac (9,10).

In our retrospective study, we aimed to show the effects of different anesthetic applications on recurrence in the surgical treatment of ganglion cysts.

MATERIAL AND METHOD

The study was carried out with the permission of Sakarya University Medical Faculty Clinical Researches Ethics Committee (Date: 08.08.2022, Decision No: 04-155097-223). Because the study was designed retrospectively, no written informed consent form was obtained from patients.

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One hundred and forty-two patients were operated on due to ganglion cysts at surgical margins by a single surgeon in a single center between 2017-2019.

A total of 135 patients met the inclusion criteria(cysts larger than 1 cm in diameter), and patients with cysts outside the dorsal region of the wrist, recurrent cases and those who did not regularly attend follow-up visits for at least 12 months were excluded from the study. Preoperative anesthesia consultation was requested from the patients who stated that they could not tolerate LA, and an axillary block with RA was performed. LA was given to the patients who stated that they could tolerate the pain. The patients were divided into two groups: Those who underwent LA were named Group I (72 patients), and those who underwent RA were named Group II (63 patients). The groups were evaluated according to the development of recurrence at the postoperative 3rd, 6th, and 12th months. 1000 mg of cephazolin sodium was administered to the patients intraoperatively. The surgical technique consisted of approaching the dorsal ganglion cyst with a transverse incision made directly over the cyst. A tourniquet was also used in Group II patients. All layers were carefully dissected to expose the pedicle of the cyst and prevent its rupture. Following the excision of the cyst and control of bleeding, the layers were closed anatomically. An elastic bandage wrapped around the wrist. The patients were discharged with oral antibiotics and NSAID prescriptions 4 hours postoperatively with the advice of the anesthesiologists.

Statistical Evaluation

Statistical analyses were performed with NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA) package program. In addition to descriptive statistical methods (mean, standard deviation) used, the distribution of the variables was checked with the Shapiro-Wilk normality test. The Independent t-test was used for the comparison of normally distributed variables and the Chi-square test was used to compare qualitative data. The results were evaluated at the significance level of $p<0.05$.

RESULTS

The mean age of the patients was 39.3 (15-73) years. The mean follow-up times were 16,32±2,72 months and 16,02±2,45 months for groups I and II, respectively. Among the 72 patients in Group I, 27 were males and 45 were females. In this group, operations were performed on 44 right and 28 left extremities. Of the 63 patients in Group II, 22 were males and 41 were females, with 37 right and 26 left extremities operated on. The mean operation times were 20,21±4,78 minutes, and 15,48±4,64 minutes for groups I and II, respectively. Recurrence was observed in 14 (19.44%) Group I patients, and 5 (7.94%) Group II patients within the first six postoperative months (**Table 1**).

Table 1: The demographic, surgical, and follow-up data of the patients

	Local Anesthesia n=72		Regional anesthesia (Axillary Block) N=63		p
Age	39.96±13.5		38.68±12.89		0.577
Gender					0.756
Males	27	37.50%	22	34.92%	
Females	45	62.50%	41	65.08%	
Lateralization					0.778
Right	44	61.11%	37	58.73%	
Left	28	38.89%	26	41.27%	
Follow-up time	16.32±2.72		16.02±2.45		0.499
Duration of operation	20.21±4.78		15.48±4.64		0.0001
Recurrence					0.046
No	58	80.56%	58	92.06%	
Yes	14	19.44%	5	7.94%	

There were no significant differences between the LA and RA (axillary block) groups in terms of mean age or gender distributions (p=0.577, and p=0.756, respectively), lateralization of cysts (p=0.778), or follow-up times (p=0.499). The duration of operation of the RA (axillary block) group was significantly shorter than that of the LA group (p=0,0001), (**Figure 1**), similar to recurrence rates (p=0,049).The risk of recurrence in the LA group was 2.8 (0.95- 8.28) times higher compared to that in the RA group (**Figure 2**).

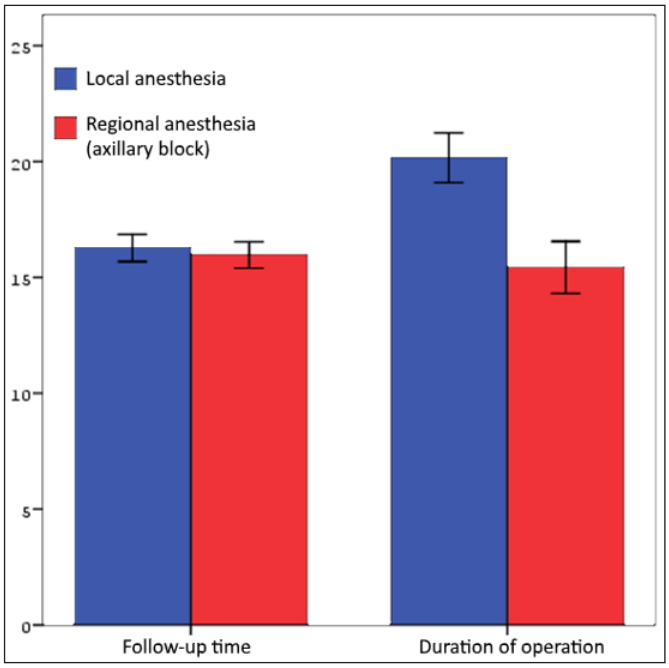

Figure 1: The comparison of follow-up time and duration of operation with respect to anesthesia types

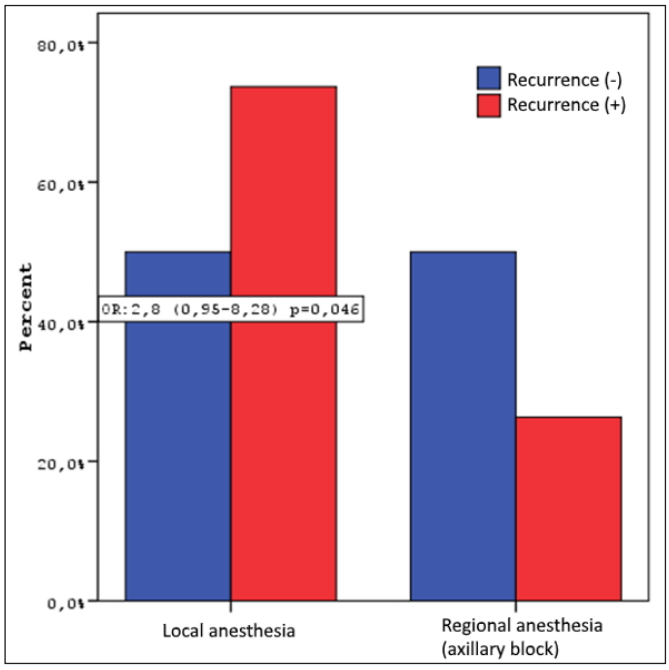

Figure 2: Recurrence rates with respect to anesthesia types

DISCUSSION

The purpose of the surgery in ganglion cysts is the complete excision of the cyst with its sac. Careful dissection is aimed to expose the pedicle of the cyst and prevent its rupture (9-12). Failure to resect the cyst pedicle, capsule connections, and part of the capsule is associated with a high rate of recurrence (11-14). The most common complication after surgical excision is recurrence, with a rate of 40%. The most significant reason for recurrence is the incomplete excision of the cyst due to insufficient dissection. Studies show that the recurrence rate decreases to 5% in cases where the entire cyst complex, including the pedicle and associated joint capsule, is removed (13,14).

RA has advantages over LA in the development of recurrence in surgical treatment. In our study, we found the recurrence rates to be significantly lower in patients who received RA compared to those who received LA, the operation time to be considerably shorter, and total excision to be considerably easier owing to the use of tourniquets and the looseness of the tissue in RA.

Suen et al. (15) reported that non-surgical treatment was largely ineffective in the treatment of ganglion cysts and that surgical intervention reduced recurrence rates compared to conservative treatment. Trivedi et al.(16) reported that blunt force was effective in the treatment of ganglion cysts and no recurrence was observed in their 24-month follow-up. Chaudhary et al. (17) stated that surgical excision is the gold standard in ganglion treatment, but the complication rate after surgical excision is significantly higher than in aspiration treatment, also reporting that the most common complications were wound infection, neuroma, and hypertrophic scar.

Öztermeli et al. (18) reported that 83.3% of volar ganglion cysts and 16.7% of dorsal ganglion cysts recurred and they performed all operations under local anesthesia using a tourniquet. They attributed the high recurrence rate in volar cysts to the anatomical structure of this region, with which we disagree. Since the operation of the patients under RA instead of LA will allow for a comfortable dissection of deep tissues, total removal of the cyst will be possible. We think that the high recurrence rates in this study are due to the partial excision of the cyst due to operating under local anesthesia . Meyerson et al. (19) reported that the previous aspiration of the cyst increased recurrence rates and the recurrence rate of ganglion cysts in children was 5.3% . Sinha et al. (20) reported a high recurrence rate of 90% in their study using aspiration and steroid injection in the treatment of ganglion cysts. On the other hand, Graham et al. (21) reported the recurrence rate as 9.8% after the reoperation of recurrent ganglion cysts.

There are various limitations to our study, two of which are the lack of the randomization of patients preoperatively and the retrospective design. Also, although the number of patients seems sufficient to reach accurate results, we think that further studies with more patients may be more beneficial.

CONCLUSION

Although many methods are used in the treatment of ganglion cysts, the gold standard is surgical treatment. Surgical treatment should aim to minimize recurrence, for which the total excision of the cyst is essential. Anesthetic conditions must be suitable for total excision for both the surgeon and the patient. Regional anesthesia allows tourniquet application with deeper and longer-lasting anesthesia compared to local anesthesia, increasing surgical comfort and providing total dissection of the cyst within a short time. We predict that choosing regional anesthesia over local anesthesia for well-selected ganglion cyst patients will further reduce recurrence. Hoping that our study will shed light on future studies, we think that more comprehensive studies are needed.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Sakarya University Medical Faculty Clinical Researches Ethics Committee (Date: 08.08.2022,, Decision No: 04-155097-223).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients**.**

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

MEDICINE PALLIATIVE CARE

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Prognostic role of preoperative neoadjuvant chemotherapy in patients with tongue cancer

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ABSTRACT

Aim: This study aimed to investigate the relationship between preoperative neoadjuvant chemotherapy (NAC) and overall survival in patients with tongue cancer who underwent glossectomy.

Material and Method: The study included 35 tongue cancer patients who underwent glossectomy. Twenty patients did not receive any treatment before surgery (control group). Fifteen patients received two cycles of cisplatin-containing NAC prior to surgery. Five-year overall survival findings were compared between the groups.

Results: Median pathological depth of invasion was lower in the NAC group compared to the control group (7 vs. 9 mm, p=0.037). The mortality rate was lower in the NAC group (26.7% vs. 50.0%, p=0.008). Increased depth of invasion was independently associated with increased risk of mortality, while receiving NAC was independently associated with decreased risk of mortality. The risk of mortality was 6.25-fold lower (1/0.16) in the NAC group compared to the control group (HR: 0.16, 95% CI: 0.004-0.72, p=0.017).

Conclusion: Patients who underwent NAC plus surgery were associated with a higher probability of 5-year overall survival compared to patients who underwent surgery alone. These findings may be inspiring for the role of NAC prior to surgery in the prognosis of patients with tongue cancer.

Keywords: Depth of invasion, neoadjuvant chemotherapy, prognosis, tongue cancer

INTRODUCTION

Tongue cancer, which is the most common form of malignancy in the head and neck area, has significant morbidity and mortality rates (1). The primary treatment for tongue cancer is surgery, which is followed by radiation therapy and chemotherapy. Despite new treatment strategies, the 5-year overall survival rate has not changed significantly (2). Treatment success and overall survival depend on tumor location, stage, depth of invasion, resection margin, and pathological TNM stage (3).

Preoperative neoadjuvant chemotherapy (NAC) is a therapeutic strategy applied to preserve functions and reduce mortality risk (4). NAC can reduce tumor burden, prevent micrometastatic disease, improve surgical outcomes, and potentially play a prognostic role (5). However, studies to date report conflicting results regarding the efficacy of NAC (4-6). In previous meta-analysis studies involving head and neck cancer patients, NAC did not significantly improve overall survival, while a combination regimen of NAC with 5-fluorouracil (5-FU) and cisplatin increased overall survival compared to single-agent NAC (7, 8), some studies have reported that the combination of NAC including docetaxel offers better overall survival (9-11). However, these studies included various head and neck cancer subtypes and the frequency of tongue cancer patients was low. Therefore, more evidence is needed on the prognostic role of NAC in tongue cancer patients.

This study aimed to investigate the relationship between preoperative NAC and overall survival in patients with tongue cancer who underwent glossectomy.

MATERIAL AND METHOD

This retrospective study was carried out in the Gazi University Faculty of Medicine's Department of Otorhinolaryngology. The study was performed in accordance with the Declaration of Helsinki and approved by the Gazi University Faculty of Medicine Clinical Researches Ethics Committee (Date: 04/2011, Decision No: 92).

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Study Population

A total of 75 patients (≥18 years old) who had tongue cancer and underwent glossectomy between January 2006 and January 2012 were evaluated retrospectively. Among these patients, those with pathology other than squamous cell carcinoma, those with a previous history of malignancy, and those with missing data were excluded. Finally, 35 patients were included in the analysis. The decision of NAC was at the discretion of the senior surgeon. Twenty patients did not receive any treatment before surgery (control group). Fifteen patients received two cycles of cisplatin-containing NAC prior to surgery.

Demographic, clinical and 5-year overall survival data of the patients were obtained from the hospital database and pathology and radiology archives. While clinical stages were determined according to examination notes and radiological images of the patients, pathological findings were determined according to pathology reports.

Statistical Analysis

The normality of numerical data was evaluated with the Kolmogorov-Smirnov test. Data were presented as mean±standard deviation or median (min-max) according to normal distribution. Categorical variables were expressed as numbers and percentages. Cox regression analyses were conducted to establish any possible factors independently associated with mortality. Overall survival plots were made with Kaplan-Meier analysis. Values of $p < 0.05$ were taken to be statistically significant. All data were analyzed using IBM SPSS Statistics for Windows 20.0 (IBM Corp., Armonk, NY, USA) and MedCalc 11.4.2 (MedCalc Software, Mariakerke, Belgium).

RESULTS

The median age of the patients who had tongue cancer and underwent glossectomy was 58 years (range: 24-77 years) and the majority of them were male (68.6%). The rates of pathological T2 (51.4%) and pathological N0 (65.7%) stages were higher. Median pathological depth of invasion was 9 mm (range: 2-18 mm) and median tumor size was 2 cm (range: 0.3-5.7 cm). Surgical margins were positive in 5.7% of the cases. Perineural invasion was observed in 3 patients, lymphovascular invasion in 3 patients, and lymph node metastasis in 13 patients (**Table 1**).

Median pathological depth of invasion was lower in the NAC group compared to the control group (7 vs. 9 mm, p=0.037). Other demographic and clinical characteristics did not differ significantly between the NAC group and control group. The mortality rate was lower in the NAC group compared to the control group (26.7% vs. 50.0%, p=0.008) (**Table 1**).

Table 1. Patients' characteristics and clinical findings

Variables	All population n=35	NAC		p
		Yes n=15	No n=20	
Age, years	58 (24-77)	55 (24-74)	60 (28-77)	0.074
Male gender, n (%)	24 (68.6)	9 (60.0)	15 (75.0)	0.563
cT, n (%)				0.215
T1	6 (17.1)	1 (6.7)	5 (25.0)	
T2	21 (60.0)	9 (60.0)	12 (60.0)	
T3	8 (22.9)	5 (33.3)	3 (15.0)	
cN, n (%)				0.818
N0	18 (51.4)	7 (46.7)	11 (55.0)	
N1	10 (28.6)	4 (26.7)	6 (30.0)	
N2	7 (20.0)	4 (26.7)	3 (15.0)	
pT, n (%)				0.810
T1	8 (22.9)	4 (26.7)	4 (20.0)	
T2	18 (51.4)	8 (53.3)	10 (50.0)	
T3	9 (25.7)	3 (20.0)	6 (30.0)	
pN, n (%)				0.792
N0	23 (65.7)	9 (60.0)	14 (70.0)	
N1	6 (17.1)	3 (20.0)	3 (15.0)	
N2	6 (17.1)	3 (20.0)	3 (15.0)	
Tumor size, cm	2 (0.3-5.7)	1.5 (0.3-5.7)	2.1 (1.1-5.0)	0.501
Difference, n (%)				0.644
Well	24 (68.6)	9 (60.0)	15 (75.0)	
Moderate	8 (22.9)	4 (26.7)	4 (20.0)	
Poor	3 (8.6)	2 (13.3)	1 (5.0)	
Depth of invasion, mm	9 (2-18)	7 (2-11)	9 (3-18)	0.037
Surgical margins, n (%)				0.496
Negative	33 (94.3)	15 (100.0)	18 (90.0)	
Positive	2 (5.7)	0	2 (10.0)	
Lymphovascular invasion, n (%)	3 (8.6)	1 (6.7)	2 (10.0)	0.999
Perineural invasion, n (%)	3 (8.6)	1 (6.7)	2 (10.0)	0.999
Extracapsular extension, n (%)	0	0	0	-
Lymph node metastasis, n (%)	13 (37.1)	6 (40.0)	7 (35.0)	0.999
Mortality, n (%)	14 (40.0)	4 (26.7)	10 (50.0)	0.008

Data are shown as median and min - max or number and percentage (%).
Abbreviations: cT, clinical T stage; cN, clinical N stage; pT, pathological T stage; pN, pathological N stage.

Mean follow-up time was 40.0±4.1 months. Findings associated with 5-year overall survival are presented in **Table 2**. Increased age, NAC administration and increased depth of invasion were found to be factors associated with 5-year overall survival. Multivariable regression analysis showed that increased depth of invasion was independently associated with increased risk of mortality, while receiving NAC was independently associated with decreased risk of mortality. The risk of mortality was 6.25-fold lower (1/0.16) in the NAC group compared to the control group (HR: 0.16, 95% CI: 0.004-

0.72, p=0.017). A 1-mm increase in depth of invasion increased the risk of mortality by 1.3-fold (HR: 1.38, 95% CI: 1.05-2.00, p=0.030) (**Table 3**).

The 1-year overall survival probability was 93% and the 5-year overall survival probability was 73% in the NAC group. The 1-year overall survival probability was 72% and the 5-year overall survival probability was 45% in the control group (**Figure 1**).

Table 3. Independently factors associated with 5-year mortality

Variables	Multivariable Cox Regression		
	HR	95% CI	p
Age, years	1.03	0.98-1.08	0.177
Neoadjuvant chemotherapy, n (%)	0.16	0.04-0.72	0.017
Depth of invasion, mm	1.38	1.05-2.00	0.030
	-2Log Likelihood=11.76, p<0.001		

Abbreviations: CI, confidence interval; HR, hazard ratio

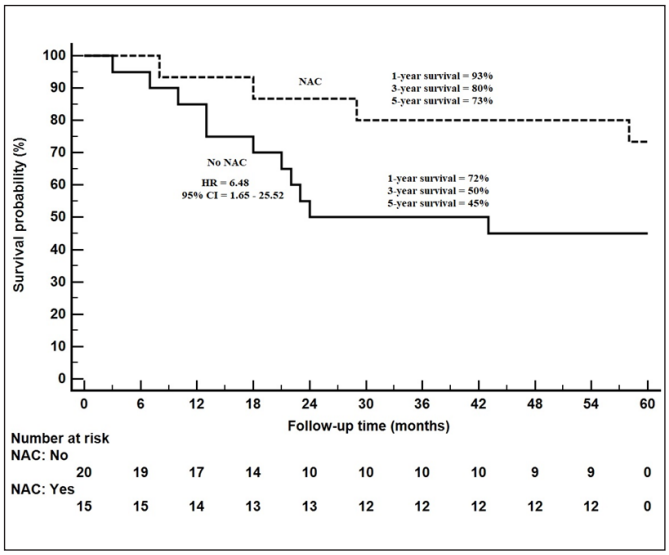

Figure 1. Five-years mortality risk in patients with and without preoperative neoadjuvant chemotherapy

Table 2. Factors associated with 5-years overall survival

Variables	Overall Survival		Univariable Cox Regression		
	Alive n=21	Exitus n=14	HR	95% CI	p
Age, years	55 (24-74)	65 (36-77)	1.04	1.00-1.09	0.043
Male gender, n (%)	12 (57.1)	12 (85.7)	3.38	0.76-15.07	0.111
Neoadjuvant chemotherapy, n (%)	11 (52.4)	4 (28.6)	0.15	0.04-0.61	0.008
cT, n (%)					
1	5 (23.8)	1 (7.1)	ref		
2	10 (47.6)	11 (78.6)	2.84	0.37-22.03	0.319
3	6 (28.6)	2 (14.3)	1.68	0.17-16.21	0.653
cN, n (%)					
0	13 (61.9)	5 (35.7)	ref		
1	5 (23.8)	5 (35.7)	2.56	0.78-8.40	0.122
2	3 (14.3)	4 (28.6)	2.08	0.55-7.83	0.277
pT, n (%)					
1	6 (28.6)	2 (14.3)	ref		
2	10 (47.6)	8 (57.1)	1.28	0.27-6.10	0.753
3	5 (23.8)	4 (28.6)	2.11	0.41-10.95	0.375
pN, n (%)					
0	14 (66.7)	9 (64.3)	ref		
1	5 (23.8)	1 (7.1)	1.01	0.22-4.68	0.992
2	2 (9.5)	4 (28.6)	1.87	0.57-6.12	0.301
Tumor size, cm	2 (0.3-5.7)	2.1 (1-3.5)	0.93	0.58-1.50	0.759
Difference, n (%)					
Well	15 (71.4)	9 (64.3)	ref		
Moderate	4 (19.0)	4 (28.6)	0.86	0.26-2.88	0.810
Poor	2 (9.5)	1 (7.1)	1.57	0.33-7.48	0.569
Depth of invasion, mm	8 (2-13)	13 (9-18)	1.36	1.03-1.80	0.030
Surgical margins, n (%)					
Negative	19 (90.5)	14 (100.0)	ref		
Positive	2 (9.5)	0	2.46	0.31-19.81	0.397
Lymphovascular invasion, n (%)	1 (4.8)	2 (14.3)	1.48	0.33-6.65	0.607
Perineural invasion, n (%)	2 (9.5)	1 (7.1)	0.90	0.12-6.96	0.922
Lymph node metastasis, n (%)	8 (38.1)	5 (35.7)	1.37	0.49-3.87	0.552

Data are shown as median and min - max or number and percentage (%).
Abbreviations: cT, clinical T stage; cN, clinical N stage; pT, pathological T stage; pN, pathological N stage.

DISCUSSION

In this study, NAC was found to improve 5-year overall survival. The depth of invasion was lower in the NAC group. Increased depth of invasion was an independently associated with increased risk of mortality. These associations were independent of the pathological stage of the disease.

NAC is cited as a therapeutic strategy for functional preservation, relapse control, and reduction of mortality risk (4). It has been suggested that NAC is associated with a high response rate in untreated patients with head and neck cancers (2). Assessment of tumor response to NAC includes histopathologic evaluation of tumor regression in resected specimens (12). In our study, pathological depth of invasion was lower in the NAC group and tumor size was relatively smaller. These findings support the potential role of NAC in reducing tumor burden. Tumor size reduction following NAC can reduce the extent of surgery, provide better preservation of function, and improve quality of life (13). On the other hand, preoperative NAC may also play a prognostic role in reducing surgical margins (5). This was consistent with the finding of negative surgical margins in all patients who received NAC. However, it still remains unclear whether NAC can reduce the rates of distant metastasis or locoregional relapse (3). The rates of lymphovascular invasion, perineural invasion, and lymph node metastasis were not significantly different in the NAC group compared to the control group in the present study. In an experimental study of a mouse model of oral squamous cell carcinoma, mice were divided into surgery, preoperative NAC plus surgery, surgery plus postoperative NAC, and untreated groups. After 28 days of follow-up, cervical lymph node metastasis rates were lower in the preoperative NAC plus surgery group than the other groups (14). DNA microarray studies have shown that the gene expression profiles of metastatic tumors, including lymph node metastasis, are different compared to primary tumors (15, 16). Thus, gene differences in metastatic tumors may result in differences in the response to NAC. This may explain the similar lymph node metastasis rates of the NAC group and the control group.

Previous studies have reported that depth of invasion is an independent predictor of metastatic tumors (17, 18). In the 8th edition of the American Joint Committee on Cancer's staging manual, the depth of tumor invasion was accepted as a prognostic factor in tumor staging (19). In our study, NAC was associated with lower depths of invasion. Since NAC targets control of local disease and systemic micrometastasis, the characteristics and response of the primary tumor may be more closely related to prognosis (12). It is known that there is a high correlation between radiological depth of invasion and pathological depth of invasion (20, 21). Therefore, changes in the radiological depth of invasion and tumor size may be important for the evaluation of the response of the tumor to NAC. However, a standard method for determining radiological depth of invasion in the preoperative period has not been established yet.

The 5-year overall survival rates of tongue cancer patients range from 32% to 55% (22, 23). In our study, those who received NAC had an approximately 6-fold lower risk of mortality and NAC was an independently associated with decreased risk of mortality. The probability of both 1-year and 5-year overall survival was higher in the NAC group. A prospective study of 198 patients with resectable oral cavity cancer compared the 10-year overall survival rates of patients who underwent only surgery and those who received preoperative NAC (24). There was no significant difference in 10-year overall survival between the groups. However, the probability of overall survival at the 10-year follow-up was 76% for patients with a pathological complete response to NAC compared to 41% for patients who did not respond to NAC (24). A previous study involving patients with hypopharyngeal carcinoma reported that preoperative NAC improved overall survival (25). In contrast, a meta-analysis study showed that NAC did not confer a significant advantage in terms of disease-free survival or overall survival at the 2-year follow-up (23). Similarly, another head and neck cancer meta-analysis including 87 studies showed no increase in overall survival following NAC (8). However, the patients with tongue cancer in these studies constituted only small fractions of the total populations.

Different NAC regimens can cause significant differences in overall survival. Combination regimens containing 5-FU, cisplatin, or taxane offer greater advantages in improving overall survival compared to single-agent regimens (8). Moreover, previous studies have reported that the triple regimen containing taxane increases the probability of overall survival compared to the double regimen containing cisplatin plus 5-FU (26). In our study, the NAC regimen consisted of 2 cycles of cisplatin. The use of single-regimen NAC was associated with the clinical approach of the physicians planning treatments in the years in which patients were included. Considering the conflicting findings for NAC regarding overall survival, prospective studies with larger patient populations are needed, especially studies containing both single regimens and combination regimens.

The strengths of this study are the assessment of long-term prognosis in patients with tongue cancer and its inspiring findings between prognosis and preoperative

NAC. However, this study has some important limitations. The main limitation was the single-center retrospective design together with a small sample. Secondly, the response status to NAC could not be evaluated. Thirdly, due to the retrospective design, patients' relapse data was missing and therefore could not be evaluated. Fourthly, the effect of chemotherapy on the depth of tumor invasion could not be evaluated, since data on the pre-treatment values of tumor invasion depth could not be reached. The importance of overall survival was limited due to the lack of data on locoregional recurrence and disease-free survival, which are the main prognostic parameters, and the inability to shown that the cause of death was disease-related. Finally, data on the toxicity status of patients following NAC were not available. That may play an important role in the overall survival of patients (26, 27).

CONCLUSION

Patients who underwent NAC plus surgery were associated with a higher probability of 5-year overall survival compared to patients who underwent surgery alone. However, NAC was associated with lower depths of invasion. These findings may be inspiring for the role of NAC prior to surgery in the prognosis of patients with tongue cancer.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Gazi University Medicine Faculty Clinical Researches Ethics Committee (Date: 04/2011, Decision No: 92).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients**.**

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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Evaluation of dry eye parameters in patients with conjunctival papilloma following surgical excision with adjuvant mitomycin-C

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ABSTRACT

Aim: To evaluate the changes in tear osmolarity levels, tear function tests, and dry eye symptom scores in patients with conjunctival papilloma following surgical excision with adjuvant Mitomycin C (MMC).

Material And Method: Thirty patients diagnosed with conjunctival papilloma were enrolled in the study. Tear osmolarity, fluorescein break-up time (FBUT), Schirmer I test and eyelid margin score were evaluated at baseline and 1st, 3rd, and 6th months after conjunctival surgery with adjuvant 0.02% MMC were recorded. Dry eye symptom questionnaire scores obtained preoperatively and at the 1st, 3rd, and 6th months after surgery were also recorded. The mean values of test results noted at each control visit were compared.

Results: The mean age of the study population was 37±9.5 years. Schirmer I test scores, FBUT values, dry eye symptom scores, eyelid margin scores, and tear osmolarity values showed a significant difference between the preoperative measurements and follow-up visits ($p<0.05$). This difference was more apparent at the postoperative 1st-month visit. Measurement values showed that dryness peaked at the postoperative 1st month and gradually decreased afterward reaching the preoperative values at the postoperative 6th-month visit.

Conclusion: This study showed that conjunctival papilloma surgery with MMC is associated with transiently increased dry eye symptom scores and abnormal tear function tests.

Keywords: Conjunctival papilloma, Mitomycin C, tear osmolarity, dry eye disease

INTRODUCTION

Conjunctival papilloma is an acquired benign tumor that originates from the conjunctival stratified squamous epithelium. HPV infection is reported as the main risk factor which has 44-92% detection rates in the lesions (1). Conjunctival papillomas are encountered more commonly in men between the ages of 21 and 40 years with a progressive decrease in the incidence thereafter (2,3).

Various medical and surgical approaches have been described in the management of conjunctival papillomas (4). "No-touch" wide resection of the conjunctival lesions has been the traditionally performed method (5). Still, recurrences can be encountered after excision which can result in more severe conjunctival proliferations than the original lesions (6). For this reason, Mitomycin C (MMC) is commonly administered intraoperatively as an adjuvant agent to prevent recurrences (4).

Dry eye disease (DED) is characterized by the loss of homeostasis of the tear film accompanied by ocular symptoms (7). Objective evidences of DED are; reduced tear breakup time (TBUT), lower Schirmer score without topical anesthesia, and increased tear osmolarity measurements. Tear osmolarity measurement technology recently became available and the results showed increased osmolarity in all subtypes of DED with good sensitivity and specificity (8,9).

There have been several reports on the effect of MMC use for conjunctival papilloma excision (2-4). However, no known studies have described the development and course of DED in patients undergoing conjunctival papilloma excision with adjuvant MMC. In this study, we evaluated the changes in tear osmolarity levels, tear function tests, and dry eye symptom scores in patients with conjunctival papilloma following surgical excision with adjuvant MMC.

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MATERIAL AND METHOD

Thirty patients (12 female and 18 male) who underwent conjunctival papilloma excision surgery and completed 6-month follow-up visits between September 2020 and November 2022 at our Ocular Oncology Unit were retrospectively involved in this study design. Approval for the study was granted by the local Ethics Committee of our hospital with permit number (Date: 14/12/2022, Decision No: E1-22-3044). All procedures were carried out by the ethical rules and the principles of the Declaration of Helsinki. Hospital medical records and patient charts were reached to collect the study data. Patients with any serious systemic disease (e.g., primary Sjögren's syndrome), vitamin B12 deficiency, pregnancy, breastfeeding, history of smoking, current drug use, active ocular infection or allergy, previous ocular surgery, and use of contact lenses were excluded. Patients with recurrent diseases were also excluded.

Each patient preoperatively underwent a complete eye examination. Fluorescein break-up time (FBUT) testing, Schirmer I test (without anesthesia), eyelid margin score, tear osmolarity, and Ocular Surface Disease Index (OSDI) test scores were evaluated at baseline, and at the 1st, 3rd, and 6th months after surgery. For FBUT, a fluorescein strip moistened with preservative-free saline solution is applied to the inferior palpebral conjunctiva. The time passed between a blink and the appearance of the first dark spot is measured through the cobalt blue filter of the slit lamp. For Schirmer I test, a standard 5x35 mm strip of Schirmer paper was placed at the junction of the middle and lateral one-third of the lower eyelids. Patients were asked to keep their eyes closed. After 5 minutes, the strips were removed and the length of wetting was recorded. Eyelid margin score was noted on a 0-3 scale and the evaluation was as follows: eyelid margin irregularity (presence/absence), vascularity of the eyelid margin (presence/absence), occlusion of glands at the lid margin (presence/absence), and displacement of the mucocutaneous junction (presence/absence). All measurements were performed in the same order in the same examination room by the same examiner (CB). The OSDI questionnaire has 12 questions about individuals' ocular and visual symptoms in general, performance in certain activities, and certain weather conditions. Responses were evaluated on a scale of 0 to 4. A final score is calculated which ranges from 0 to 100 with scores 0 to 12 representing normal, 13 to 22 representing mild dry eye disease, 23 to 32 representing moderate dry eye disease, and greater than 33 representing severe dry eye disease (10).

As a rule, a 'No-touch' wide resection principle is followed for the surgical management of conjunctival papilloma cases at our center. The procedure is done under monitored anesthesia care with a regional block. Conjunctival forceps and blunt scissors are used for excision while extra care is taken not to touch the tumor. The lesion base is always cauterized after excision. Next, a 2x5-mm sponge soaked in a solution of 0.02% MMC is placed over the exposed sclera. The conjunctiva and tenon capsule are then pulled over the sponge with forceps, and the sponge is held in contact with the tissues for 5 minutes. Afterward, the sponge is removed and the ocular tissue is irrigated with saline solution. Primary closure with conjunctival advancement is performed. Topical antibiotic ointment and steroid drops are prescribed to be instilled every 6 hours daily. Steroid drops are tapered and discontinued after 2 weeks. Topical antibiotic drops are ceased after 1 week. Sutures are removed in the first week after the surgery. Follow-up examinations are performed on days 1, 7, 15, and 30, and then the 3rd and 6th months. Each visit covers a complete eye examination and an OSDI questionnaire filled out by the patient. All results are included in the patient's medical charts.

Data analysis was performed using the IBM SPSS 25.0 (Armonk, NY: IBM Corp.) statistical package program. Descriptive statistical methods (frequency, percentage, mean, standard deviation, median, and min-max) were used when evaluating the data. The conformity of the data to the normal distribution was evaluated by Kolmogorov-Smirnow and Shapiro-Wilk tests, skewness-kurtosis, and graphical methods (histogram, Q-Q Plot, Stem and Leaf, Boxplot). Repeated Measures Anova Test (repeated measures analysis of variance) was used for the comparison of repeated measurements. Post-hoc analysis was also performed to detect the significant differences between the measurements in different time intervals. The statistical significance level was accepted as $p=0.05$.

RESULTS

Thirty patients (12 female, 18 male) with a mean age of 37±9.5 years were enrolled. Schirmer I test scores, FBUT values, dry eye symptom scores, eyelid margin scores, and tear osmolarity values were compared between the baseline measurements and the follow-up visits after surgery (**Table** 1).

A statistical difference was found for FBUT and Schirmer I test results at the 1st and 3rd month visits and other measurement times; thus, 1st month values were the lowest ($p<0.05$). Similarly, tear osmolarity comparisons revealed increased osmolarity at the 1st and 3rd month visit, the 1st month being the highest ($p<0.05$). Both FBUT, Schirmer I test and tear osmolarity results showed that dryness peaked in the 1st month after surgery and gradually resolved to reach the preoperative values at

the 6th month visit after surgery. Eyelid margin scores also showed the same monthly pattern as the test results mentioned above, pointing to increased dryness after papilloma excision reaching the highest level in the 1st month followed by the 3rd month (p<0.05).

Table 1. Comparison of the preoperative and postoperative mean values of the dry eye parameters

Test	Mean±SD
Fluorescein Break-up Time (seconds)	
Preoperative 1	12.8±1.6
Postoperative	
1. month 2	9.7±2.0
3. month 3	11.4±1.8
6. month 4	12.4±1.3
P*	<0.001
Difference present between	2 and 1-3-4 3 and 1-2-4
Tear Osmolarity (mOsm/L)	
Preoperative 1	305.8±13.4
Postoperative	
1. month 2	324.5±9.1
3. month 3	316.1±17.8
6. month 4	308.7±19.1
P*	<0.001
Difference present between	1-4 and 2-3
Eyelid Margin Score	
Preoperative 1	1.0±0.7
Postoperative	
1. month 2	1.9±0.9
3. month 3	1.3±0.8
6. month 4	1.0±0.5
P*	<0.001
Difference present between	2 and 1-3-4 3 and 2-4
Schirmer I (mm)	
Preoperative 1	13.6±2.1
Postoperative	
1. month 2	10.3±1.9
3. month 3	11.9±1.6
6. month 4	13.1±1.6
P*	<0.001
Difference present between	2 and 1-3-4 3 and 1-2-4
OSDI Symptom Score	
Preoperative 1	13.5±0.9
Postoperative	
1. month 2	15.2±1.2
3. month 3	13.7±0.7
6. month 4	11.9±0.7
P*	<0.001
Difference present between	2 and 1-3-4 4 and 1-2-3

*: Repeated Measures Anova Test (Mean±SD)

OSDI scores were also found to be significantly higher at the 1st month visit than the preoperative scores (p<0.05). The mean OSDI score was found to be indistinctive of the preoperative mean value at the 3rd month visit, plus, 6th month visit mean OSDI value was even found to be significantly lower than the preoperative mean OSDI value (p<0.05). Graphs showing FBUT, Schirmer test results, tear osmolarity, dry eye symptoms and eyelid margin scores change over time were represented in **Figure 1**.

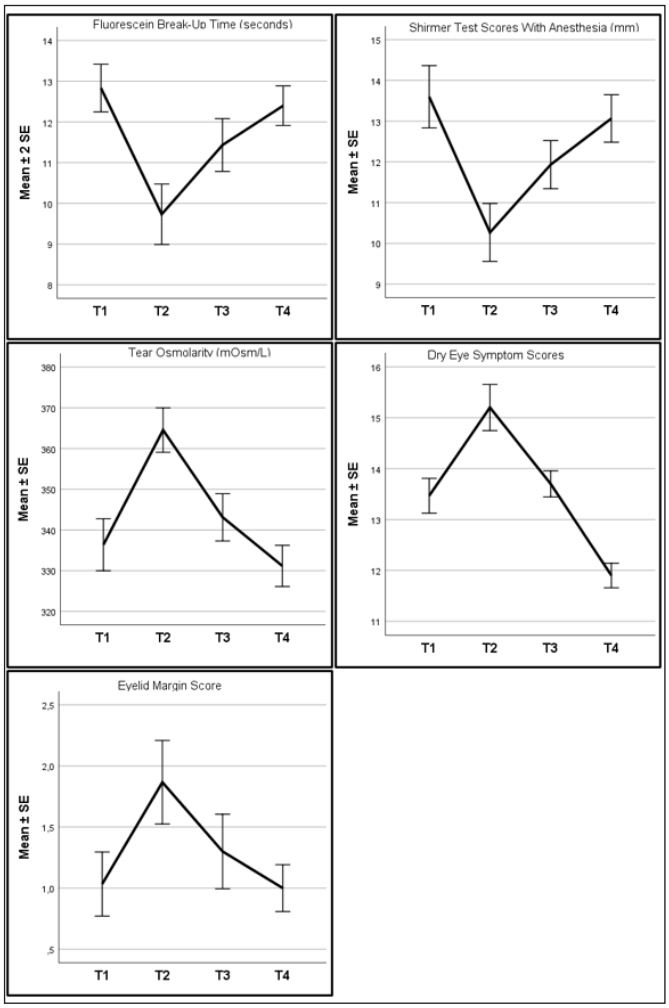

Figure 1. Graphs showing fluorescein break-up time, schirmer test results, tear osmolarity, dry eye symptom, and eyelid margin scores change over time

DISCUSSION

Conjunctival papilloma patients can have symptoms depending on the size and location of the tumor. Although smaller lesions are usually asymptomatic, larger lesions may cause foreign body sensation and dryness due to inadequate eyelid closure and chronic mucus production (1).

In this study, it was detected that conjunctival papilloma excision with MMC is associated with a transient increase in tear osmolarity and abnormal tear film function tests.

Before its use in ocular surface neoplasia, MMC had been widely used in glaucoma and pterygium surgeries for its antiproliferative effect on subconjunctival fibroblasts. MMC is considered a safe chemotherapeutic agent in treating ocular surface neoplasia. Transient side

effects including tearing, ocular pain, blepharospasm, keratoconjunctivitis, conjunctival hyperemia, and punctate epithelial keratopathy are common (11). Complications and side effects of MMC, when used in different surgical procedures, arise from direct contact of the MMC with the ocular surface. The effect of MMC use in photorefractive keratectomy had been evaluated previously and it was found that adjuvant MMC did not cause any exacerbation in dry eye symptoms (12). However, to our knowledge, no study had previously evaluated the effect of MMC use on tear function tests and dry eye symptom scores in conjunctival papilloma patients.

Tear osmolarity contributes to the pathogenesis of ocular surface damage and its measurement is one of the most objective parameters of DED. Increased tear osmolarity triggers inflammatory changes that may result in damage to the epithelial surface of the cornea and the conjunctiva (13). Tear osmolarity threshold values might vary from 305mOsm/L to 316mOsm/L, depending on the research (8,14,15). Currently, most researchers believe that the 316mOsm/L threshold better discriminates between mild and moderate-severe dry eye, while the 308mOsm/L threshold is widely accepted as the most sensitive value for discriminating between normal eyes and those presenting with early stages of the disease (14, 16). TearLab osmometer (TearLab, San Diego, CA, USA) reliability studies also revealed a sensitivity of 81% and a specificity of 80% when using the threshold value of 308 mOsml/L (17). In this study, we found that the mean preoperative osmolarity value was in the normal range. However, the mean osmolarity value reached 324.5±9.1 mOsm/L at the 1st month visit after surgery which is a value accepted to indicate severe DED. At the 3rd month visit mean osmolarity value was found to be lower (316.1±17.8 mOsm/L) than the 1st month value but still indicated moderate DED. Moreover, mean osmolarity returned to the normal cut-off value at the 6th month which is statistically not different than the mean preoperative value. These findings with tear osmolarity were further supported and reflected by TBUT, Schirmer I test, and eyelid margin score results. All tests revealed that DED peaked at the 1st month after surgery with a gradual decrease thereafter and a relative resemblance to preoperative values at the 6th month postoperatively.

OSDI questionnaire is used in this study to assess dry eye symptoms. We found that the mean OSDI score significantly increased in the 1st month after surgery and there was a continuous decrease in the next follow-up visits. At the postoperative 6th month visit, the OSDI scores were even detected to be significantly lower than the preoperative values. Although the OSDI questionnaire is not frequently used in the evaluation of patients with conjunctival papillomas, significantly higher OSDI scores in patients with pterygium compared to healthy controls had been previously reported (18,19). It was also shown that eyes with pterygium had significantly higher tear osmolarity levels than control fellow eyes without pterygium (20,21). Like pterygium, papilloma is an ocular surface proliferative disease associated with conjunctival inflammation. On the other hand, conjunctival papillomas are generally smaller and they are associated with less conjunctival inflammation than pterygium cases. Therefore, we found that conjunctival papilloma cases were associated with similar tear osmolarity levels, tear function tests, and OSDI scores with the normal population preoperatively. Our study results indicate that adjuvant MMC caused a secondary imbalance in the tear content which peaked in the postoperative first month. However, this effect was temporary and the test results returned to preoperative state at the postoperative 6th month. Still, care should be taken for the development of DED in these patients, even if minimum MMC is used intraoperatively.

Limitations of the study are the retrospective design and the limited number of patients. A prospective study evaluating tear parameters in conjunctival papilloma patients undergoing excision surgery with and without MMC would better reflect the effect of MMC. However, all papilloma surgeries are done with MMC at our center to prevent recurrences and we were not able to enroll a control group due to the retrospective design. Still, our study provides a valuable contribution to the literature about the changes in tear osmolarity levels, tear function tests, and dry eye symptom scores in patients with conjunctival papilloma following surgical excision with adjuvant MMC.

CONCLUSION

This study showed that conjunctival papilloma-affected eyes were associated with similar tear osmolarity levels and tear function tests with the normal population preoperatively. It was also determined that MMC applied to the conjunctiva during surgery negatively affected the ocular surface causing increased tear osmolarity and diminished tear function tests. Nevertheless, DED signs and symptoms and osmolarity values decreased through the follow-up period which indicates that the effect of MMC use during papilloma excision surgery is temporary.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara City Hospital Ethics Committee (Date: 14/12/2022, Decision No: E1-22-3044)

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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How to explain a machine learning model: HbA1c classification example

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ABSTRACT

Aim: Machine learning tools have various applications in healthcare. However, the implementation of developed models is still limited because of various challenges. One of the most important problems is the lack of explainability of machine learning models. Explainability refers to the capacity to reveal the reasoning and logic behind the decisions made by AI systems, making it straightforward for human users to understand the process and how the system arrived at a specific outcome. The study aimed to compare the performance of different model-agnostic explanation methods using two different ML models created for HbA1c classification.

Material and Method: The H_2O AutoML engine was used for the development of two ML models (Gradient boosting machine (GBM) and default random forests (DRF)) using 3,036 records from NHANES open data set. Both global and local model-agnostic explanation methods, including performance metrics, feature important analysis and Partial dependence, Breakdown and Shapley additive explanation plots were utilized for the developed models.

Results: While both GBM and DRF models have similar performance metrics, such as mean per class error and area under the receiver operating characteristic curve, they had slightly different variable importance. Local explainability methods also showed different contributions to the features.

Conclusion: This study evaluated the significance of explainable machine learning techniques for comprehending complicated models and their role in incorporating AI in healthcare. The results indicate that although there are limitations to current explainability methods, particularly for clinical use, both global and local explanation models offer a glimpse into evaluating the model and can be used to enhance or compare models.

Keywords: Machine learning, explainable artificial intelligence, glycated hemoglobin

INTRODUCTION

In healthcare, machine-learning (ML) models are used for various tasks, such as image and signal analysis, disease diagnosis, treatment planning, and drug discovery (1). The use of ML models to improve patient care is a novel approach, but its implementation in clinical practice is still limited (2).

Explainability can be defined as the capability of making the decision-making process of AI systems transparent and understandable for human users, it includes how the decision was reached and how the system arrived at a particular conclusion (3). It is one of the most important limitations, and it has long been a question of great interest in a wide range of fields, including medicine (4). More recently, there has been growing number of publications that focus on explainable artificial intelligence (xAI) (5).

The debate continues regarding the best strategies for the appropriate application of explainability tools. To date, there has been little agreement about what constitutes sufficient explainability and xAI suffers from insufficient application, and limited studies have investigated whether xAI contributes to ML model use in medicine(4,6). Model-agnostic explainability techniques refers to methods or techniques that can be applied to any model, regardless of its architecture or learning algorithm, and these methods can be further categorized into local and global methods. While global interpretability focuses on understanding the overall functioning and decision-making processes of a model, local interpretability focuses on understanding the reasoning behind individual predictions made by the model (5,7).

Diabetes mellitus is a chronic medical condition characterized by high blood sugar levels resulting from defects in insulin production, insulin action, or both. Monitoring HbA1c levels is critical for managing diabetes and preventing complications such as kidney damage, nerve damage, and cardiovascular disease (8). The aim of this study is to develop an ML model that utilizes

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routine laboratory and clinical data for hemoglobin A1c prediction and investigate the effectiveness of cutting-edge global and local explainability tools that are used for prediction explanations by comparing different models. To achieve this goal, two different ML algorithms were developed and applied to both local and global explainability model predictions.

MATERIAL AND METHOD

Data Source and HbA1c Classification

All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Open data sets were utilized for the study. Therefore, ethics committee approval was not obtained. The National Health and Nutrition Examination Survey data sets between 2014–2017 were used (9). Only records of adults aged 18 years and older were included in the study. Twenty-eight parameters, including clinical laboratory results and clinical information, were selected for ML model development. Regarding prediction, quantitative hemoglobin A1c (A1c) results were split into the following three classes according to the criteria recommended by the American Diabetes Association: normal (<5.7%), prediabetes (5.7%–6.4%), and diabetes (>6.4%) (10). The descriptive statistics of the included parameters are given in **Table 1**.

Machine-Learning Model Development

Pre-process, data cleaning, and generation of training and test sets: Data preparation, the creation of ML models, and statistical analyses were all completed using R statistical software version 4.2 (11). The model explanations were carried out using the H_2O and DALEX packages (12,13). The data set was composed of 3,036 records that contained all selected parameters. Therefore, there were no missing values in the data set. The data were split into training (70%, n=2,114) and test sets (30%, n=912) using stratification according to A1c, age, and sex.

Table 1. Clinical laboratory results and demographic features of the study population and feature importance for the developed models

Parameter	n (%)	Min	Max	Mean (SD)	Median (IQR)	Feature Importance1	
						ML Model	
						DRF	GBM
Age		18	80	44.7 (17.8)	41 (30)	0.36*	0.15*
ACR, Urine, mg/g		0.94	7980	39.1 (257)	6.54 (8.07)	0.07	0.01
Albumin, g/L		21	54	42.1 (3.59)	42 (5)	0.08	0.01
ALP, U/L		23	347	71.9 (24)	69 (26)	0.06	0.01
ALT, U/L		3	181	25 (16.5)	21 (14)	0.06	0.02
AST, U/L		8	289	24 (13.4)	21 (8)	0.04	0.01
BMI kg/m²		15.5	65.3	29.1 (6.9)	28 (8.5)	0.10	0.02
BUN, mg/dL		2	79	14.4 (5.63)	14 (6)	0.07	0.00
Calcium, mg/dL		7.8	10.5	9.27 (0.329)	9.3 (0.5)	0.06	0.00
Cholesterol, mg/dL		76	433	182 (39.6)	178 (52)	0.09	0.03
Creatinine, mg/dL		0.3	6.73	0.91 (0.29)	0.88 (0.29)	0.08	0.01
Glucose, mg/dL		19	434	104 (34.9)	95 (17)	0.99*	0.98*
HDL-C, mg/dL		6	151	51.6 (15.2)	49 (19)	0.08	0.01
Hemoglobin g/dL		6.3	19	14.5 (1.55)	14.6 (2)	0.09	0.02
Lymphocyte, %		7	94.5	31.2 (8.64)	30.7 (11.5)	0.07	0.01
MCV, fL		51.6	114	88.6 (6.19)	89.1 (6.6)	0.09	0.05*
Neutrophil, %		3.6	85.8	56.7 (9.37)	57 (12.5)	0.09	0.03
Platelet, 10^3 cells/µL		14	662	232 (61.7)	225 (75)	0.08	0.02
RBC, 10^6cells/µL		2.52	6.82	4.9 (0.50)	4.9 (0.66)	0.07	0.01
Bilirubin, mg/dL		0	2.8	0.57 (0.309)	0.5 (0.3)	0.07	0.02
Total Protein g/L		56	90	71.9 (4.25)	72 (6)	0.07	0.01
Triglyceride, mg/dL		10	2140	109 (88.5)	89 (76.2)	0.09	0.02
Uric acid, mg/dL		1.8	18	5.69 (1.47)	5.6 (2)	0.08	0.01
Waist Circ., cm		63.2	170	99.9 (17.2)	98.4 (22.5)	0.14*	0.02
WBC, 10^3 cells/µL		2.5	117	6.88 (2.85)	6.6 (2.4)	0.07	0.01
Sex						0.03	0.00
Male	2201 (72.5%)						
Female	835 (27.5%)						
HbA1c Class							
Normal	1898 (62.5%)						
Prediabetes	788 (26.0%)						
DM	350 (11.5%)						

ACR: Albumin creatinine ratio, Circ: Circumference, DRF: Distributed Random Forest, GBM: Gradient Boosting Machine, IQR: Interquartile range, SD: Standard deviation, 1 Scaled Importance, * Top three features

To identify the important features for developing a ML model, the study utilized the Boruta feature selection algorithm. This algorithm generated a shadow feature for each attribute by shuffling the values of the original attributes across properties. The importance of the features was then categorized into three classes: "discard" (red), "speculative" (blue), tentative (yellow) and "keep" (green) to identify the significant features (14). According to the Boruta analysis results Monocyte % parameter was excluded for ML development. Details of Boruta analysis were given in supplementary material.

Utilization of the AutoML tool: In the study, ML models were developed using the H_2O AutoML engine. H_2O is an open source, distributed ML platform that can perform all ML model development steps, including data processing, feature engineering, model building, hyperparameter optimization, and performance evaluation. The H_2O engine was utilized to develop ML models for the multinomial (multiclass) classification of A1c. Gradient boosting machine (GBM) and default random forests (DRF) models were selected as candidate algorithms. All model development-related steps were performed by the AutoML tool using the training data set. Because of the unequal distribution of A1c classes, the "balance_classes" option was used. This feature could be utilized to equalize the distribution of classes in a dataset. When activated the majority classes are either undersampled or the minority classes are oversampled. The resulting model will correct the final probabilities using a monotonic transform (12). Further, during the model development phase, hyperparameters optimization was performed using k-fold cross-validation (k=10). Finally, multiple models that were developed by the AutoML tool were evaluated using an automatically split leaderboard data set, and the winning tuned models were determined. In the study, the best models were used for the explainability method comparison.

Model explainability comparison: Model agnostic explainability methods were applied to the developed ML models. Both global and local explainability approaches were used to compare the effectiveness of the explainability methods for the DRF and GBM ML models.

Global exploration: Global methods are useful for understanding the overall patterns and behaviors of a ML model. They provide an average understanding of the model's performance. These types of methods are particularly helpful when the person building the model wants to gain a general understanding of how the model works or troubleshoot any issues with the model. In the context of the study, the following global explorations were performed to compare the internal reasoning of two ML models:

a. Performance metrics: (i) The mean per class error is the average of the errors of each class in multinominal models. It represents the misclassification of the data across the classes, and lower metrics indicate a better performance. (ii) The area under the receiver operating characteristic curve (AUC) is a metric that evaluates the model's performance for distinguishing true positives and negatives and is normally used for binominal classification problems. However, it is also possible to calculate the AUC for multinominal models using different approaches. In the study, the method that was suggested by Till was used to calculate the AUC (15). Because of the imbalanced classes, the one vs. one calculation method was used for the AUC calculation (iii) The area under the precision recall curve (AUCPR) is important and is not affected by the true negatives. Therefore, it is preferred for imbalanced data sets (15). When dealing with imbalanced data, many true negatives often make it difficult to see the impact of changes in other metrics, such as false positives. AUCPR is more responsive to changes in true positives, false positives, and false negatives than the AUC, making it a better choice for evaluating highly imbalanced data sets (12).

b. Variable importance (VIP): Variable importance is the measurement of how much each feature contributes to the ML model's predictions. This method ranks the features based on their relative importance to the model. Therefore, VIP can give a broad overview of the model's characteristics. There are several methods to measure variable importance, such as permutation importance and importance based on Shapley additive explanations (SHAP) values (16, 17). In the study, VIP values were calculated for all parameters. The significance of each variable is determined by evaluating the relative impact of the variable in the tree-building process based on its frequency of being chosen as a splitting point and the decrease in squared errors across all trees (12).

c. Partial dependence profiles (PDPs): PDPs provide visual feedback for the interpretation of any black box model by showing the influence of different features or feature subsets. It also shows the marginal effect of a variable for the average prediction (5). The impact of a variable can be determined by observing the change in the average response (12). PDPs do not take into consideration all possible feature interactions. Therefore, they can provide limited accurate information about the model. Despite this, they frequently provide helpful information, which substantially aids in understanding black box models, particularly when most of these interactions are low. They can be used for improving

ML models, comparing different models, and evaluating model performance (5). PDP plots were created for the four most important parameters (glucose, age, waist circumference, and mean corpuscular volume (MCV) to investigate and compare the prediction patterns of the two models.

Local exploration (single row prediction): In contrast to global exploration, local exploration methods assist in comprehending how a model generates a prediction for an individual data point. In the study, cases with the highest model prediction score and incorrect predictions were selected for local exploration. The following local explorations were used:

a. Breakdown plots for additive attributions: Breakdown explainability is a method for understanding the contribution of each feature to a specific prediction made by a ML model. It breaks down the prediction into the contributions of individual features and shows how each feature contributes to the final prediction. This type of explainability is particularly useful for understanding how a model arrived at a specific prediction and can help identify any biases or errors in the model (5, 18).

b. SHAP: This method assigns a unique importance value to each feature, indicating the contribution of that feature toward the model's output for a particular prediction. It is based on the game theory and aims to improve interpretability by calculating the significance of each feature for individual predictions. The objective of SHAP is to clarify the prediction of a specific data point x by calculating the impact of each feature on the prediction. The method utilizes certain visualization techniques to display how the predictors affect the predicted values. It also allows for the identification of feature interactions and provides global and local explanations (17, 18).

RESULTS

The demographic features of patients and clinical laboratory result summaries are given in **Table 1**. As shown in this table, the records had wide spectrum of laboratory results. Additionally, there was a distinctive class imbalance between A1c classes and sex.

Table 2 summarizes the prediction errors for DRF and GBM models. There was no misclassification for the DRF ML model on the training set. However, prediabetes and diabetes prediction error rates were lower for the GBM model on the test set.

Table 3 provides the performance metrics for both models. When the performance metrics were evaluated, both models had similar AUC and AUCPR metrics. However, DRF had a lower mean per class error for the test set, while DRF was lower for the test set.

In **Figure 1**, PDF plots were given for the top important features for both models, which provides information related to all data sets. Figures 2 and 3 show the breakdown and SHAP plots, respectively, for four selected test set records. These plots cover three correct classifications and one misclassification for the DRF model. All model details, including the hyperparameters, are provided in the Supplementary Material.

DISCUSSION

The study aimed to compare the performance of different model-agnostic explanation methods using two different ML models created for A1c prediction. The results showed that model explanation methods provide important contributions for both evaluating models internally and comparing different models. Moreover, it was found that using a combination of local and global explanation models is more effective for explaining and comparing models than using a single

Table 2. Multinominal classification confusion matrix for the developed ML models

Model	Class	Training Set				Test Set			
		Normal	PreD.	DM	Error	Normal	PreD.	DM	Error
DRF	Normal	1329	0	0	0.0%	548	21	0	3.6%
	PreD	0	551	0	0.0%	178	52	7	78%
	DM	0	0	244	0.0%	36	17	53	5%
GBM	Normal	1259	67	3	5.3%	518	50	1	8.9%
	PreD	187	356	8	35.4%	117	101	19	57%
	DM	6	18	220	9.9%	5	23	78	26%

DRF: Distributed Random Forest, GBM: Gradient Boosting Machine, PreD: Prediabetes

Table 3. Calculated performance metrics for the developed ML models

Model	Data Set	Mean per Class Error	AUC	AUC Precision Recall	Accuracy	Macro F1
DRF	Training	0.00	1.00	1.00	1.00	1.00
	Test	0.44	0.85	0.84	0.72	0.63
GBM	Training	0.17	0.96	0.96	0.86	0.85
	Test	0.31	0.88	0.86	0.76	0.71

AUC: Area under curve, DRF: Distributed Random Forest, GBM: Gradient Boosting Machine

explanation model. However, there are some limitations related to these tools, such as limited interpretability and the required computation power. Although these tools helped the end user (e.g., clinicians) to understand some predictions, they only provided a general idea.

The first finding that model explanation techniques contribute to prediction explanations is supported by the conclusions derived from PDP plots. When examining the PDP graphics in **Figure 2**, the relationship between glucose levels and A1c is clearly visible. The known relationship between glucose and A1c is that estimated average glucose (eAG)= 28.7×A1c(%)– 46.7 can be easily observed with both models (19). In both the DRF and GDM models, the predictions for A1c quickly change according to the blood glucose levels. The effect of age can also be seen in a similar way in these plots. It has also been mentioned in the literature that PDP graphics can be easily interpreted by field experts because they provide explanation by simplification (3). Another use of PDP is to compare the effect of features for different models, as shown in **Figure 2**. The effect of waist circumference, which is more meaningful for the DRF model, can be observed in **Figure 2**. Relation between DM and waist circumference was also reported by Feller et al. (20). However, when it comes to the interaction between multiple parameters, the power of these graphics decreases. The assumption of independence is the biggest issue with PDP (5).

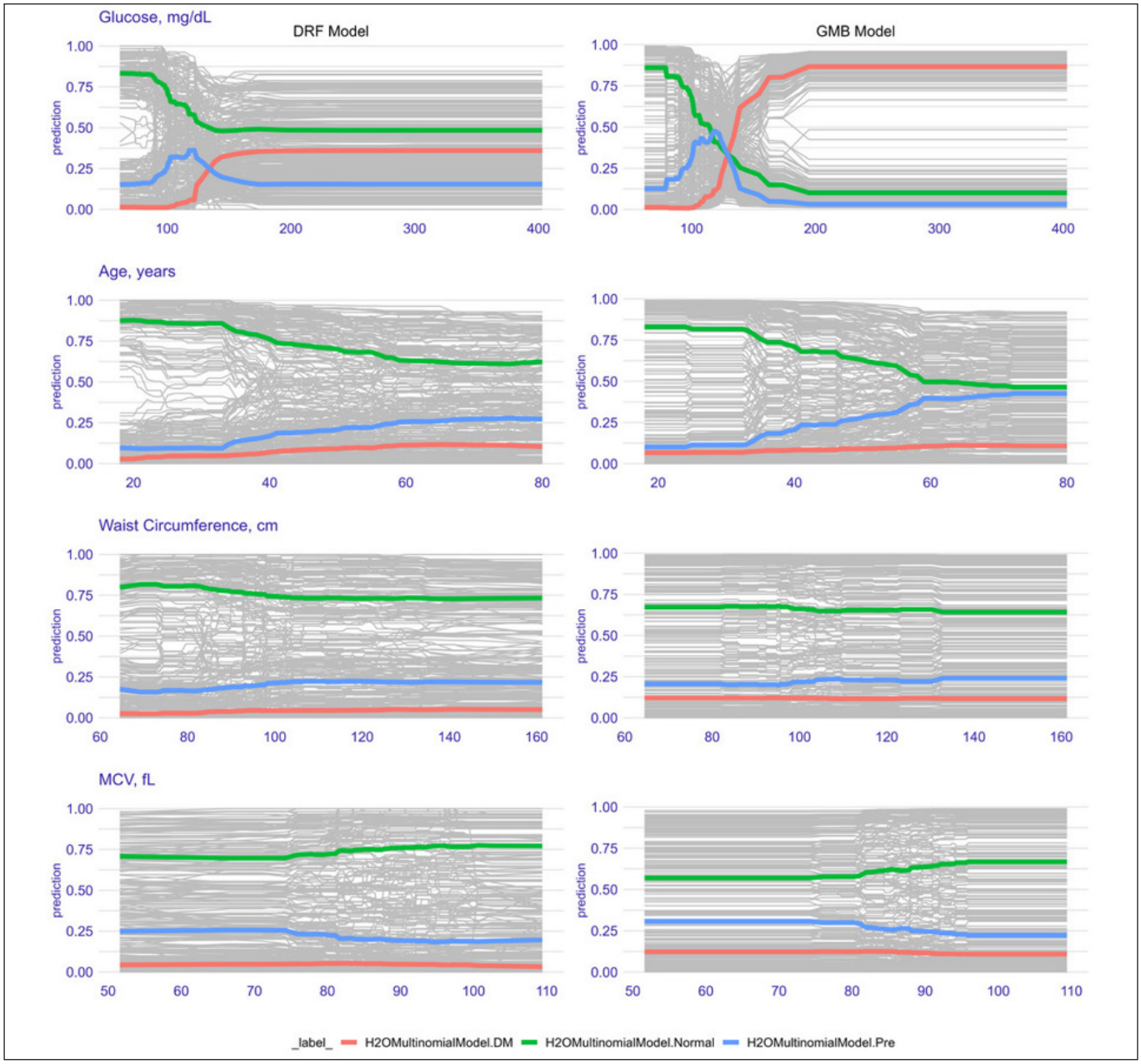

Figure 1. Partial dependence plots for the four most important features of the DRF and GMB models.
The Partial dependence lines for normal prediction classes are green, pre-diabetes prediction classes are blue, diabetes mellitus prediction classes are yellow, and ceteris-paribus profiles are gray lines.
DRF: Distributed Random Forest, GBM: Gradient Boosting Machine.

Local explanation techniques explain specific predictions, which provide details about the inner workings of the model instead of using all model data. Therefore, they can be also used for understanding the model's decision-making process. Breakdown plots in **Figure 2b** precisely show each feature's contribution to the final prediction. The relationship between serum glucose and age, which can also be observed by global methods, on normal, prediabetes, and diabetes predictions are clearly shown case by case. Especially for unexpected predictions, local explanation methods reveal the cause of the model's failed reasoning, which makes it possible to improve the model (18). For example, **Figure 2d** shows that an individual with a diabetic A1c level has been incorrectly classified as normal. This situation can be caused by majority case drift caused by the number of records with normal A1c levels during the development of the model, which presents a 0.716 intercept score in **Figure 2**. When detecting the issue, different data pre-processes could be considered for imbalanced data to improve the model. SHAP plots also allow for the identification of feature interactions and provide global and local explanations. SHAP values can also be used for variable importance by calculating them for the entire dataset (21).

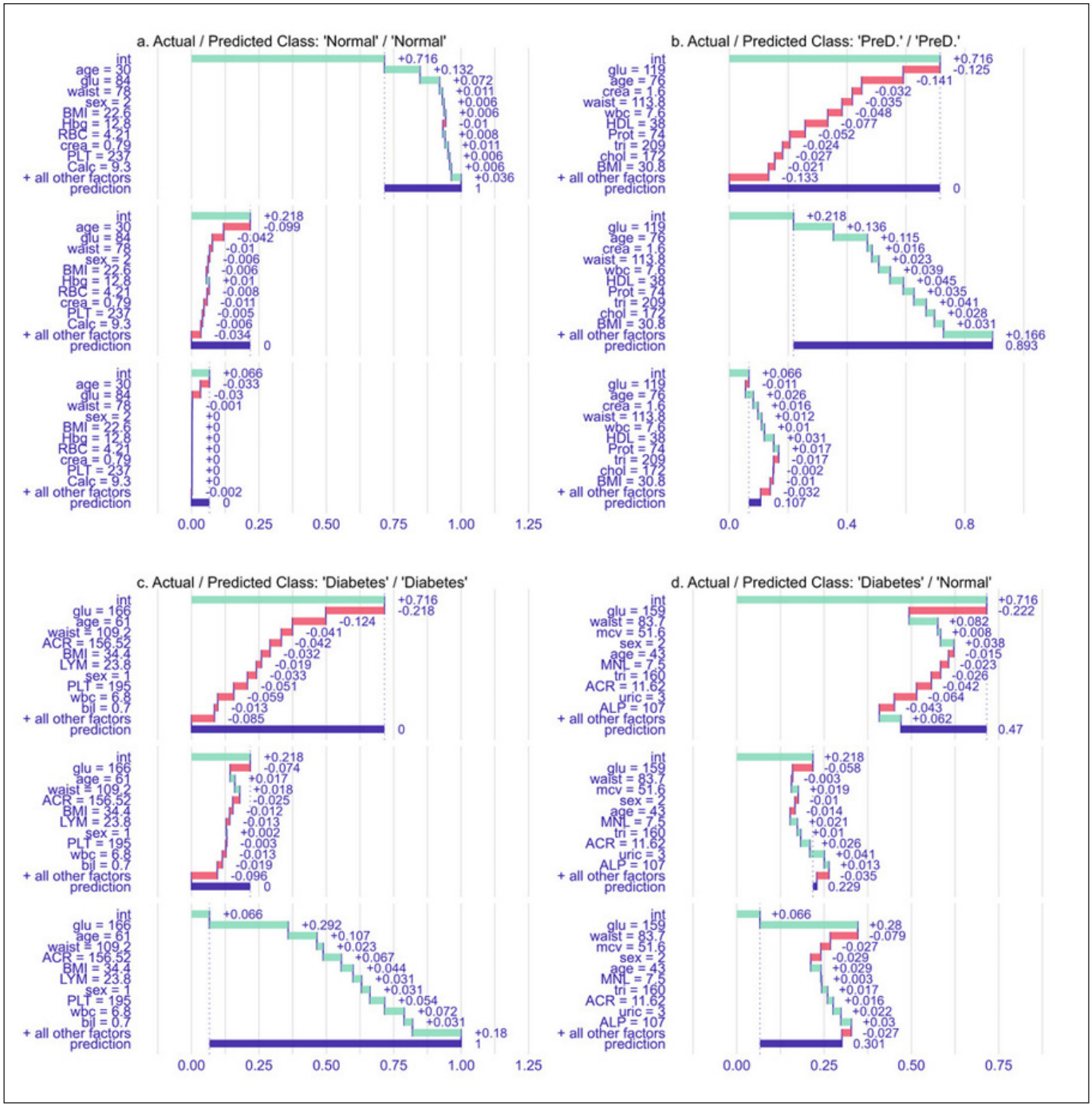

Figure 2. Breakdown plots for additive attributions of Distributed Random Forest model for the test set.
The green and red bars indicate positive and negative changes in the mean predictions, respectively. The blue bar shows the prediction for the instance of interest.

Another important finding was for the DRF ML model, while there was no classification error for the training set, there were classification errors in the test set as expected (**Table 2**). Moreover, the training set had better performance metrics compared to test set (**Table 3**). These results suggest overfitting for the DRF model. Therefore, limiting the depth of individual trees, increasing the number of trees in the forest, and using techniques such as bagging and feature subsetting can help to prevent overfitting (12). Additionally, in both data sets classification between normal and prediabetic patients was more distinctive than prediabetic and diabetic classification (**Table 2**). Interestingly this finding was similar with clinical setting and this distinction is considered as challenging. Prediabetes is a condition that exists on a continuum between normal blood glucose levels and diabetes. And is characterized by higher-than-normal blood glucose levels but not high enough to be classified as diabetes. The borderline nature of prediabetes means that there can be significant overlap between normal and pre-diabetic patients in terms of their blood glucose levels, making it challenging to accurately separate the two groups (8, 19).

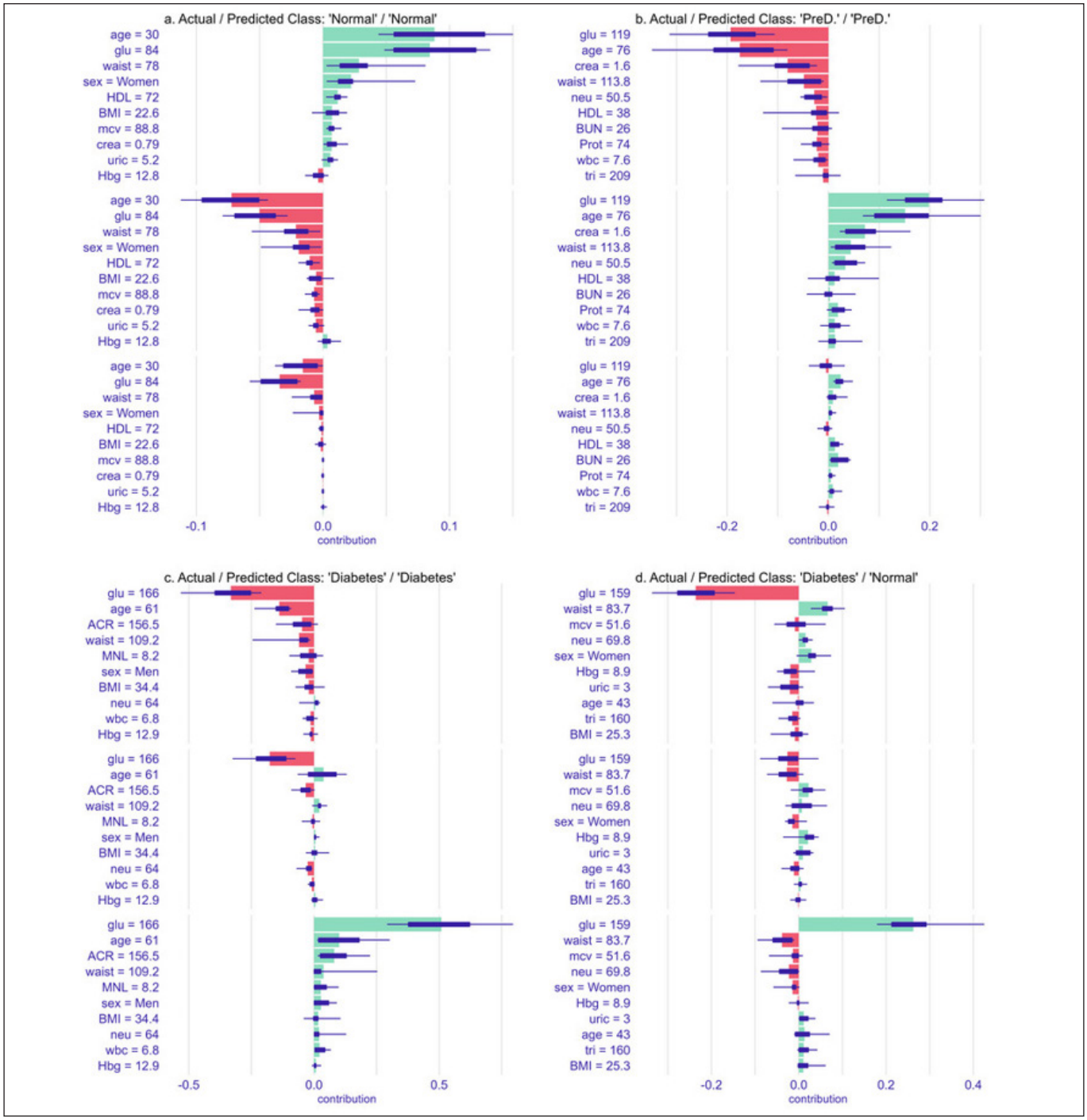

Figure 3. Plots of Distributed Random Forest model Shapley values for the test set.
Red and green bars present negative and positive Shapley values, respectively.

In the study, model-agnostic methods were applied for xAI. Model-agnostic explanations are considered consistent across different models, which means they can be easily used for multiple model comparisons. Additionally, their model-independent nature provides developers with more options for selecting models during development. An alternative to model-agnostic interpretation is using only interpretable models, but this may result in reduced performance and limits the choice of models that can be used (5).

Different methods have been proposed to assess and quantify the quality of explanations generated by xAI systems, as shown in this study. Nonetheless, there is currently no widely accepted standard for determining whether an xAI system is more understandable to a user than a non-xAI system. Some methods rely on subjective evaluations such as surveys to gauge user satisfaction with the explanations. Other methods are more objective, such as determining whether the explanations improve the user's decision-making performance (4). Instead of providing specific, valid justifications for a model's predictions, it is more accurate to view explainability techniques as overall explanations of how a model operates (3). As in the current study, these tools are still far from interpreting results in a clinical context.

This research has several limitations. First, the use of glucose for A1c prediction can be considered a bias. However, the glucose parameter was specifically selected for the demonstration of local and global explanations of strong and weak features. Second, preprocessing for imbalance classes for both diabetes classes and sex could also increase model effectiveness. However, since the aim of the study is not to create models with the best performance but to evaluate the effectiveness of explanation tools, simpler methods were preferred while creating models. Additionally, during training, the "imbalanced_classes" option was activated in the AutoML tool. The final limitation refers to the included ML model types, as only tree-based models were included in the study. However, using different models such as deep learning can provide different perspectives for model explainability.

CONCLUSION

The current study assessed the importance of transparent ML methods in understanding complex models and how it promotes the integration of AI in healthcare. Results showed that despite the limitations of current explainability methods, especially for the clinical approach, both global and local explanation models provide an insight into model evaluation, and they can be used to improve or compare models.

Abbreviations

A1c: hemoglobin A1c, **AUC**: area under the receiver operating characteristic curve, **AUCPR**: area under the precision recall curve, **DRF**: default random forests, **eAG**: estimated average glucose **ML**: machine-learning, **xAI**: explainable artificial intelligence, , **GBM**: Gradient boosting machine, **MCV**: mean corpuscular volume, **PDPs**: Partial Dependence Profiles, **SHAP**: Shapley additive explanations, Variable Importance (VIP)

ETHICAL DECLARATIONS

Ethics Committee Approval: Not applicable. An open-source dataset was utilized for the study.

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Author Contributions: The author declares that he has responsible for the design, execution, and analysis of the paper and that he has approved the final version.

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Predictive value of C-reactive protein to albumin ratio and systemic immune-inflammation index for the long-term mortality in COVID-19

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ABSTRACT

Aim: Several studies have investigated the association between biomarkers and short-term prognosis in the coronavirus infectious disease 2019 (COVID-19). However, data on the long-term prognosis are limited. To determine the predictive value of systemic immune-inflammation index (SII) and C-reactive protein (CRP) to albumin ratio (CAR) for in-hospital and 1-year outcomes during COVID-19.

Material and Method: The primary outcomes were in-hospital and 1-year mortality. The secondary outcomes were the intensive care unit (ICU) need at admission and transfer to the ICU later on.

Results: The study included 449 (53.6%) males and 389 (46.4%) females with a mean age of 53.8±18.5 years. Previously known heart failure (HF), COVID-19-related HF, acute renal failure (ARF), diabetes mellitus, hypertension, coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD)/asthma, high CO-RADS scores (>4), low ejection fraction (EF), higher CAR and SII were associated with an increased in-hospital and 1-year mortality ($p<0.05$). After multivariate analysis; CAR, SII, ARF, and diabetes mellitus were independent predictors of in-hospital and 1-year mortality,whereas CAD was only an independent predictor of 1-year mortality. After ROC analysis, CAR cut-off levels of 2.54 and 2.23 predicted in-hospital and 1-year mortality, respectively ($p<0.001$). The SII cut-off levels of 1274 and 1191 predicted in-hospital and 1-year mortality, respectively ($p<0.001$).

Conclusion: CAR and SII can be used as valuable prognostic indexes to predict both the short-term and long-term mortality in COVID-19.

Keywords: Systemic immune-inflammation index, SII, C-reactive protein to albumin ratio, CAR, long-term mortality, COVID-19

INTRODUCTION

The coronavirus infectious disease 2019 (COVID-19) outbreak has affected about 524 million people worldwide, causing over 6 million deaths despite the application of nearly 12 billion doses of vaccines (1). Several studies have shown that the main factor in COVID-19 is the extreme inflammatory response and the ensuing uncontrolled cytokine storm, which affects not only the respiratory system but many other systems, causing clinical deterioration and death (2). Therefore, the course of infection may be more severe in diseases such as diabetes, hypertension, heart failure (HF), and coronary artery disease (CAD), in which inflammation plays a key role in the pathophysiology (3). The virus may also cause thrombotic events such as myocardial infarction, stroke, and pulmonary embolism through endothelial damage, autonomic dysregulation, and microvascular dysfunction in both short and long term (4-6).

There is a growing number of studies investigating the relationship of thromboinflammatory parameters with the severity of the COVID-19, the intensive care unit (ICU) need, and short-term mortality (7-9). The systemic immune-inflammation index (SII) (calculated

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as neutrophil x platelet/lymphocyte) and C-reactive protein (CRP) to albumin ratio (CAR) are the novel indexes developed to determine the inflammatory and immunothrombotic status of patients with various cancer types (10-11). Then, SII and CAR have been suggested to be more valuable than other many inflammatory biomarkers in predicting major adverse cardiovascular events and the severity of diseases such as CAD and pulmonary embolism (12-13). Recently, several studies have been conducted investigating the role of CAR and SII in the prognosis of COVID-19 but mostly presenting short-term results(7,8).

Since the data on long-term prognostic parameters are lacking, we aimed to investigate the effectiveness of the CAR and SII as inflammatory and immunothrombotic parameters in predicting the ICU need, in-hospital, and 1-year mortality due to COVID-19.

MATERIAL AND METHOD

Study Design, Clinical and Laboratory Parameters

This single-center, case-control, and cross-sectional study was approved by the Kırıkkale University Faculty of Medicine Clinical Researches Ethics Committee (Date: 25.05.2022, Decision No: 2022.05.20). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants. The study included a total of 838 patients having a history of COVID-19 confirmed by positive real-time polymerase chain reaction (PCR) between April 2020 and April 2021. Exclusion criteria were as follows; pregnancy, younger age of 18 years, decompensated HF (not new onset HF or euvolemic patients with known HF), significant valvular heart disease, ongoing systemic inflammatory conditions such as flu, diarrhea, and urinary tract infection unrelated to SARS-CoV-2 infection, history of liver disease (with liver function parameters >3x upper normal value), autoimmune disease and hematologic or malignant disease. Patients' demographics, clinical characteristics, medical history, radiological, and clinical outcome data were obtained through the electronic patient database. The laboratory parameters, measured within the first 24 hours of hospital admission, were obtained through the electronic patient database. The SII was calculated as the ratio of the product of total neutrophil count and platelet count to lymphocyte count. The CAR was calculated as the ratio of serum CRP to the serum albumin level.

Thorax Computed Tomography Imaging

All patients were imaged at presentation with multidetector computer tomography (CT) using the TOSHIBA Alexion/ Advance Edition (Toshiba Medical Systems Corporation, Japan, 1.25 mm section thickness) with 64-detector rows. All scans were acquired without an intravenous contrast agent, with the patient in a supine position during end inspiration. CT indications were as follows: patients having moderate-to-severe respiratory symptoms and high index of clinical suspicion of COVID-19, showing unexplained clinical deterioration and/or where other concurrent lung pathology needs exclusion, COVID-19-positive patients with associated co-morbidities (age >65 years, diabetes mellitus, hypertension, obesity, cardiovascular disease, chronic respiratory disease, immune-compromise, etc.). CT imaging was also indicated in patients having indeterminate chest X-ray findings despite having mild symptoms and recorded oxygen saturation of <93 percent at rest while breathing room air or de-saturation on six-minute walk test. The CO-RADS classification was used to categorize the level of COVID-19 suspicion (14). According to that system, the degree of suspicion is classified into five levels from very low (CO-RADS 1) to very high (CO-RADS 5).

Echocardiographic Measurement

Standard 2-dimensional echocardiography was performed on all subjects lying in the left lateral decubitus position with a Vivid 7 Doppler echocardiographic unit (GE Vingmed Ultrasound, Horten, Norway) using a 3.5-MHz transducer. Echocardiographic measurements were made according to ACC and AHA standard protocols(15). We utilized two-dimensional and M-mode echocardiography to investigate ejection fraction (EF). An EF of less than 50% was defined as HF.

Outcome

The primary outcomes were in-hospital and 1-year mortality after the diagnosis of the COVID-19. The secondary outcomes were the ICU need at admission and transfer to the ICU later on. In-hospital death was defined as death during the index hospital stay related or non-related to COVID-19. One-year mortality was defined as death related or unrelated to COVID-19 within 1 year from diagnosis. Indications for transfer to the ICU was as follows: i) Respiratory rate>30/minute, ii) SpO2<94% on room air, iii) PaO2/FiO2<300, iv) Lung infiltration>50% on X-ray or CT, v) Need for positive pressure ventilation, ECMO, or mechanical ventilation, vi) Shock vii) Cytokine release syndrome.

Statistical Analysis

SPSS 25.0 (IBM Corporation, Armonk, New York, United States) program was used in the analysis of the variables. Quantitative variables with a normal distribution were specified as the mean±standard deviation and categorical variables were specified with number and percentage values. The conformity of quantitative data to normal distribution was assessed with the Kolmogorov-

Smirnov test. Independent Samples T-Test was applied in the comparison of continuous variables showing normal distribution. Odds ratio with 95% confidence intervals was used to determine how many times more effects were caused by those who were exposed to a risk factor than those who were not. Logistic regression analysis was applied in the univariate and multivariate analyses to determine the independent predictors of both in-hospital and 1-year mortality. The ROC curves were used to determine the cut-off values of cardiac biomarkers to predict mortality. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 838 patients were analyzed in our study, including 449 (53.6%) males and 389 (46.4%) females with a mean age of 53.8±18.56 years. Demographic, clinical, imaging, and laboratory characteristics of the patients were presented in **Table 1**. In our study, in-hospital mortality was 67 (9.7%) and 1-year total mortality was 86 (11.5%) in the follow-up. As presented in **Table 2**, there was a significant relationship between higher values of the CAR and the ICU need at admission, transfer to ICU later on, in-hospital mortality, and 1-year mortality (p=0.001 for the transfer to ICU, p<0.001 for the rest). Similarly, a significant relationship was found between the higher values of SII and ICU need at admission, transfer to ICU later on, in-hospital mortality, and 1-year mortality (p=0.003 for the transfer to ICU, p<0.001 for the rest).

Table 2. The relationship of inflammatory indexes with the intensive care unit need and mortality

	n,%	CAR Mean±SD	p	SII Mean±SD	p
ICU (at admission)			<0.001		<0.001
No	661 (75,3%)	1.18±1.80		940.35±1225.39	
Yes	177 (24.7%)	4.18±4.19		2976.72±3241.18	
Transfer to ICU			0.001		0.003
No	682 (82%)	1.66±2.80		1270.21±2066.37	
Yes	156 (18%)	2.51±2.59		1808.79±1749.30	
In-hospital mortality			<0.001		<0.001
No	771 (90.3%)	1.26±1.70		1204.13±1870.97	
Yes	67 (9.7%)	8.24±4.34		3284.68±2630.48	
1-year mortality			<0.001		<0.001
No	752 (88.5%)	1.14±1,46		1144.03±1671.62	
Yes	86 (11.5%)	4.25±0.45		3350.51±3333.72	

Abbreviations: ICU: Intensive care unit, Independent Samples T Test (Bootstrap), Mean±standard deviation for normal distribution, and n (%) for categorical data.

Table 1. Demographic, clinical, imaging, and laboratory characteristics of the patients

	Total (n=838)	In-hospital mortality (n=67)	1-year mortality (n=86)
Gender (male), n (%)	449 (53.6)	34 (50.7)	41 (47.7)
Age, years	53.8±18.56	71±14.22	71.3±13.25
BMI, kg/m²	21.31±3.12	21.02±3.58	21.01±3.57
Smoking, n (%)	359 (42.8)	27 (40.3)	38 (44.2)
Clinical risk factor, n (%)			
Hypertension	255 (30.4)	38 (56.7)	52 (60.5)
Coronary artery disease	117 (14.0)	33 (49.3)	44 (51.2)
Diabetes mellitus	136 (16.2)	39 (58.2)	47 (54.7)
Heart failure (known)	71 (8.5)	28 (41.8)	37 (43.0)
Heart failure (COVID-19-related)	23 (2.7)	14 (20.9)	15 (17.4)
Acute kidney failure	28 (3.3)	24 (35.8)	26 (30.2)
COPD/Asthma	172 (20.5)	22 (32.8)	29 (33.7)
Stroke	9 (1.1)	8 (11.9)	9 (10.5)
Transfer to ICU, n (%)	158 (18.6)	12 (17.9)	15 (17.4)
ICU need (at admission), n (%)	177 (21.1)	47 (70.1)	63 (73.3)
Laboratory and Imaging Findings			
Ejection fraction,%	55.10±8.10	43.07±13.92	43.78±13.76
CO-RADS score	3.05±1.65	4.66±0.70	4.62±0.72
CAR	1.82±2.78	8.24±4.34	7.72±4.25
SII	1370.47±2021.07	3284.68±2630.48	3350.51±3333.72
C-reactive protein, mg/dL	6.51±9.22	26.75±13.44	25.28±13.27
Albumin, g/dL Normal range (3.5-5.5 g/dL)	3.82±0.42	3.28±0.36	3.32±0.36
White blood cells, (10^9/L)	8.98±4.26	14.29±6.16	13.47±6.18
Neutrophils, (10^3/μL)	6.52±4.18	12.19±5.70	11.46±5.72
Lymphocytes, (10^3/μL)	1.93±1.06	1.43±1.02	1.36±0.96
Platelets, (10^9/L)	246±77.5	246.2±87.1	249.9±85.2

Mean±standard deviation for normal distribution, and n (%) for categorical data. Abbreviations: BMI: Body mass index; CAR: c-reactive protein/albumin ratio; COPD: Chronic obstructive pulmonary disease; CO-RADS: Coronavirus Disease 2019 (COVID-19) Reporting and Data System; ICU: Intensive care unit; SII: Systemic immune-inflammation index

Table 3 provides information about univariate and multivariate logistic regression analysis results of patients' in-hospital and 1-year mortality. Univariate logistic regression analysis results revealed that patients with known HF, COVID-19-related HF, acute renal failure (ARF), diabetes mellitus, hypertension, CAD, chronic obstructive pulmonary disease (COPD)/asthma, high CO-RADS scores (> 4), low EF, higher CAR and SII were significantly associated with both the increased in-hospital and 1-year mortality (p=0.011 of in-hospital mortality for the COPD/Asthma, p=0.002 of 1-year mortality for the COPD/Asthma, p<0.001 for the rest). After the multivariate logistic regression analysis, CAR values (odds ratio (OR): 1.46; 95% confidence interval (CI): 1.29-1.65; p<0.001) and SII values (OR: 1.00; 95% CI: 1.00-1.00; p=0.021) remained as significant predictors of the in-hospital mortality as well as ARF (OR: 12.6; 95% CI: 3.20-49.61; p<0.001) and diabetes mellitus (OR: 2.99; 95% CI: 1.23-7.26; p=0.015). In addition, CAR (OR:1.72; 95% CI: 1.50-1.99; p<0.001), SII (OR: 1.00; 95% CI: 1.00-1.00; p<0.001), ARF (OR: 15.74; 95% CI: 2.77-89.36; p=0.002), diabetes mellitus (OR: 2.63; 95% CI: 1.09-6.34; p=0.031), and CAD (OR: 3.99; 95% CI: 1.34-11.83; p=0.013) were independent predictors of 1-year mortality.

Table 4 presents the analyzes of CAR and SII values in predicting in-hospital and 1-year mortality. CAR predicted in-hospital mortality at the cut-off value of ≥ 2.54 with a sensitivity of 89.6% and a specificity of 88.8% (p<0.001). The sensitivity and specificity of SII at the cut-off value of ≥ 1274.07 were 77.6% and 77.4%, respectively (p<0.001). Similarly, CAR had a sensitivity of 88.4% and a specificity of 88.4% at the cut-off value of ≥ 2.23 in predicting 1-year mortality (p<0.001). The sensitivity and specificity of SII at the cut-off value of ≥ 1191.20 were 76.7% and 76.9%, respectively (p<0.001). In the ROC analysis of CAR and SII values designed to estimate in-hospital mortality, the area under the curve (AUC) values were 0.956; (95% CI: 0.936-0.976; p<0.001) and 0.809; (95% CI: 0.752-0.865; p<0.001), respectively. In the ROC analysis of CAR and SII designed to estimate 1-year mortality, the AUC values were 0,953; (%95 CI: 0,932-0,974; p<0.001) and 0,807; (%95 CI: 0,758-0,857; p<0.001), respectively (**Figure**).

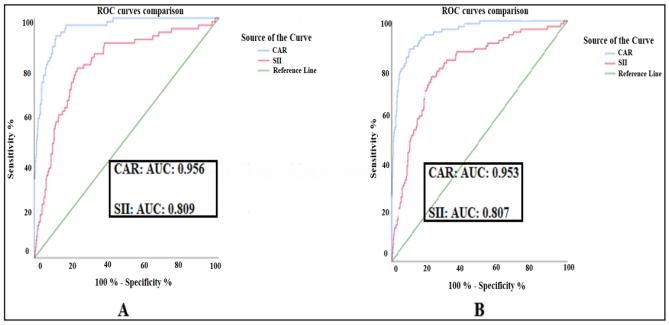

Figure. Comparison of ROC curves of CAR and SII values for predicting in-hospital (A) and one-year mortality (B) in patients with COVID-19

Abbreviations: AUC: Area under the curve; CAR: C-reactive protein/albumin ratio; CI: Confidence interval; SII: Systemic immune-inflammation index

Table 3. Risk factors associated with in-hospital and 1-year mortality according to univariate and multivariate logistic regression analysis

Risk Factors	In-hospital mortality (n=67)				1-year mortality (n=86)			
	Univariate		Multivariate		Univariate		Multivariate	
	OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p
HF (known)	12.15 (6.84-21.59)	<0.001	1.13 (0.11-10.41)	0.925	15.94 (9.21-27.58)	<0.001	1.40 (0.16-11.82)	0.754
HF (COVID-19 related)	22.36 (9.25-54.05)	<0.001	3.16 (0.33-29.84)	0.314	19.94 (8.05-47.93)	<0.001	1.61 (0.13-19.10)	0.705
ARF	107.02 (35.54-322.21)	<0.001	12.60 (3.20-49.61)	<0.001	162.50 (37.66-701.16)	<0.001	15.74 (2.77-89.36)	0.002
DM	9.67 (5.69-16.44)	<0.001	2.99 (1.23-7.26)	0.015	8.97 (5.56-14.49)	<0.001	2.63 (1.09-6.34)	0.031
HT	3.34 (2.01-5.56)	<0.001	1.07 (0.41-2.81)	0.882	4.13 (2.60-6.56)	<0.001	2.40 (0.94-6.15)	0.066
CAD	7.93 (4.67-13.48)	<0.001	1.79 (0.56-5.68)	0.321	9.74 (5.98-15.85)	<0.001	3.99 (1.34-11.83)	0.013
COPD/Asthma	2.02 (1.17-3.47)	0.011	0.94 (0.36-2.46)	0.912	2.16 (1.33-3.51)	0.002	0.81 (0.32-2.05)	0.664
CO-RADS (> 4)	19.55 (7.04-54.24)	<0.001	2.76 (0.62-12.25)	0.180	14.58 (6.64-32.02)	<0.001	1.66 (0.49-5.62)	0.409
EF (< 50%)	0.87 (0.85-0.90)	<0.001	0.95 (0.88-1.03)	0.293	0.87 (0.85-0.89)	<0.001	0.93 (0.85-1.00)	0.930
CAR	1.75 (1.60-1.93)	<0.001	1.46 (1.29-1.65)	<0.001	1.89 (1.70-2.09)	<0.001	1.72 (1.50-1.99)	<0.001
SII	1.00 (1.00-1.00)	<0.001	1.00 (1.00-1.00)	0.021	1.00 (1.00-1.00)	<0.001	1.00 (1.00-1.00)	<0.001
	R2=0.71, -2 log-likelihood=162.56				R2=0.76, -2 log-likelihood=164.70			

Abbreviations: ARF: Acute renal failure; CAD: Coronary artery disease; CAR: C-reactive protein/albumin ratio; CI: Confidence interval; COPD: Chronic obstructive pulmonary disease; CO-RADS: Coronavirus Disease 2019 (COVID-19) Reporting and Data System; DM: Diabetes mellitus; EF: Ejection fraction; HF: Heart failure; HT: Hypertension; OR: Odds ratio; SII: Systemic immune-inflammation index

Table 4. Analysis of predictive values of inflammatory biomarkers in predicting in-hospital and 1-year mortality

	AUC	%95 CI	Cut-off	Sensitivity (%)	Specificity (%)	p
In-hospital mortality						
CAR	0.956	0.936-0.976	≥ 2.54	89.6	88.8	<0.001
SII	0.809	0.752-0.865	≥ 1274.07	77.6	77.4	<0.001
1-year mortality						
CAR	0.953	0.932-0.974	≥ 2.23	88.4	88.4	<0.001
SII	0.807	0.758-0.857	≥ 1191.20	76.7	76.9	<0.001

Abbreviations: AUC: Area under the curve; CAR: C-reactive protein/albumin ratio; CI: Confidence interval; SII: Systemic immune-inflammation index

DISCUSSION

The main findings of this study are as follows i) CAR and SII were independent predictors of in-hospital mortality as well as ARF and diabetes mellitus were other independent predictors; ii) CAR, SII, ARF, diabetes mellitus, and CAD were independent predictors of 1-year mortality; iii) Higher values of CAR and SII were significantly associated with increased ICU need at admission and transfer to ICU later on.

Several studies have been conducted on the predictive values of laboratory parameters and scoring systems such as the CO-RADS, regarding the severity and short-term prognosis of COVID-19 (7,8,14). However, data on the long-term consequences of COVID-19 in patients with and without comorbid diseases are limited to only special populations such as the elderly and patients with chronic kidney disease (16-18). Walle-Hansen et al. (16) investigated the functional status, age-related changes in health-related quality of life, and mortality in the elderly at a 6-month follow-up after COVID-19 onset. They found that more than half of patients had negative changes in cognitive and physical function, and that one out of three had significant deterioration in mobility to sustain their daily lives. Similarly, in a large cohort, the 1-year mortality was high in the elderly irrespective of the severity of the disease (17). In another study, Carriazo et al. (18) investigated the effect of COVID-19 on 1-year mortality in hemodialysis patients and concluded that mortality was significantly higher in those with COVID-19, particularly within 3 months after onset. Furthermore, basal CRP levels were higher in those with COVID-19 and 30% of deaths were due to vascular endothelium deterioration suggesting the possible long-term effect of inflammation on the risk of ischemic and bleeding events.

CRP, a positive acute-phase reactant, plays an important role in many stages of the host response to infection including apoptosis, phagocytosis, nitric oxide (NO) release, and production of cytokines, particularly interleukin-6 and tumor necrosis factor-α (19). Albumin, a negative acute phase reactant, has several functions such as antioxidant/anticoagulant activity, anti-inflammatory, and anti-platelet aggregation (20). Increased CRP and decreased albumin levels are associated with increased inflammatory status and thrombotic events such as ischemic heart disease, acute coronary syndrome, and stroke (20, 21). CAR, calculated as the proportion of CRP-to-albumin level, is thought to be a more accurate indicator of inflammatory status than CRP or albumin alone (7). In many studies, CAR has been used as an important parameter to predict the severity and short-term prognosis of COVID-19 and compared or combined with many other parameters (9,22). Different cut-off values have been determined for CAR to predict mortality risk. Li et al. (9) investigated the in-hospital mortality of 465 patients diagnosed with COVID-19 and showed that compared to the NLR and PLR, high CAR levels (>1,843) were the strongest independent predictor of in-hospital mortality, ICU admission, invasive mechanical ventilation, and a longer hospital stay. Lucijanic et al. (22) defined and validated four CAR prognostic categories (<1.0, 1.0–2.9, 3.0–5.9, and ≥6.0) and found that higher CAR values were associated with the increased in-hospital mortality. Moreover, the 6-month mortality in patients with a CAR >2.92 after discharge was 11.4%. In our study, the cut-off values of ≥2.54 and ≥2.23 were significant predictors of in-hospital and 1-year mortality, respectively.

SII is another inflammation parameter having a prognostic value in many cancer types (10). In the pathophysiology of COVID-19, gene expression changes in platelets and increased platelet-platelet and platelet-leukocyte interactions are important in terms of increasing thrombotic events in the prognosis (23). Therefore, that index has been investigated in many studies with different cut-off values regarding the predictive value of the severity and prognosis of COVID-19 (8,24,25). Fois et al. (8) investigated COVID-19-related in-hospital mortality using the SII, total index of systemic inflammation (AISI), NLR, derived NLR (dNLR), PLR, mean platelet volume/platelet ratio (MPR), neutrophil/lymphocyte x platelet ratio (NLPR), monocyte/lymphocyte ratio (MLR), and systemic inflammation response index (SIRI). They found that only SII was the strongest parameter to predict in-hospital mortality with a cut-off value of 1835. Similarly, Acar et al24 found that SII was an independent predictor of in-hospital mortality with a cut-off value of 2699. In contrast, Kudlinski et al25 suggested that SII and CRP did not predict in-hospital mortality. We found the cut-off values of SII to predict in-hospital and 1-year mortality as 1274 and 1191, respectively. The reason for our lower cut-off values can be explained by the fact that the patients included in those studies had comorbid diseases that may affect the results. The study conducted by Kudlinski et al. (25) included 285 patients, and more than 10% of the study participants were composed of patients with diseases such as cancer, autoimmune disease, and immunosuppression, which may cause higher baseline SII values. Moreover, those with thyroid disorders comprised 8% of all patients included in the study. Endocrine disorders such as thyroid gland dysfunction may also cause significant changes in circulating levels of neutrophil, and platelet in the blood which explains the higher cut-off values compared to our study (26). We excluded the patients with any type of cancer and endocrine disorders to evaluate the relationship of the CAR and SII with the prognosis more objectively.

Although both SII and CAR may provide important information about the prognosis of COVID-19, in the study of Xue et al. (27) in which these two parameters were compared, although SII was superior in predicting disease severity compared to many parameters such as NLR, it was inferior to CAR. Supporting this study, we found that CAR had higher sensitivity and specificity than SII in predicting in-hospital and 1-year mortality which makes CAR more preferable.

Our study has many different aspects from previous studies. To the best of our knowledge, this is the first study presenting the data on the long-term mortality of COVID-19 in the general population. It is very important to use systemic scoring systems to minimize the risk of error in the interpretation of imaging findings of COVID-19. Therefore, we confirmed that the CAR and SII values correlated with disease severity using the CO-RADS scoring system. As an advantage compared to many other studies, ejection fraction values of patients with pre-existing HF and COVID-19-related HF were available in our study. Importantly, our study included a larger number of patients than many previous studies.

Our study has several limitations. First of all, this was a retrospective and single-center study. Second, the treatments such as steroids used in COPD/Asthma patients may have caused changes in inflammatory parameters. Third, the arrhythmias such as atrial fibrillation may affect the prognosis of the patients by causing thrombosis with a synergistic effect and pulmonary congestion, so the ECG findings of the patients could also be presented. Fourth, the D-dimer levels and viral load could also be presented with CAR and SII, as it provides valuable information in predicting thrombotic events and mortality. Fifth, we did not present the accurate cause of the deaths within one year after the diagnosis of COVID-19.

CONCLUSION

CAR and SII can be used as key parameters to predict both short-term and long-term prognosis from the time of diagnosis in patients with COVID-19.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kırıkkale University Faculty of Medicine Clinical Resaerches Ethics Committee (Date: 25.05.2022, Decision No: 2022.05.20).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: No conflict of interest was declared by the authors.

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Original Article

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Diagnostic value of preoperative blood parameters in periprosthetic joint infections

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ABSTRACT

Aim: Diagnosis of periprosthetic joint infection (PJI) is not easy and it is made by presenting of combined findings rather than a single finding. The aim of this study is to investigate the role of blood parameters in diagnosing PJI.

Material and Method: Revisions of total knee replacement and total hip replacement operated by the same surgeon between 2008 and 2018 were included in this study. Preoperative blood parameters of the patients were recorded. 69 primary arthroplasty patients with similar demographic characteristics to the patients were also included as the control group.

Results: 214 arthroplasty patients, 79.0% of whom were female (n=169), were included in this study. The patients were divided into 3 groups; 32.2% were primary arthroplasty, 36.9% were aseptic revision arthroplasty, and 30.8% were septic revision arthroplasty. There was no difference between the three groups in terms of demographic characteristics. In pairwise comparisons, preoperative erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), lymphocyte, and platelet-to-lymphocyte rate (PLR) parameters were found to be significantly different in the septic group when compared to both the aseptic group and the primary arthroplasty group. Further analyzes were performed to evaluate the diagnostic performances of ESR, CRP, lymphocyte, and PLR in PJI relative to aseptic patients by plotting to receive operating characteristic curves.

Conclusion: Lymphocyte, PLR, ESR, and CRP may have diagnostic value in predicting PJI. Therefore, these parameters may be helpful in deciding on revision arthroplasty for PJI.

Keywords: Periprosthetic joint infection, knee arthroplasty, hip arthroplasty, blood parameters, revision arthroplasty

INTRODUCTION

Periprosthetic joint infection (PJI) may develop after total knee arthroplasty and total hip arthroplasty. In the United States, the annual incidence rate of PJI has been shown to increase from 1.99% to 2.18% for hip arthroplasty and from 2.05% to 2.18% for knee arthroplasty from 2001 to 2009 (1) which are the most frequently performed orthopedic surgeries all over the world (2) , continues to be the most challenging and most devastating complication. 60-70 % of PJI occurs in the first two years (3,4). It constitutes a huge economic burden in social and individual health expenditures (5-7). The most common cause of early failure after total knee and hip arthroplasty is PJI (8,9).

Although PJI is the worst dream of orthopedic and traumatology surgeons, there is no gold standard method defined in the literature to make the diagnosis (10). Rather than a single finding for diagnosis; it is important to have clinical, radiological, and laboratory results together. The diagnosis is made by meeting the combined diagnostic criteria used by internal branches (rheumatological diseases), which orthopedic and traumatology surgeons are not very accustomed to. In 2011, the Musculoskeletal Infection Society (MSIS) group defined 2 major and 4 minor criteria Parvizi et al. (11) Later in 2018, Parvizi et al. (12) accepted the presence of two positive cultures or sinus tracts as the major criterion and diagnosis for PJI. Again, Parvizi et al. calculated weights of high serum C-reactive protein (CRP) (>1 mg/dL), D-dimer (>860 ng/mL), and erythrocyte sedimentation rate (ESR) (>30 mm/hour) were 2, 2, and 1 point, respectively. In addition, increased synovial fluid white blood cell count (>3000 cells/μL), alpha-defensin (signal-to-cut ratio >1), leukocyte esterase (++), polymorphonuclear percent (>80%), and synovial CRP (>6, 9 mg/L) scored 3, 3, 3, 2, and 1, respectively. Patients with a total score equal to or greater than 6 were considered infected. However, most of these tests are not easily available and expensive (12,13).

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The aim of this study is to investigate the role of serum biomarkers in the diagnosis of PJI, which are simple, inexpensive, and easily obtained before the operation and do not impose additional time and cost on the patient.

MATERIAL AND METHOD

The study was carried out with the permission of Ankara City Hospital No:1 Clinical Researches Ethics Committee (Date: 28.04.2021, Decision No: E1-21-1783). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Revisions of total knee arthroplasty and total hip arthroplasty operated by the same surgeon between 2008 and 2018 were included in this study. Preoperative blood parameters and demographic characteristics of the patients were recorded. Among the patients who underwent revision arthroplasty in our clinic in the mentioned years, patients who met the infection criteria (14). were included in the septic group (Group 3, n=66) and a 2-stage revision was performed, while patients who did not show any signs of infection were included in the aseptic group (Group 2, n=79) and a one-stage revision was performed. Primary arthroplasty patients with demographic characteristics similar to the septic and aseptic revision arthroplasty groups and operated by the same surgeon were also included in the control group (Group 1, n=69).

Patients with hematological disease, those with infections other than PJI, and those with autoimmune disease were excluded from the study.

Statistical analysis was performed using the SPSS 25.0 for Windows (SPSS, Inc.; Chicago, USA) package program. As for statistical analysis, categorical variables in the descriptive findings section were number, percentage and continuous variables were mean ± standard deviation and median (minimum, largest value). Pearson's chi-square or Fisher's Exact tests were used in the comparison of categorical variables. The conformity of continuous variables to normal distribution was evaluated by analytical (Kolmogorov-Smirnov and Shapiro-Wilks analysis) and visual (histogram and probability graphs) methods. Since the normal distribution could not be determined, the Kruskal-Wallis test was used for comparisons between three independent groups. When a significant difference was detected, the groups were compared in pairs to determine the source of the difference, and the level of significance was determined according to Bonferroni correction. The groups that differed after the Bonferroni correction were accepted as the source of the difference. ESR, CRP, PLR, and Lymphocyte values were evaluated by receiver operating curve (ROC) analysis whether these values predicted PJI. The area under the curve (AUC) and cut-off values, sensitivity, specificity PPV, and NPV of these cut-off values are presented. A value of $p<0.05$ was accepted as statistically significant.

RESULTS

A total of 214 arthroplasty patients, 79.0% of whom were female (n=169), were included in this study. The mean age of the participating patients was 69.25±8.45. Thirty-five (16.4%) of the patients are smokers. Most of the patients were knee arthroplasty (primary or revision) patients (82.7%). Postoperative complications developed in 20 patients (9.3%). A positive culture was obtained in 39 patients (18.2%) (**Table 1**).

Table 1: Demographic characteristics of the patients

N=214		
Gender, n %		
Male	45	21.0
Female	169	79.0
Age Avr±Sd 69,25±8,45, median 70 (min: 39- max 93)		
Smoker, n %		
No	179	83.6
Yes	35	16.4
Side, n %		
Right	112	52.3
Left	101	47.2
Bilateral	1	0.5
Placement, n %		
Knee	177	82.7
Hip	37	17.3
Complication (other), n%		
No	194	90.7
Yes	20	9.3
Reproduction, n %		
No	175	81.8
Yes	39	18.2
Situation, n %		
Normal	69	32.2
Aseptic	79	36.9
Septic	66	30.8

Avr±Sd: Average±Standard deviation

The patients were divided into 3 groups; 32.2% (n=69) were primary arthroplasty (Group 1), 36.9% (n=79) were aseptic revision arthroplasty (Group 2), and 30.8% (n=66) were septic revision arthroplasty (Group 3).

There was no difference between the three groups in terms of demographic characteristics such as gender, side, and smoking (**Table 2**).

Table 2. Comparison of demographic and laboratory results of the groups

N=214	Group 1: Normal (n=69)	Group 2: Aseptic (n=79)	Grup 3: Septic (n=66)	p Value
Gender, n (%)				0.075*
Male	10 (23.8)	13 (31.0)	19 (45.2)	
Female	59 (34.3)	66 (38.4)	44 (27.3)	
Side, n (%)				0.690*
Right	37 (33.0)	41 (36.6)	34 (30.4)	
Left	31 (30.7)	38 (37.6)	32 (31.7)	
Bilateral	1 (100.0)	-	-	
Smoker, n (%)				0.795*
No	56 (31.3)	67 (37.4)	56 (31.3)	
Yes	13 (37.1)	12 (34.3)	10 (28.6)	
Placement, n (%)				0.023*
Knee	64 (36.2)	63 (35.6)	50 (28.2)	
Hip	5 (13.5)	16 (43.2)	16 (43.2)	
Complication (other), n (%)				<0.001*
No	69 (35.6)	72 (37.1)	53 (27.3)	
Yes	-	7 (35.0)	13 (65.0)	
ESR, Avr±Sd	19.9±11.6•	19.8±15.5*	37.5±26.9**	<0.001**
CRP, Avr±Sd	5.1±3.8•	9.2±22.0*	23.9±36.7**	<0.001**
Plt vol, Avr±Sd	8.2±1.0	8.4±1.0	8.0±0.8	0.057**
Plt, Avr±Sd	296.5±96.1	284.9±91.9*	324.7±103.3*	0.016**
Leu, Avr±Sd	8.4±2.8	8.1±2.7	7.7±3.1	0.159**
Neu, Avr±Sd	5.7±2.4	5.3±2.4	5.3±3.0	0.152**
Lymph, Avr±Sd	3.8±15.9•	2.2±2.1*	1.6±0.6**	0.003**
Mono, Avr±Sd	0.5±0.2◊•	0.4±0.2◊	0.4±0.2•	0.010**
RDW, Avr±Sd	14.4±1.5	14.6±1.9*	15.5±1.7*	<0.001**
NLR, Avr±Sd	3.3±1.8	3.0±2.8	3.9±3.5	0.061**
MLR, Avr±Sd	0.3±0.2b◊	0.2±0.2◊*	0.3±0.2*	0.003**
PLR, Avr±Sd	174.2±86◊•	37.6±12.8◊*	222.4±111.6**	<0.001**
PMR, Avr±Sd	662.5±324•	711.2±258	811.8±291.7•	0.006**
LMR, Avr±Sd	7.7±30.6◊	5.3±3.1◊*	4.2±1.8*	0.003**
PltVol/Plt, Avr±Sd	0.031±0.011	0.032±0.010*	0.028±0.011*	0.005**

*: Chi Square Test, Avr±Sd: Average±Standard deviation, **: Kruskal Wallis Test, According to the Bonferroni correction, there was a signifficant difference in pairwise comparisons (between ◊: Group 1 and 2, •: Group 1 and 3, * Group 2 and 3) (p<0,016).

28.2% of those with knee arthroplasty were septic, 43.2% of those with hip arthroplasty were septic and there was a significant difference between the groups (p=0.023). There was a significant difference between the groups in terms of the presence of additional complications (p<0.001) (**Table 2**).

When the blood values of the patients were examined, there was a significant difference between the groups in terms of ESR, CRP, platelet, lymphocyte, monocytes, red blood cell distribution width (RDW), monocytes-to-lymphocyte rate (MLR), platelet-to-lymphocyte rate (PLR), platelet-to- monocytes (PMR), , lymphocyte-to-monocytes (LMR), and platelet volume/platelet (Pv/Plt) (**Table 2**).

The distribution of some blood parameters according to the groups is shown in **Figure 1**.

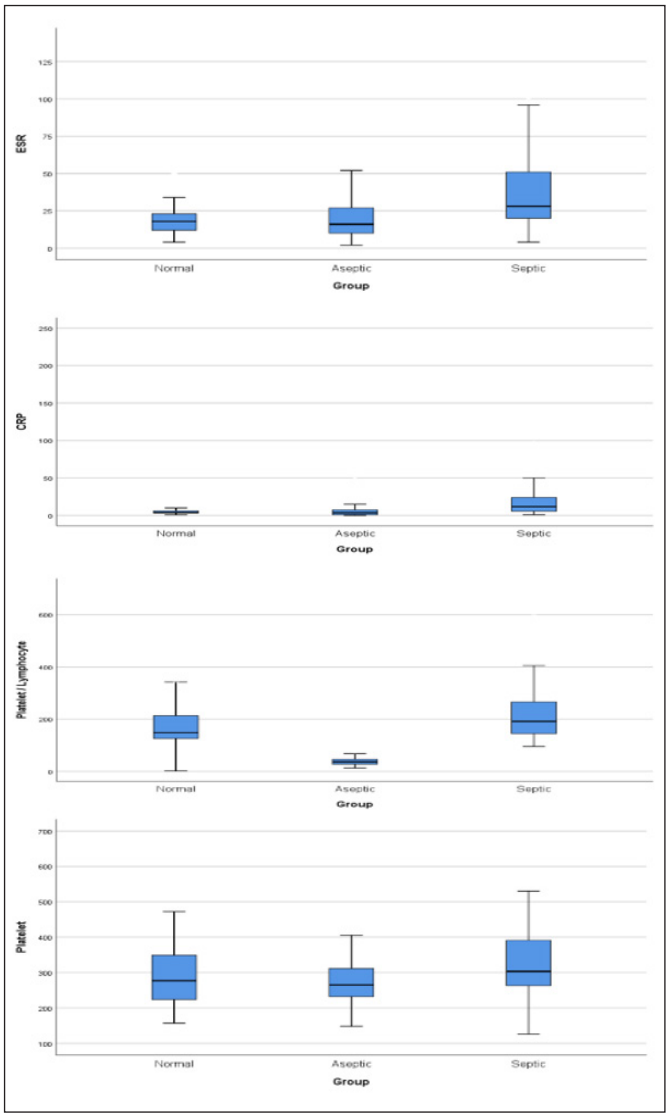

Figure 1. Distribution of some parameters according to the groups
ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein

In pairwise comparisons according to Bonferroni correction, group 1 and group 2 have some differences in terms of monocyte value (p=0.010), MLR (p=0.002), PLR (p=<0.001), LMR (p=0.002 group 1 and group 3 have some differences in terms of ESR (p<0.001), CRP (p<0.001), lymphocyte (p=0.013), monocytes (p=0.008), PLR (p=0.002), PMR (p=0.003); and group 2 and group 3 have some differences in terms of ESR (p<0.001), CRP (p<0.001), platelet (p=0.004), lymphocyte (p=0.001), RDW (p=0.001), MLR (p=0.007), PLR (p<0.001) and LMR (p=0.007) and Pv/Plt (p=0.001) (**Table 2**). As a result, preoperative ESR, CRP, lymphocyte, and PLR parameters were significantly different in the septic group compared to both the aseptic group and the control group. Therefore, the diagnostic performances of ESR, CRP, lymphocyte, and PLR in PJI relative to aseptic patients were evaluated by plotting receiving operating characteristic (ROC) curves (**Figure 2**).

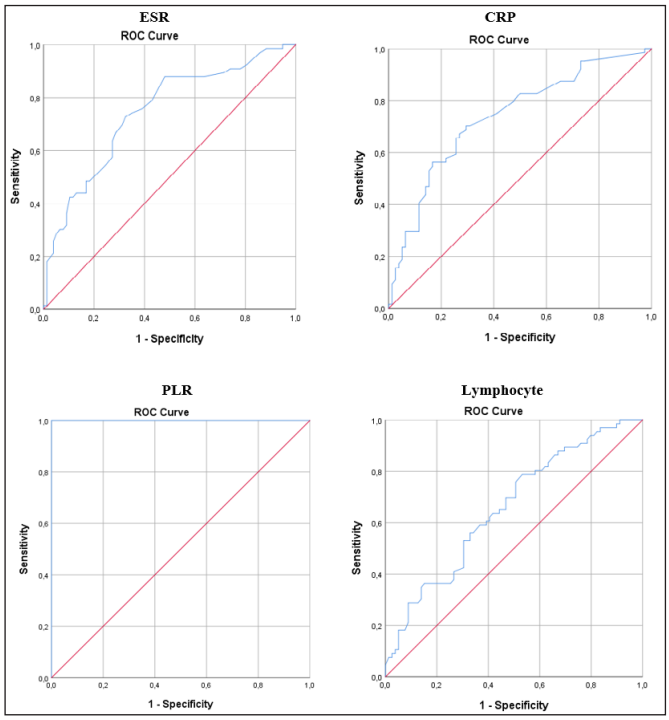

Figure 2: ROC analysis of some blood parameters

ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, PLR: Rplatelet-to-lymphocyte rate, ROC: Receiver operating curve

As a result of analysis, the cut-off values obtained for ESR, CRP, lymphocyte, and PLR parameters and specificity, sensitivity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV), and area under the ROC curve (AUC) values comprehensively presented in **Table 3**. It was observed that values of 21.5 for ESR, values of 6.74 for CRP, values of 1.725 for lymphocyte, and values of 85.5 for PLR were predictive of PJI ($p<0.001$, $p<0.001$, $p=0.001$, $p<0.001$, respectively). The combined effects of specificity, sensitivity, PPV, and NPV values for PLR were 100% (**Table 3**).

DISCUSSION

This study compared some preoperative blood parameters among patients who underwent primary arthroplasty, septic revision arthroplasty, and aseptic revision arthroplasty. Preoperative PLR, ESR, and CRP values were higher and lymphocyte values were lower in patients with septic revision arthroplasty compared to patients with aseptic revision arthroplasty and primary arthroplasty. Further analyzes were performed to evaluate the diagnostic performances of ESR, CRP, lymphocyte, and PLR in PJI relative to aseptic patients by ROC curves. The findings suggested that elevated ESR, CRP, and PLR values and decreased lymphocyte values are valuable parameters in diagnosing PJI.

Diagnosis of PJI is based on a detailed history and physical examination, along with a review of serological tests and radiographs (15). In addition, isolation of the causative organism from fluid or tissue cultures obtained from the affected joint is very important for treatment and prognosis, but usually it is difficult to obtain a positive culture in patients with clinically suspected PJI after arthroplasty. The literature agrees that almost half of PJI patients do not have growth in culture (16). Parvizi et al. (12) found culture negative in almost all patients with suspected diagnosis in their study published in 2018 . In our study, there was no growth in 27 (41%) of 66 PJI patients. We think that the reason for this is the antibiotics that were started in the outpatient clinic conditions in the preoperative period. This high rate reveals the importance of auxiliary findings of blood biomarkers in the diagnosis of PJI.

Many biomarkers have been defined in the diagnosis of PJI infection in recent years. Wyatt et al. (17) reported to have 100% sensitivity and 96% specificity, alpha defensin is an important biomarker for synovial fluid, but its high cost is suggestive. Although the major criteria are the same in different clinical studies, the minor criteria are different and there is no consensus yet (17-20). In 2018, Parvizi et al. (12) investigated the role of preoperative blood and synovial fluid values. They found significant elevation of CRP, ESR and D-dimer in the blood. Similarly, high CRP and ESR were found to be significant for PJI in this study.

The predictive role of blood biomarkers (monocytes, lymphocytes, neutrophils, platelets) in various diseases and cancers has been investigated, but studies investigating their predictive role in the diagnosis of PJI are very limited. Trimula et al. (18) reported that PLR, CRP, and ESR in PJI patients achieve significantly higher sensitivity and specificity rates of 97% or more for PJI (PLR: 99.03%; 98.80%). Paziuk et al. (19) showed that platelet count and mean platelet volume (MPV) were significantly higher in PJI patients compared to the aseptic revision group. Similarly, Xu et al. (20). showed that preoperative fibrinogen level and platelet count

Table 3. ROC curves evaluation of diagnostic performances of preoperative ESR, CRP, lymphocyte and PLR in septic revision arthroplasty

N=143	Cut off	Sensitivity (%)	Specificity (%)	PPV %	NPV %	AUC (%95 CI)	p
ESR	21.5	72.7	67.5	65.8	74.3	0.745 (0.663-0.826)	<0,001
CRP	6.74	70.3	70.5	66.2	74.3	0.738 (0.655-0.820)	<0,001
PLR	85.5	100.0	100.0	100.0	100.0	(1.000-1.000)	<0,001
Lymp	1.725	60.6	60.8	56.3	64.9	0.658 (0.569-0.746)	0,001

ROC: Receiving operating characteristic curves, Sens: Sensitivity, Spec: Specificity, PPV: Positive Predictive Value, NPV: Negative Predictive Value, AUC: Area under the ROC curve, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, Lymp: Lymphocyte, PLR: Platelet-to-lymphocyte rate

were predictive in the diagnosis of PJI. In this study, preoperative ESR, CRP, lymphocyte, monocytes, PLR and PMR values were found to be significantly different in the septic group compared to the control group. Also, preoperative ESR, CRP, lymphocyte, platelet, RDW, MLR, PLR, LMR and Pltvl/Plt values were found to be significantly different in the septic group compared to the aseptic group. In addition, ESR, CRP, lymphocyte, and PLR parameters were significantly different in the septic group compared to both the aseptic group and the control group. 21.5 cut-off value for ESR, 6.74 for CRP, 1.725 for lymphocyte, and 85.5 for PLR were found to be predictive for diagnosis of septic revision arthroplasty. Therefore the results suggested that it may be useful to evaluate these blood parameters when deciding on revision surgery.

There are some limitations of this study. For PJI, which is a combined diagnosis, it focused only on blood biomarkers and synovial fluid values were not mentioned. Another limitation is the retrospective nature of the study. In addition, some conditions that may affect blood parameters (drug use, another active infection, alcohol) were not recorded. The strength of this study is that it is the first to evaluate multiple blood biomarkers together in the diagnosis of PJI.

CONCLUSION

Lymphocyte, PLR, ESR, and CRP are easy biomarkers that are simply available from routine laboratory examination and may have diagnostic value in predicting PJI. Therefore, these parameters may be useful in deciding on revision arthroplasty for PJI.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara City Hospital No:1 Clinical Researches Ethics Committee (Date: 28.04.2021, Decision No: E1-21-1783).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: No conflict of interest was declared by the authors.

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Original Article

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Factors affecting complications in 31 cases of elastofibroma dorsi after marginal resection in a single center

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ABSTRACT

Aim: Elastofibroma dorsi (ED) is an uncommon benign connective-tissue tumor, usually seen in the subscapular region of women after the fifth decade. We present the clinical features, management, and long-term outcomes of cases of ED treated surgically in a single institution.

Material and Method: The data of 31 patients (7 male, 24 female) with a histopathological diagnosis of ED between January 2010 and January 2021 and mean age of 56.6 years were reviewed retrospectively from their records. The mean follow-up duration was 80.2 (19-144) months. Nine cases were bilateral. Marginal resection surgery was performed in all cases diagnosed radiologically and clinically, and preoperative biopsies were performed for three patients. The results were evaluated using a visual analogue scale (VAS) for pain during follow-up.

Results: Complications such as chronic pain (n=5), hematoma (n=5), seroma (n=5), and infection (n=2) were seen in 11 patients (35%) in the early postoperative period and improved over the course of follow-up. A local recurrence observed in one patient during follow-up was re-excised. Significantly more complications were observed in patients with bilateral ED (p=0.015), manual laborers and heavy laborers (p=0.013), patients with comorbidities (p=0.006), those who slept in the supine position (p=0.031), and those who underwent synchronized surgery (p=0.013). In addition, statistically significantly more complications were observed in cases of masses with longer longitudinal length (p=0.016), patients with longer preoperative symptom duration (p=0.009), and longer operative times (p=0.025). The average VAS score improved significantly from 4.97 to 1.52 after surgery (p<0.001).

Conclusion: While satisfactory results were obtained over a long follow-up duration after marginal resection, many complications were encountered in the early postoperative period. The decision for resection should be made after a comprehensive evaluation of symptoms and lesions, patients should be informed about complications, and follow-up periods should be prolonged after meticulous surgery.

Keywords: Elastofibroma dorsi, marginal resection, subscapular mass, benign tumor

INTRODUCTION

Elastofibroma dorsi (ED) is a slow-growing benign fibroblastic pseudotumor in the infrascapular region. ED typically presents as an ill-defined mass lying over the costal periosteum at the 6th to 8th ribs, underneath the rhomboid major, latissimus dorsi, or serratus anterior muscles (1,2). It is especially common in women over the age of 50 and it constitutes 1-2% of chest wall primary tumors without malignant potential (1,3). However, it has been stated in some studies that its incidence varies between 1% and 16% with asymptomatic cases (3,4). It usually entails a unilateral lesion (60% right-sided), but it has been reported to be bilateral in 10-66% of cases (3-5).

Most patients are asymptomatic. With increased size of the mass, patients present with complaints of local pain that increases with shoulder movements, limitation of movement, a mobile mass with a rubbery consistency, or scapular snapping (5,6). Laboratory and pulmonary function test results are normal (2). Because of its typical localization and clinical features, it is often diagnosed after radiological examinations. Magnetic resonance imaging (MRI) is the mainstay of diagnosis of ED due to its high sensitivity and specificity (7). MRI demonstrates a heterogeneous, unencapsulated, soft tissue mass that is lenticular, poorly circumscribed, and most often with intermixed linear-intensity adipose tissue within fibrous tissue (1,7) (**Figure 1**).

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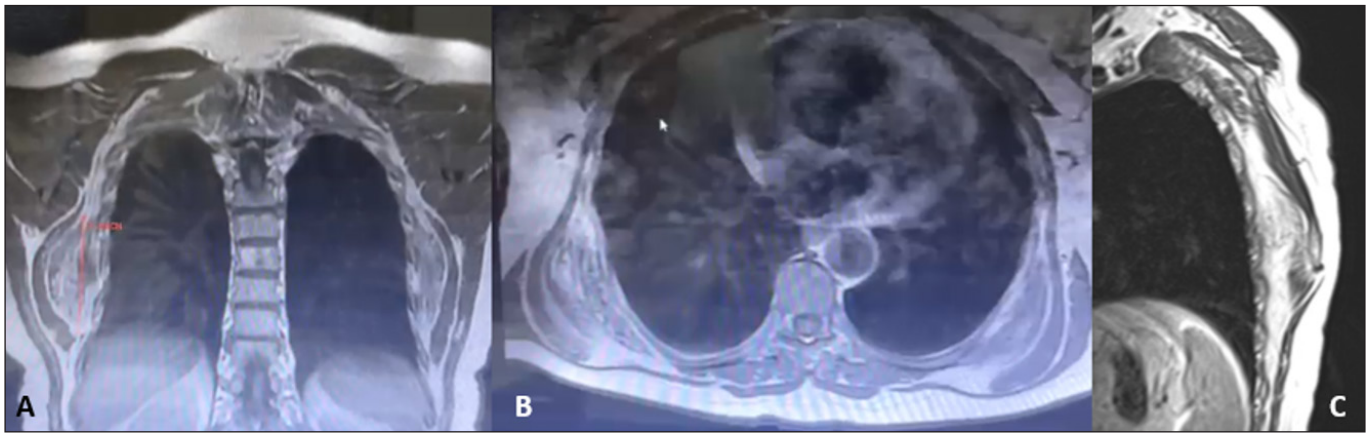

Figure 1. Coronal (A), axial (B), and sagittal (C) MRI images of bilateral elastofibroma dorsi.

Although it has been stated that biopsy is often unnecessary, it is recommended in suspicious cases with atypical clinical and radiological findings without a contralateral mass (1,8). It can be confused with other tumors of the periscapular region and misdiagnosed as sarcoma. The definitive diagnosis is made histopathologically (1). Marginal resection with a muscle-sparing approach is a generally accepted technique for symptomatic and/or large ED (1,4,5). Although significant improvement in the preoperative symptoms of patients is observed, postoperative complications such as seroma and hematoma are seen at varying rates due to the poorly circumscribed mass and its high vascularity (4,9,10).

As a limited number of studies have reported the long-term surgical outcomes of ED and the number of cases is small, clearly defined treatment guidelines and optimal approaches have not yet been determined. In this study, we aimed to determine the clinical and demographic factors affecting the postoperative complications and long-term results of patients with ED in a single center and to contribute to the literature by sharing our experiences.

MATERIAL AND METHOD

The study was carried out with the permission of University of Health Sciences Dr. Abdurrahman Yurtaslan Ankara Oncology Health Applications and Research Center Clinical Researches Ethics Committee (Date: 06.10.2021, Decision No: 10-1419). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Forty masses of 31 consecutive patients (7 male and 24 female), who were surgically treated by the orthopedics and traumatology, and thoracic surgery clinics in our oncology center between January 2010 and January 2022 and were diagnosed with ED histopathologically with a follow-up period of at least 12 months, were included in this study. Mean age was 56.6±12.06 (19-74) years. Demographic data, clinical presentations, and complications were obtained from the patients' records and analyzed retrospectively (**Table 1**).

Table 1. Perioperative demographic and clinical features and complications of 31 patients with elastofibroma dorsi

Parameters	n (%) or mean±SD
Age, mean±SD	56.68±12.06
Gender, n (%)	
Female	24 (77.4%)
Male	7 (22.6%)
Occupation, n (%)	
Housewife	16 (51.6%)
Civil officer	6 (19.4%)
Manual/heavy labor	9 (29%)
BMI, mean±SD	26.56±3.82
BMI <25	11 (35.5%)
BMI ≥25	20 (64.5%)
Comorbidities, n (%)	13 (41.9%)
Operation side, n (%)	
Right	14 (45.2%)
Left	8 (25.8%)
Bilateral	9 (29.0%)
Surgery, n (%)	
Unilateral	22 (71.0%)
Synchronized bilateral	6 (19.4%)
Two-sequence bilateral	3 (9.7%)
Time of follow-up, weeks	
Mean±SD	80.26±33.06
Longitudinal length of ED	
Mean±SD	70.55±19.97
Symptoms, n (%)	
Pain	21 (42%)
Feeling of mass	15 (30%)
Restriction of movement	8 (16%)
Snapping scapula	6 (12%)
Duration of symptoms, months	7.61±6.83
Sleeping in the supine position, n (%)	
Yes	14 (45.2%)
No	17 (54.8%)
VAS score	
Preoperative	4.97±1.27
Postoperative	1.52±1.06
Drain removal time, days	
Mean±SD	1.65±0.87
Complications, n (%)	
None	20 (64.5%)
Pain	5 (16.1%)
Seroma	5 (16.1%)
Hematoma	5 (16.1%)
Infection	2 (6.4%)
Recurrence of ED, n (%)	1 (3.2%)
Operative time, minutes	53.55±4.20
Hospitalization time, days	
Mean±SD	2.55±0.40

SD: Standard deviation, BMI: Body mass index, ED: Elastofibroma dorsi, VAS: Visual analogue scale

The masses in our patients were located on the right side (n=14), left side (n=8), and bilaterally (n=9). Twenty-five patients (7 manual laborers, 2 heavy laborers, and 16 housewives) had jobs that required more than 10 years of extensive physical effort. All of these cases were symptomatic; the most common symptoms were pain and palpable mass. The overall mean of the longitudinal length of excised masses was 70.55±19.97 (45-115) mm. All of our patients had subscapular masses, and plain conventional X-rays and MRI (**Figure 1**) were requested as radiological examinations. The diagnosis was made based on physical examination, characteristic findings, and radiological imaging. Biopsy was performed for 3 atypical cases with difficulty in diagnosis.

Atypical and prominent symptoms (27/31) and patient's preference (4/31) were considered as surgical indications. The average time from the onset of symptoms to surgery was 7.61±6.83 (2-36) months. After general anesthesia, marginal resection surgery with a muscle-sparing approach was performed with an oblique incision from the lower end of the scapula (**Figure 2**). While the mass was bluntly separated from the upper muscle planes, it was dissected from the rib cage and scapula with the help of cautery. After meticulous hemostasis, a Hemovac drain was placed in the operation area for large or difficult-to-dissect tumors. Penrose drains were used in other cases. The mean hospitalization time was 2.55±0.40 (1-9) days and the time to drain removal was 1.65±0.87 (1-4) days. No patients required blood transfusions. Synchronized bilateral surgery was performed in 6 of 9 bilateral cases, while surgery was performed in two consecutive sessions for the remaining 3 patients.

The diagnosis was confirmed histopathologically. Local cryotherapy for the first 48 hours postoperatively and immobilization for 1 week was recommended. A shoulder arm sling and compression bandage were applied for the first 15 days. Passive shoulder movements were started at the end of the 1st week and active movements from the end of the 1st month. In the postoperative period, no restrictions were applied to movements, except for shoulder abduction and heavy activities of the affected upper extremity. Clinical outcomes were evaluated preoperatively and postoperatively using a visual analogue scale (VAS) for pain. All of the complications that we observed in the postoperative period improved during follow-up. In the follow-ups, it was observed that our patients had returned to their normal daily living activities with almost complete shoulder movement without pain.

Statistical analysis: All analyses were carried out using IBM SPSS Statistics 25.0 (IBM Corp., USA). Means and standard deviations were used to represent quantitative data. A statistical significance threshold of $p<0.05$ was applied. Preoperative and postoperative VAS scores were compared using the paired-sample t-test. The Mann-Whitney U test was carried out to compare variables without normal distribution. Comparisons of categorical data between groups of dependent variables were performed with chi-square tests. Pearson chi-square, Fisher exact, or continuity correction was applied as appropriate. Binary logistic regression analysis was performed to evaluate variables that could be associated with whether or not complications occurred. Multivariate logistic regression analysis was used to determine the factors associated with complication and recurrence rates.

RESULTS

A total of 18 complications were observed in 11 (35.4%) patients during an average follow-up duration of 80.2 (19-144) months after histologic resections of masses with tumor-free margins. Specific complications were as follows: pain (n=5), hematoma (n=5), seroma (n=5), and infection (n=2). Complications were managed conservatively (needle aspiration, puncture, compressive dressing, antibiotherapy, immobilization) in 10 of 11 cases. One patient was re-operated on in the first postoperative month for wound infection. While the mean VAS score was 4.9 (3-7) preoperatively, it decreased to 1.8 (0-5) postoperatively, which constituted a statistically significant difference ($p<0.001$) (**Table 2**). All our patients verbally stated that all complaints were resolved and limitations of shoulder movements improved after marginal resection.

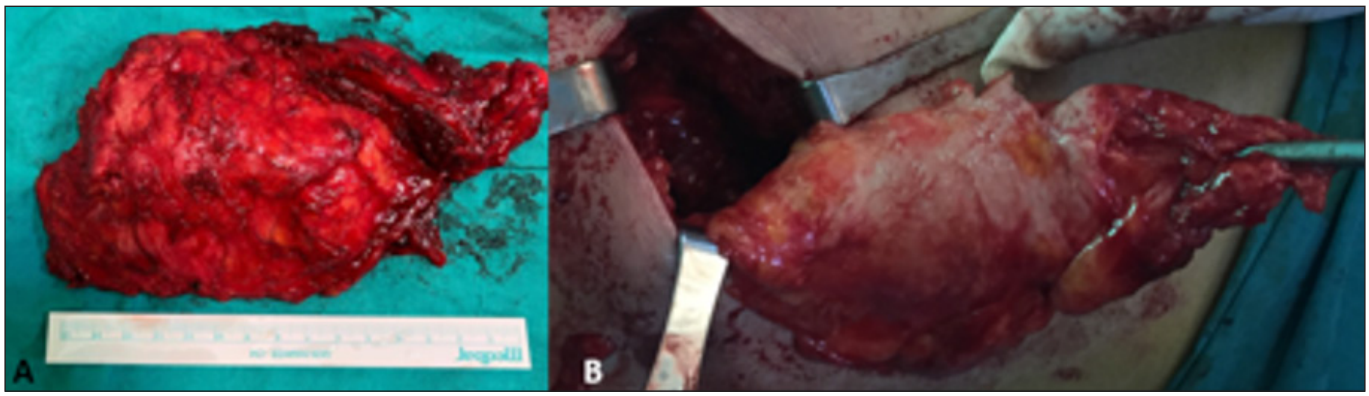

Figure 2. Post-excision (A) and intraoperative (B) images of elastofibroma dorsi mass

Table 2. Comparison of preoperative and postoperative visual analogue scale scores

	Mean	Standard Deviation	Std. Error of Mean	t	df	p
Preoperative and postoperative visual analogue scale scores	3.452	0.768	0.138	25.035	30	<0.001*

* Paired samples t-test

The complication rates were significantly higher among patients with bilateral ED, those with comorbidities, and those who were manual or heavy laborers (p=0.015, p=0.006, and p=0.013, respectively). The complication rate was also higher among patients who underwent synchronized surgery (n=6) compared to unilateral surgery (n=22) and among patients who slept in the supine position (n=14) (p=0.013 and p=0.031, respectively). Delayed wound healing, hematoma, and seroma were more common among patients who slept in the supine position in the group with complications, being seen in 8 of 11 cases. There was no difference in complication rates in terms of age, gender, or body mass index (BMI) (p>0.05) (**Table 3**). Multivariate logistic regression analysis showed that longitudinal mass length, operative time, and preoperative symptoms were positively correlated with complications (p=0.016, p=0.025, and p<0.01, respectively). While a significant positive relationship was found between drain removal time and complications, the positive relationship between hospitalization time and complications was not statistically significant (p=0.041 and p=0.068, respectively).

Table 3. Analysis of risk factors for postoperative complications and recurrence

Factors	Complications p-value*	Recurrence p-value*
Age	0.157	0.242
Gender (male/female)	0.652	1.000
Unilateral or bilateral mass	0.015	0.503
Occupation (housewife, manual labor, heavy labor)	0.013	0.118
BMI <25 or BMI ≥25	0.262	1.000
Comorbidities (yes/no)	0.006	0.196
Sleeping in the supine position	0.031	1.000
Preoperative biopsy diagnosis (yes/no)	0.121	1.000
Unilateral/synchronized surgery	0.013	1.000

*: Chi-square test, BMI: Body mass index, ED: Elastofibroma dorsi

The longitudinal length of the masses was positively correlated with the weight of patients, BMI, and postoperative VAS scores (p=0.013, p=0.06, and p=0.037, respectively). Length was not correlated with preoperative VAS score, duration of symptoms, operative time, or hospitalization time (p>0.05) (**Table 4**). There were no significant differences in the parameters evaluated in terms of recurrence (p>0.05) (**Table 3**). However, the local recurrence observed in one patient in the bilateral surgery and manual/heavy labor groups, who slept in the supine position and had a high preoperative VAS score, was re-excised.

Table 4. Multivariate logistic regression analysis of factors associated with complications

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
(Constant)	-1.265	0.445		-2.841	0.010
Age	0.003	0.004	0.067	0.734	0.471
BMI	0.019	0.014	0.156	1.364	0.187
Time of follow-up	-0.001	0.002	-0.088	-0.808	0.428
Longitudinal length of the mass	0.006	0.002	0.268	2.615	0.016
Duration of symptoms	0.020	0.007	0.283	2.875	0.009
Preoperative VAS score	-0.061	0.051	-0.164	-1.182	0.250
Duration of operation	0.006	0.003	0.297	2.412	0.025
Time to removal of drain	0.145	0.091	0.268	1.586	0.128
Duration of hospitalization	0.065	0.032	0.312	2.062	0.052

DISCUSSION

ED is an uncommon, benign, poorly circumscribed connective-tissue tumor classically located in the subscapular region (5,8). Although ED is mostly unilateral and usually located on the right side, some studies reported bilateral involvement in 10% to 50% of cases (2,4,5,11,12). The rates of right-sidedness (45.2%), left-sidedness (25.8%), and bilaterality (29.0%) in our study are consistent with the literature. In addition, it has been reported that large lesions are more common in women and the elderly (3,5,11). In our study, which had a female/male ratio of 24/7, no significant relationship was found between the size of the masses and gender or age. This is likely because our study group comprised symptomatic patients who all underwent surgery.

ED is often asymptomatic, and symptoms vary depending on the size and localization of the lesion (5,6). In a series of 76 cases that were treated surgically, the most common symptoms were pain and functional limitations (9), while in our series, pain (42%) and feeling the mass (30%) were most common. Limitations of shoulder abduction and feelings of stiffness were particularly observed in symptomatic patients in previous reports (5,6), consistent with our study, and these symptoms improved after surgery. While some researchers reported a relationship between the dimensions of the ED and the severity and presence of symptoms (12), other findings have suggested no such relationships (11). Our study revealed a positive and significant correlation between tumor size and variables including weight, BMI, postoperative VAS score, and complications. The absence of a relationship between tumor size and

symptoms in our study was probably due to the fact that our study group included only symptomatic patients who underwent surgery.

Although different theories have been proposed for the etiology of ED, the main accepted view is elastin degeneration caused by repetitive microtraumas (2,12-14). It is frequently seen in people who perform manual labor involving arm strength (15) and in housewives (5), and it has also been reported 10 years after latissimus dorsi flap harvesting (16). In our study, 25/31 patients (Housewife-16, Manual/heavy labor-9) did work that required manual labor and more complications were seen in this group; these findings support the microtrauma hypothesis.

If all pathognomonic criteria (age, localization, and snapping sound) are present, the lesion can be confidentially diagnosed with at least one radiological examination, preferably MRI (7,8,14). It has been shown that the diagnostic value of radiological imaging for ED is high and biopsy is not necessary for clinically and radiologically typical cases (1,7,17,18). Since we preferred MRI for diagnostic purposes, we performed a biopsy for only one patient; two patients admitted to our clinic had biopsies performed at another hospital previously.

As in our cases, no metastasis or malignant transformation has been reported in the literature despite the proximity of ED to the thorax and its high vascularity (7). The differential diagnosis should consider benign tumors such as fibrolipoma and neurofibroma, aggressive tumors such as desmoid fibromatosis, and sarcomas (7,11,12). Due to the variety of clinical manifestations, ED may be misdiagnosed as rotator cuff tear, subacromial bursitis, cervical pathologies, or chronic back pain. In order not to cause delays in diagnosis, shoulder and neck problems should be revealed with a careful physical examination (5,9,14). The fact that our patients were treated in different clinics during the preoperative symptom duration of 10 months supports this.

The management and follow-up of ED are somewhat controversial. The standard surgical treatment method recommended for ED is marginal resection, which has minimal morbidity (5-7). It has been suggested to avoid surgery in asymptomatic cases even if the mass size is large (11). As in our study, it was reported that there were significant decreases in preoperative VAS scores after surgery (14,17). In addition, preoperative symptoms and shoulder functions recovered completely after surgery. We also recommend conservative treatment in asymptomatic cases due to high rates of postoperative complications.

Although long-term complications are rare, as in our study, temporary complications such as postoperative seroma or hematoma (4,9,10) and chronic pain (7,9,12) have been reported, especially when the resected tumor mass is large. In the literature, studies report complication rates as high as 43% (10,12,17) and as low as 10% (5,7,9,19). In our study, seroma, hematoma, and pain were observed frequently in 35% of the patients. While some researchers have stated that complications such as postoperative seroma or hematoma are more common in cases with large resected tumor masses (7,10,17,19), some have reported no differences (4). No significant complications were reported after the marginal excision of masses with a mean size of 9.6 cm (18). It is known that postoperative complications are more common in elderly patients and those with comorbidities (11). Although we did not find a significant relationship between age and complications, we observed a significant positive relationship between complications and the size of the mass, consistent with previous studies. It has also been reported that more hematoma develops in cases with large masses and shorter durations to drain removal (10), and that operative times are longer and complication rates are higher in patients with BMI of >25 (4). We think that the high complication rate seen in our study is related to early shoulder movements. In our study, no significant relationship was found among drain removal time, complications, and lesion size. This may have been due to the relatively short durations until drain removal and hospitalization time among our patients. While we statistically observed larger masses in people with higher BMI values, we did not find a significant relationship between BMI and complications. This may be because it is not easy to identify the presence of seroma/hematoma in obese individuals.

More complications were reported after synchronous surgeries performed in bilateral cases (1,12), and it was recommended that this approach only be applied in cases where masses are large and symptomatic (12). We encountered a significantly higher rate of complications in synchronous surgeries (6/9) compared to sequential surgery (1/3) among our bilateral cases. It has been reported that preoperative discomfort is increased due to mechanical irritation, postoperative care becomes more difficult (11), and sleep disorders are observed more often in patients who have a habit of sleeping in the supine position (14). In our study, significantly more complications were observed in 14/31 patients who slept in the supine position.

Recurrence after marginal resection is extremely rare (5,12) and was observed only in cases with incomplete resection (1,5) and positive macroscopic-microscopic margins (3,15). A 4.5% recurrence rate was found in a

previous study (19), but studies with higher recurrence rates also exist in the literature (8,17). For a patient who was referred to us with recurrence after surgery in another hospital, a successful result was obtained by performing excision for the recurrence. ED formation in the contralateral scapular region, which was followed conservatively, was observed in two other patients during follow-up.

Aspiration drainage (12,18,19), compressive bandages (7,9), and shoulder immobilization (5,10,12) are recommended to prevent postoperative seroma/hematoma formation. There is no consensus in the literature regarding the ideal time to drain removal (5,9), postoperative shoulder immobilization (5,10), or the duration of postoperative follow-up (1,4,5). Drains were removed based on clinical observation, with Hemovac drains used in cases with bleeding and Penrose drains in other cases. We followed the patients at short intervals for the first 6 months and then recommended annual follow-up appointments.

The limitations of our study are its retrospective and monocentric nature and the lack of a control group. However, a large number of cases, a long follow-up period, and a diverse patient population are the strengths of the study.

CONCLUSION

In symptomatic cases of ED, marginal resection with a muscle-sparing approach is a safe and effective surgical method providing satisfactory clinical results. The decision for resection should be made after a comprehensive evaluation of the symptoms and the lesion. Elderly obese patients who sleep in the supine position and have comorbidities should particularly be informed about possible complications. Careful surgery and hemostasis, prolongation of the time to drain removal and follow-up periods, and avoidance of synchronized surgery in bilateral cases are beneficial in preventing complications.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of University of Health Sciences Dr. Abdurrahman Yurtaslan Oncology Health Applications and Research Center Clinical Researches Ethics Committee (Date: 06.10.2021, Decision No: 10-1419).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the manuscript, and they have approved the final version.

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Original Article

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The vaccination characteristics and mortal causes analysis of COVID-19 deaths at a district level

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ABSTRACT

Aim: This study aims to analyze some demographic characteristics, vaccination status, and mortal causes of COVID-19 deaths retrospectively at a district level.

Material and Method: This cross-sectional study retrospectively analyzed 357 COVID -19 deaths between March 11, 2020, and April 30, 2022, in a large district of Istanbul with low socioeconomic status. Age, sex, marital status, date of death, causes of death, vaccination status and dates, and PCR test data (considered diagnostic data) were obtained from the District Health Directorate records.

Results: More than half of those who died were male (51.8%). The mean age was 71.1±13.3 years. As age increases, the death number also increases. 72.0% of all deaths were over 65 years old. The marital status of more than half of the deaths (54.8%) was married. 71.7% of all deaths were unvaccinated. Of those vaccinated among deaths, 85.4% received all vaccine doses with only inactivated virus vaccine. The mean time from diagnosis (PCR positive date) to death for COVID-19 deaths is 14.3±11.0 days. The mean time from the last vaccination date to death in the vaccinated group was 123.2±90.8 days. This period was statistically significantly different between those who received a single dose of vaccine and those who received two or more doses. Most COVID-19 deaths (67.5%) were caused by respiratory diseases. Among the causes of death coded with the ICD-10 diagnosis code in the death notification system, 53.8% of the deceased had a comorbid condition.

Conclusion: The most striking result of our investigations is that most COVID-19 deaths were unvaccinated or incompletely vaccinated. Those who were vaccinated were mostly immunized with inactivated vaccines. Based on the results, it can be concluded that vaccines effectively protect COVID-19 patients from death. However, the preventive effect of inactivated vaccines against death in COVID-19 is limited.

Keywords: COVID-19, death, vaccination status, mortal causes

INTRODUCTION

COVID-19 has spread worldwide, including Turkey, shortly after the first case was detected in Wuhan, Hubei Province, China, in December 2019 (1). The disease became the most important issue worldwide causing significant economic and social losses and numerous deaths. By February 17, 2023, COVID-19 has caused more than 750 million infections and nearly 7 million deaths worldwide (2).

Few studies in the literature retrospectively analyzed COVID-19 deaths (3–5). Also, no study examined COVID-19 deaths at the population level in Turkey. Understanding the underlying causes of death is important to reduce COVID-19 deaths.

The first COVID-19 case in Turkey was reported on March 11, 2020 (6); as of February 17, 2023, 17,004,677 confirmed cases have been reported with 101,419 deaths since the first case (7). Istanbul is the province where the first case occurred in Turkey and was the most affected during the pandemic. Sultanbeyli ranks 22nd among Istanbul's 39 districts in population size and has a low socioeconomic level due to immigration. In 2022, the district's population was 358,201; 51.2% were male (8).

The aim of this study was to retrospectively investigate COVID -19 deaths in an Istanbul neighborhood with a low socioeconomic level. In this context, our study aimed to answer the following questions,

1. What are the demographic characteristics of COVID-19 deaths?
2. What is the vaccination status of those who died from COVID-19?

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3. What are the mortal causes of COVID-19 deaths reported in the death notification system?
4. What is the mean time from diagnosis to death for COVID-19 deaths, and is there an association with vaccination status?

MATERIAL AND METHOD

The study was carried out with the permission of Istanbul Medipol University Non-Interventional Clinical Researches Ethics Committee (Date: 13.10.2022, Decision No: E-10840098- 772.02-6155). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design, Population, and Data Sources

This cross-sectional study was conducted in Sultanbeyli, a low socioeconomic neighborhood of Istanbul. The research population consists of people who died of COVID-19 in this district. No random sampling was used in the study, but all COVID-19 deaths in the district between March 11, 2020, and April 30, 2022 were included.

Data Collection Method

Age, sex, marital status, date of death, and causes of death were taken from the death notification system. With the new death certificate introduced in Turkey in 2009, the causes of death were classified according to the International Classification of Diseases (ICD-10). In 2013, the document was transferred to digital media and renamed the Death Notification System. Physicians complete the death certificate for all deaths in all hospitals, health centers, family health centers, municipalities, forensic medical facilities, and other health care facilities. All completed death certificates are compiled in the provincial health directorates and forwarded to the relevant TurkStat regional directorates. The death certificate begins with Section A, which indicates the age, sex, marital status, and place of residence of the deceased. Section B contains the date and place of death. Section C divides the manner of death into natural and forensic, and communicable and non-communicable diseases. If the death was from an injury, there is a Section D that asks for the details of the injury. The document continues with sections E, which asks questions about autopsy if an autopsy was performed, F, which asks about infant mortality, and G, which addresses maternal death. Section H, which asks questions about cause of death, is divided into two subsections. The first part lists chronologically the diseases and conditions that lead directly to death. The second part lists other important situations that affect the realization of death but are not related to the disease that caused the death.

The vaccination status of the deceased individuals was obtained from the country's public health management system, where COVID-19 vaccinations were registered. In addition, the COVID-19 diagnosis dates of the people included in the study were obtained from the Statistics and Causal Analysis in Health application (SINA).

Definitions and Classification of Data

COVID-19 Death: All deaths between March 11, 2020, and April 30, 2022, for which one of the causes of death in the Death Notification System was defined as COVID-19, were considered COVID-19 deaths. The date on which the PCR test result was positive was accepted as the date of diagnosis.

Fully vaccinated: According to the CDC, individuals are considered "fully vaccinated" two weeks after receiving the second dose of a two-dose vaccine series COVID-19 (9).

Mortal causes: In the Death Notification System, diseases and conditions defined by ICD-10 codes were accepted as mortal causes.

Statistical Analysis

Continuous variables were expressed as mean±standard deviation and categorical variables as frequencies and percentages. The Shapiro-Wilk test was used to test whether a normal distribution was present. Continuous variables were compared using the Mann-Whitney U test, and categorical variables were compared using the chi-square test. All statistical analyses were performed with IBM SPSS Statistics for Windows version 25.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was set at a p-value less than 0.05.

RESULTS

Between March 11, 2020, when the first case occurred in Turkey, and April 30, 2022, there were a total of 357 deaths associated with COVID -19 in the county. There were 169 deaths in 2020, 155 in 2021, and 33 in 2022. Two people died while infected with SARS-CoV-2 for the second time. The time between two positive findings was 14.5 months for one and 17.1 months for the other.

Data on age, sex, and marital status obtained from the death notification system are shown in **Table 1**. More than half of the deceased were male (51.8%). The mean age was 71.1±13.3 years. The mean age was similar in women and men (70.7 years in men, 71.5 years in women, $p > 0.005$). The lowest age was 29 years and the highest was 98 years. As age increases, so does the number of deaths, 72.0% of all deaths were over 65 years of age. The marital status of more than half of the deceased (54.8%) was married. It is noteworthy that 38.1% of them were widowed.

Table 1. Demographic characteristics of COVID-19 deaths

Characteristic	Number	%
Sex		
Male	185	51.8
Female	172	48.2
Age groups (years)		
40>	8	2,2
40-64	92	25,8
65 ≤	257	72,0
Marital status		
Married	199	55.7
Widow	136	38.1
Single	14	3.9
Divorced	8	2.2

According to **Figure 1**, which depicts the previous vaccination status of individuals included in the study, 71.7% of deaths due to COVID -19 were unvaccinated. Of the 82 fully vaccinated individuals, 85.4% received all doses of inactivated virus vaccine (CoronaVac). Of the others, 1.7% received all doses of mRNA vaccine (BioNTech), while 1.7% received mixed doses of inactivated and mRNA vaccine.

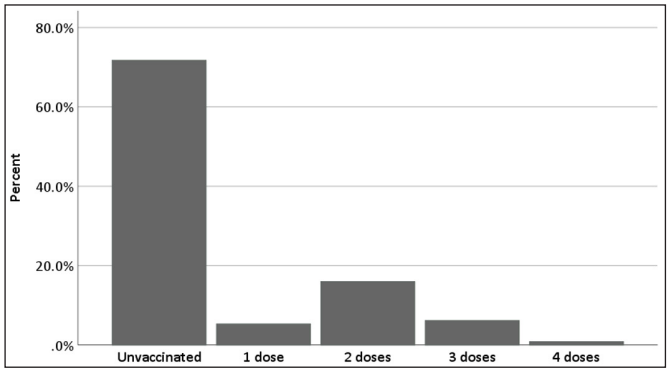

Figure 1. The vaccination status of COVID-19 deaths (%)

The mean time from diagnosis (PCR positive date) to death for COVID-19 deaths was 14.3±11.0 days (median: min-max: 0-80). No statistically significant difference was found between the fully vaccinated and the unvaccinated or incompletely vaccinated individuals in terms of time from diagnosis to death.

The mean time from the last vaccination to death in the vaccinated group was 123.2±90.8 days (median: 86.0; min-max: 8-349). While the median time is 34.0 days for those vaccinated for one dose, it is 140.0 days for those vaccinated with two or more doses (**Figure 2**). This difference was found to be statistically significant ($p < 0.001$).

Diseases reported as the cause of death in the death notification system are presented in **Table 2**. Most COVID-19 deaths (69.2%) were caused by respiratory diseases. ARDS and acute respiratory failure are the leading respiratory problems causing death in COVID-19 patients. They are followed by pneumonia-viral, bacterial, bronchopneumonia, unspecified. Shock and related conditions were observed most frequently among non-respiratory diseases, resulting in death in COVID -19 patients.

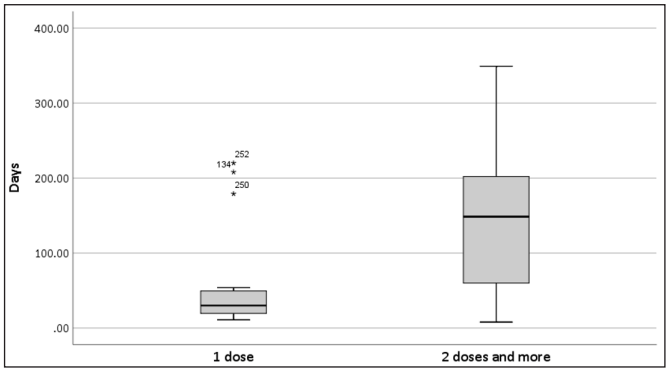

Figure 2. Time from the date of last vaccination to death, according to vaccine doses

Table 2. The reported cause of death in COVID -19 patients in the death notification system

Cause of death	Number	%
Respiratory diseases		
ARDS, Acute Respiratory Failure	187	52.3
Viral & bacterial pneumonia, bronchopneumonia, pneumonia unspecified	57	16.0
Pulmonary embolism	1	0.3
Spontaneous pneumothorax	2	0.6
Total	247	69.2
Non-respiratory diseases		
Septicaemia, Shock, Hypovolemia	75	21.0
Renal diseases	26	7.3
Cardiovascular diseases	6	1.7
Total	110	30.8

Among the causes of death coded with the ICD-10 diagnosis code in the death notification system, 53.8% of the deceased had a comorbid condition (**Table 3**). Hypertension (26.0%) ranked first among comorbid conditions. This was followed by COPD/asthma, cardiovascular disease, and diabetes mellitus with 20.3%, 18.8%, and 14.1%, respectively.

Table 3. Comorbid conditions of COVID-19 deaths

Disease	Number	%
Hypertension (HT) (All types)	50	26.0
Asthma, COPD	39	20.3
Cardiovascular diseases	36	18.8
Diabetes Mellitus (DM)	27	14.1.
Malignant neoplasms	10	5.2
Chronic kidney disease	10	5.2
Others	20	10.4
Total	192	100,0

DISCUSSION

The present study is the first to examine various demographic characteristics, vaccination status, and causes of death from COVID-19 in Turkey at the population level. All COVID-19-related deaths at the district level for two years from 2020, when the COVID-19 pandemic began, to 2022, were examined.

Most of the COVID-19-related deaths included in the current study were male. The mean age of death in this study was 71±13 years. There was no statistically significant difference between men and women regarding age. About 72% of all deaths were over the age of 65. These findings are consistent with the literature (10–14). In a meta-analysis study that included 3,1111,714 global COVID-19 cases, although there was no difference between men and women in terms of risk of contracting COVID-19, male patients were almost three times more likely than women to require an intensive care unit (ITU) (OR=2.84; 95% CI=2.06, 3.92) and a higher probability of death (OR=1.39; 95% CI=1.31, 1.47). The gender bias observed in COVID-19 is a worldwide phenomenon with few exceptions. Identifying how gender affects COVID-19 outcomes will have important implications for clinical management and mitigation strategies.

Vaccination in Turkey started on 14 January 2021 only for high-risk groups and opened to other populations on 25 June 2021. In the current study, as expected, 77% of the studied COVID-19 deaths were unvaccinated or incompletely vaccinated. Several studies showed the effect of vaccination with COVID-19 on reducing hospitalizations and deaths at the community level (15–19). An ecological study aimed to estimate the early impact of the US COVID-19 vaccination program on COVID-19 cases showed the decline in COVID-19 deaths (by 41%, 95% CI –14 to 69 among adults aged 65–74 years and by 30%, –47 to 66 among those aged ≥75 years, compared with adults aged 50 to 64 years) (19). In a retrospective study from Turkey, the length of stay in the intensive care unit and total hospital stay, the need and duration of mechanical ventilation, the percentage of severe and critically ill patients, and mortality were significantly higher in the unvaccinated or incompletely vaccinated group than in the fully vaccinated group (20).

Our findings that most COVID-19 deaths are unvaccinated or under-vaccinated can be considered an indirect indication that COVID-19 vaccines effectively reduce deaths. Additionally, our results show that the time from the last vaccination date to death was approximately 2.5 times higher in those who received two or more doses, and this difference was statistically significant. Studies that prove vaccine efficacy at the population level can help alleviate public ambivalence, not just about COVID-19 but other vaccines.

In this study, 88% of 105 people who died due to COVID-19 despite being vaccinated received all vaccine doses with only inactivated virus vaccine. Scientific evidence shows mRNA vaccines provide better immunity than inactivated virus vaccines (21–23). Our results show that a very small proportion of the COVID-19 deaths were vaccinated with the mRNA vaccine (Comirnaty) supports them. On the contrary, in a hospital-based cohort study from Turkey, no significant difference was found between the inactivated virus vaccine vaccinated group and the mRNA vaccine vaccinated group regarding mortality and admission to intensive care units (24). However, these findings should be supported by further studies comparing the efficacy of different vaccines at the population level.

In the present study, the majority of COVID -19 deaths were due to respiratory diseases such as respiratory failure and pneumonia. Among non-respiratory causes, which account for 30% of deaths associated with COVID -19, shock and related diseases rank first.

Previous studies have shown that common comorbidities are significantly associated with increased risk of adverse outcomes in patients with COVID -19 (25–28). Consistent with the literature, our study found that more than half of the deaths associated with COVID -19 had comorbidities. Hypertension was the most common comorbid condition, followed by COPD/asthma, cardiovascular disease, and diabetes. A meta-analysis showed that hypertension was significantly associated with an increased risk of adverse outcomes in COVID-19 patients based on adjusted effect estimates; this suggests that hypertension is an independent risk factor for predicting severity and mortality in COVID-19 patients (29). Therefore, COVID-19 patients with hypertension deserve further clinical attention.

Strengths and Limitations

Our study has some strengths and limitations. As it is a cross-sectional study, the results are limited to the relevant period. In addition, the reliability of the records limits our study, as we only use records to collect data. Almost a few studies in the literature have retrospectively analyzed COVID-19 deaths. They only studied at the pandemic's beginning and with small sample sizes. One of the strongest aspects of our study is that it is the first study to analyze population-level COVID-19 deaths in Turkey.

CONCLUSION

The results of our study, in line with the literature, showed that deaths from COVID-19 were elderly, males, and individuals with comorbid conditions. In particular, COVID -19 patients with hypertension need more clinical attention. Data from the current study showed that the most common cause of death in COVID -19 patients was respiratory disease. The most striking result from our results is that most COVID-19 deaths were unvaccinated or incompletely vaccinated. Those who were vaccinated were mostly immunized with inactivated vaccines. According to the results, it can be determined that vaccines effectively protect COVID-19 patients from death. However, the preventive effect of inactivated vaccines against death in COVID-19 is limited. Further and comprehensive studies of COVID-19-related deaths at the population level are needed to protect COVID-19 patients from death.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Istanbul Medipol University Non-Interventional Clinical Researches Ethics Committee (Date: 13.10.2022, Decision No: E-10840098-772.02-6155).

Informed Consent: Not applicable.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: No conflict of interest was declared by the authors.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the manuscript, and they have approved the final version.

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Original Article

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A bibliometric analysis of malnutrition in the geriatric population

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ABSTRACT

Aim: Malnutrition is a significant issue in the geriatric population. The frequency of infections, morbidity, and mortality rates are higher in malnourished patients. The purpose of this research is to evaluate scientific articles on geriatric malnutrition using statistical methods and to evaluate the topic from a novel viewpoint.

Material and Method: Statistical and bibliometric techniques were used to examine articles on geriatric malnutrition published between 1980 and 2022 in the Web of Science database. For correlation analyses, the Spearman correlation coefficient was used. To predict the number of publications in the subsequent years, a nonlinear (exponential growth model) regression analysis was performed. Trending subjects and connections were identified using keyword network visualization maps.

Results: Within the search criteria, 595 publications on geriatric malnutrition were identified between 1980 and 2022. 427 of those (articles and reviews) were included in the analysis. Since 2005, the quantity of published materials on the issue has expanded dramatically and continues to rise. The most active countries were USA and Spain, the most active author was Volkert, D., and the most active journal on the subject was Clinical Nutrition.

Conclusion: This research on geriatric malnutrition explores 427 publications, their origin countries, authors, and most used keywords. Geriatric malnutrition is one of the current trending research topics and seems more relevant every year in the aging world. This article may help physicians' and scientists' understanding of worldwide efforts on geriatric malnutrition.

Keywords: Geriatric, malnutrition, elderly, bibliometrics

INTRODUCTION

Malnutrition is a significant issue, particularly among cancer patients, intensive care patients, patients requiring major surgery, and especially in the geriatric population (1). As the geriatric population continues to rise, providing them with better healthcare is vital. In order to reduce the chance of developing chronic illnesses, a balanced diet and physical activity are frequently emphasized in older adults' nutrition. However, most research in geriatric nutrition suggests that protein-energy malnutrition (PEM) is a prevalent problem in this age range, especially in communities, hospitals, and nursing homes. Multicentre studies assessing the prevalence of PEM in acute care settings indicate that 23–60% of elderly patients are malnourished, and an estimated 22–28% are at nutritional risk (2,3).

Multiple organ systems, including the digestive tract, kidneys, heart, and lungs, can be negatively affected by malnutrition. In parallel with the deterioration of muscular strength and immunological function in malnourished elderly individuals, the risk of injury, the rate of chronic wounds, the frequency of infections, morbidity, and inevitably, the risk of mortality may rise (4). All of these issues can contribute to prolonged hospital stays and higher medical expenses (5).

2012 consensus statement from the Academy of Nutrition and Dietetics and the American Society for Parenteral and Enteral Nutrition (ASPEN) recommends diagnostic criteria for the diagnosis of malnutrition. The following diagnostic criteria indicate malnutrition if two or more criteria exist; insufficient energy intake, weight loss, loss of muscle mass, loss of subcutaneous fat, localized or generalized fluid accumulation that may mask weight loss, diminished functional status as measured by handgrip strength (6). In 2018 European Society for Clinical Nutrition and Metabolism (ESPEN) suggested a new criterion for malnutrition. In this criterion, before a diagnosis of malnutrition can be made, the patient must be determined as "at nutritional risk" by any validated nutritional risk screening method. Any of two sets of diagnostic criteria will confirm the malnutrition diagnosis. These criteria are; reduced body mass index (BMI) <18.5 kg/m2, combined weight loss and reduced BMI (age-related BMI), and reduced gender-dependent fat-free mass index (FFMI) (7).

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The Global Leadership Initiative on Malnutrition (GLIM) announced new standards in 2018. The GLIM was established to develop a worldwide consensus on the identification and diagnostic criteria for malnutrition to compare malnutrition's prevalence, treatment, and consequences accurately. The revised criteria incorporate an understanding of the significance of acute and chronic inflammation and use at least one phenotype and one etiologic criterion to diagnose malnutrition (8).

Malnutrition can be classified as disease-related malnutrition with inflammation, disease-related malnutrition without inflammation, and malnutrition/undernutrition without disease (7). Cachexia is a complex metabolic condition marked by muscle loss with or without fat loss because of an underlying disease and associated with higher morbidity (9). It is often accompanied by inflammation, insulin resistance, accelerated muscle protein breakdown, and anorexia.

Studies based on statistical and bibliometric analyses have been conducted on various important medical topics in conjunction with the rise in publications in recent years. When combined with thorough statistical methodologies, bibliometric studies provide researchers with ideas and breakthroughs for new research by revealing previous and present patterns (10,11). In recent years, the number of publications on geriatric malnutrition has steadily increased, and awareness has risen with each article.

Even though the number of global research on elderly malnutrition has increased over the past several years, only one bibliometric study has been published (12). The purpose of this study was to evaluate studies on geriatric malnutrition published between 1980 and 2022 using bibliometric and statistical methods. As a result of the analyses, we intend to identify the most influential studies, journals, authors, institutions, and countries on geriatric malnutrition, reveal cooperation between countries, reveal past and present trend issues, and provide a comprehensive summary of malnutrition in the elderly population.

MATERIAL AND METHOD

Ethics committee approval is not required in this bibliometric study.

This research was conducted in accordance with the World Medical Association Declaration of Helsinki's "Ethical Principles for Medical Research Involving Human Subjects."

Clarivate Analytics' Web of Science (WoS) database was used for the literature review. In WoS, the search terms "geriatric malnutrition," "geriatr*" AND "malnutri*," and "malnutrition AND "elderly" were used. Only the "title" section of the studies was used for the publication search. Using this search technique, all papers on elderly malnutrition, geriatric malnutrition, or articles containing terms derived from "geriatr*" and "malnutri*" in the title was found and retrieved from the WoS database. The search dates were determined to be between 1980 and 2022 (access date: 29.12.2022). Researchers can use these reproducibility codes to access comparable documents (search results may differ based on access dates): ("Geriatric malnutrition" (Title) OR "malnutrition" AND "elderly" (Title) OR "geriat*" AND "malnutri*" (Title) Timespan: 1980-2022 (Indexes Scanned: SCI-Expanded, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI)). For bibliometric network visualization, VOSviewer (Version 1.6.18, Leiden University's Center for Science and Technology Studies) software was used (13). The Tableau Software for Windows (Version 2019.4.1.; Tableau Software LLC, Seattle, WA) software was used to create a globe map.

Statistical analyses were performed using the IBM SPSS Statistics for Windows software (Version 26; IBM Corp., Armonk, N.Y., USA). Data normal distribution was evaluated with the Shapiro-Wilks test. In line with the data distribution, Spearman's correlation coefficient was used to assess the relationships between the number of articles published by world nations and multiple economic development indicators of world countries to see whether there is a relationship between economic power and the number of scientific publications (Gross Domestic Product (GDP), and GDP per capita, World Bank, 2021 data) (14). To predict the number of publications in the next years, a nonlinear regression analysis (exponential growth model) was used. In the regression analysis, R square (R2) value was utilized to measure the model's effectiveness. Results were considered statistically significant if the p-value was less than 0.05.

RESULTS

The Web of Science database included 595 papers regarding geriatric malnutrition published between 1980 and 2020. Of these publications, 397 were Articles (66.72%), 114 were Meeting Abstracts (19.16%), 30 were Reviews (5.04%), 29 were Letters (4.87%), 13 were Editorials (2.18%), and 12 (2.02%) were other types of publication (Correction, Proceedings Paper, Note).

397 articles (9 early access articles included) and 30 reviews were subjected to bibliometric analysis. 85.71%

(366) of these publications were in English, 5.62% (24) in Spanish, 4.22% (18) in German, 2.81% (12) in French, and the remaining works were published in different languages (Italian (4), Portuguese (2), Polish (1)).

The average number of citations per article was 24.62, the total number was 10511 (without self-citations: 9816), 57 publications were not cited, and the h-index of 427 articles was 53.

Active Research Areas

The top 10 research areas about geriatric nutrition were Nutrition Dietetics (171, 40.1%), Geriatrics (96, 22.5%), General Internal Medicine (62, 14.5%), Public Environmental Occupational Health (32, 7.5%), Gerontology (29, 6.8%), Nursing (15, 3.5%), Endocrinology Metabolism (12, 2.8%), Cardiac Cardiovascular Systems (8, 1.9%), Healthcare Sciences Services (8, 1.9%), Psychiatry (7, 1.6%).

Development and Future Trends of Publication

Figure 1 illustrates the distribution of the number of published papers by year. It also shows the findings of the non-linear exponential growth regression analysis performed to estimate the number of publications in 2023 and beyond. The model had a statistically significant association with the data, and the degree of agreement between the exponential growth model and the data was 79.5% (R2=0.795, p<0,001). This model predicts that 38 (95% Confidence Interval (CI): 20-73) articles will be published in 2023, 41 (95% CI: 21-79) papers will be published in 2024, and 44 (95% CI: 23-85) articles will be published in 2025 (**Figure 1**).

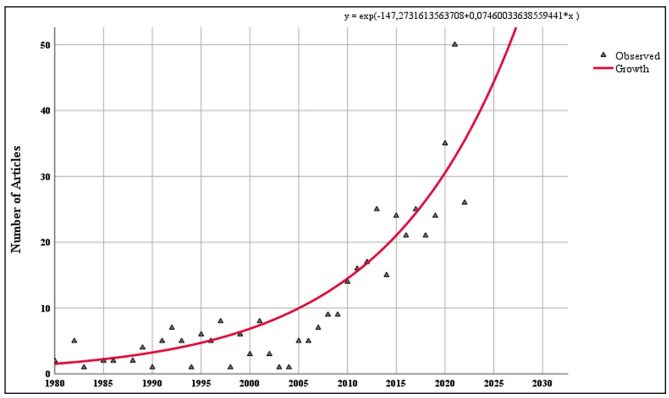

Figure 1. Distribution of geriatric malnutrition publications by year and projection of articles in the next years using the exponential growth model

Active Countries

The top 10 nations with the most papers on geriatric malnutrition were Spain (42, 9.8%), USA (42, 9.8%), France (36, 8.4%), Italy (32, 7.5%), People's Republic of China (30, 7.0%), Germany (29, 6.8%), Turkey (26, 6.0%), Australia (24, 5.6%), Japan (23, 5.4%), Netherlands (19, 4.5%) (**Figure 2**). The total link strength scores of 26 nations that contributed at least five articles to 60 nations' publications on geriatric malnutrition and had international collaboration among their authors were measured. **Figure 3** shows the collaborative clustering network map using these scores (Turkey, Poland, and South Korea did not have author links to any other country and were excluded from the map). According to the results, seven different clusters were formed (Cluster 1: Belgium, Canada, England, France, Japan, Lebanon, Cluster 2: Iran, Norway, Sweden, Taiwan, USA, Cluster 3: Austria, Germany, Netherlands, Cluster 4: Malaysia, People's Republic of China, Singapore, Cluster 5: Brazil, Spain, Cluster 6: Italy, Switzerland, Cluster 7: Australia, India). **Figure 3** also depicts the internal collaboration density map.

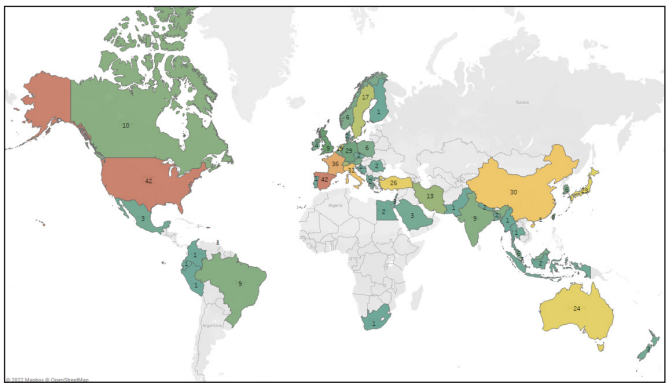

Figure 2. Global distribution of publications on geriatric malnutrition

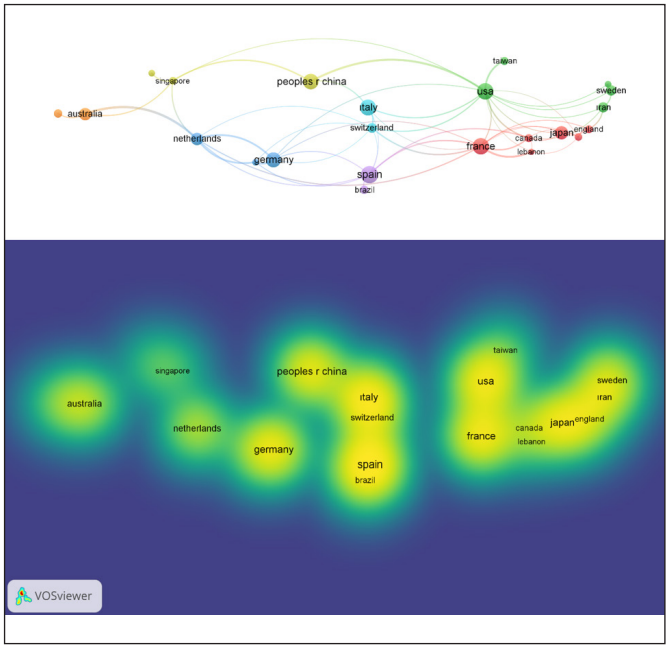

Figure 3. Network visualization map of cluster analysis and density map on worldwide cooperation on geriatric malnutrition

Correlation Analysis of Publication Count and Gross Domestic Product

There was a statistically significant correlation between the number of publications produced by nations on geriatric malnutrition and their Gross Domestic Product (GDP) and GDP per capita (r=0.611, p<0,001; r=0.296, p=0,033).

Active Authors

The top ten most active and prolific authors who have published the most articles on geriatric malnutrition are Volkert D. (11, 2.6%), Sieber CC. (7, 1.6%), Maier AB. (5,1.2%), Miller M. (5, 1.2%), Reijnierse EM. (5, 1.2%), Smoliner C. (5, 1.2%), Eschbach D. (4, 0.9%), Hebuterne X. (4, 0.9%), Isenring E (4, 0.9%), and Lipschitz DA. (4, 0.9%).

Active Institutions

The top ten institutes that generated the most publications on malnutrition in the elderly between the years 1980 and 2022 were UDICE French Research Universities (16, 3.7%), University of Erlangen Nuremberg (10, 2.3%), Vrije Universiteit Amsterdam (9, 2.1%), Assistance Publique Hopitaux Paris (8, 1.9%), Institut National de la Sante et de la Recherche Medicale Inserm (8, 1.9%), Tehran University of Medical Sciences (8, 1.9%), University of Melbourne (8, 1.9%), Flinders University South Australia (7, 1.6%), Royal Melbourne Hospital (6, 1.4%), Universite Paris Cite (6, 1.4%).

Active Journals

A total of 427 publications about geriatric malnutrition have been published in 218 distinct journals. **Table 1** includes the top 40 journals that published four or more articles, the total number of citations received by the journals, and the average number of citations per article.

Citation Analysis

Table 2 displays the 20 papers with the highest citation count among the 427 articles published between 1980 and 2022. The annual average number of citations is then presented in the final column of **Table 2**.

Co-citation Analysis

The reference sections of all 427 examined publications included a total of 10,570 studies. The top 10 publications with the highest number of co-citations (above 20) were as follows: Kondrup (2003) (Number of co-citations (NC): 69), Rubenstein (2001) (NC: 51), Vellas (1999) (NC: 49), Kaiser (2010) (NC: 47), Guigoz (1996) (NC: 40), Guigoz (2006) (NC: 39), Folstein (1975) (NC: 34), Guigoz (2002) (NC: 33), Cederholm (2015) (NC: 33), Kaiser (2009) (NC: 32).

Trending Topics

In the 427 publications published on geriatric malnutrition, 697 unique keywords were used. **Figure 4** presents the cluster network visualization for 62 keywords that appeared in at least four independent publications. **Figure 4** also depicts a network map for trend visualization and a network map for citation visualization for those 62 keywords.

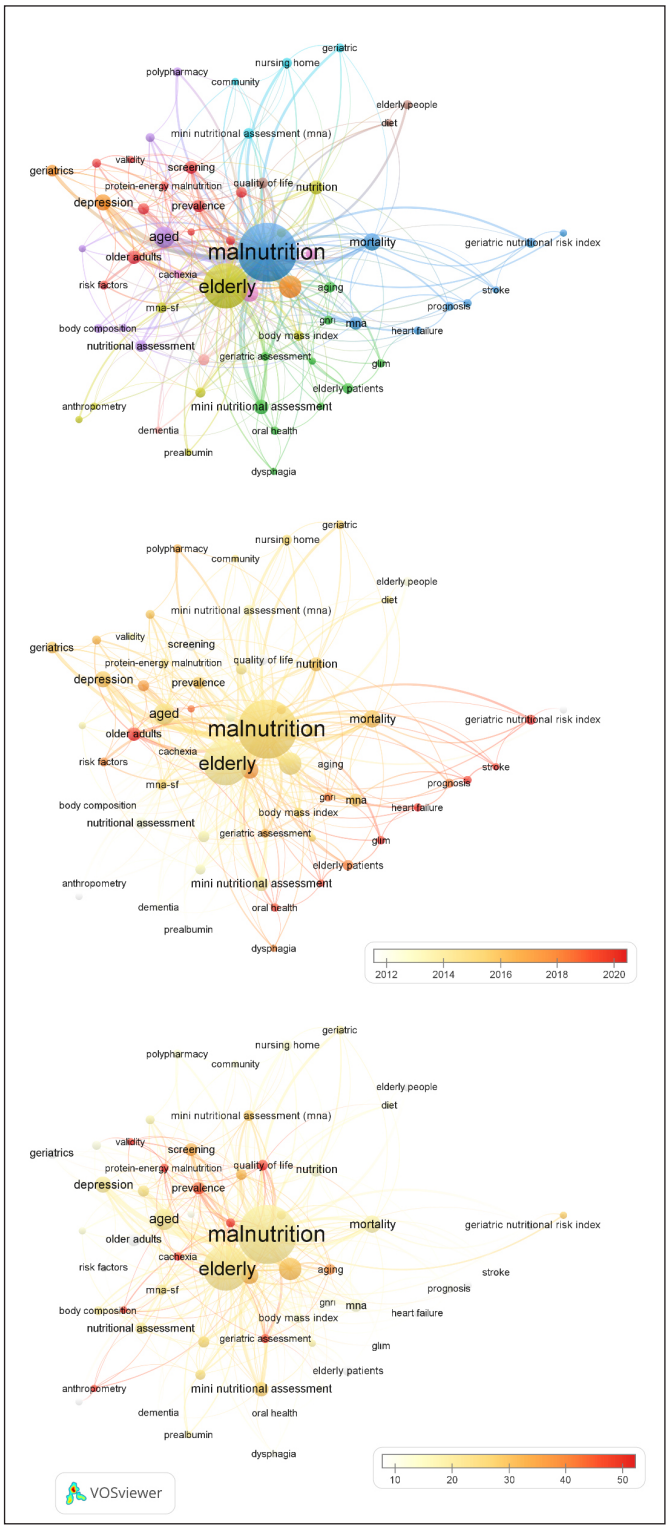

Figure 3. Keyword cluster analysis, keyword trend, and citation network visualization map of geriatric malnutrition

Table 1. The top 40 most active journals with articles on geriatric malnutrition (RC: Record Count, C: Number of Citations, AC: Average Citation per Manuscript)

Journals	RC	C	AC	Journals	RC	C	AC
Clinical Nutrition	23	1453	148.18	Zeitschrift fur Gerontologie und Geriatrie	4	42	3.38
Journal of Nutrition Health & Aging	19	733	65.1	Geriatrics & Gerontology International	4	45	7.6
Nutrients	16	151	74.7	Clinical Nutrition Espen	4	46	9
Nutricion Hospitalaria	12	188	19.43	BMC Geriatrics	4	31	6.83
Nutrition	10	379	20.58	British Journal of Nutrition	4	339	22.84
European Journal of Clinical Nutrition	10	423	71.77	Iranian Journal of Public Health	4	68	8.41
Asia Pacific Journal of Clinical Nutrition	9	109	14.18	Plos One	3	68	11.12
Journal of the American Geriatrics Society	7	519	18.42	Journals of Gerontology Series A-Biological Sciences and Medical Sciences	3	132	7.4
Aging Clinical and Experimental Research	7	88	11.69	Journal of the Academy of Nutrition and Dietetics	3	80	11.6
Nutricion Clinica Y Dietetica Hospitalaria	6	6	1.56	BMJ Open	3	76	15.19
Age and Ageing	6	310	12.63	Nutrition & Dietetics	3	65	7.15
Archives of Gerontology and Geriatrics	5	126	14.21	Experimental Gerontology	3	12	3.5
Nutrition Clinique et Metabolisme	5	5	1.55	International Journal of Nursing Studies	3	116	12.58
Clinical Interventions in Aging	5	52	8.94	Journal of Advanced Nursing	3	253	10.92
Public Health Nutrition	5	106	13.73	Ciencia & Saude Coletiva	2	17	2.25
Progress in Nutrition	5	6	2	Journal of the American College of Nutrition	2	76	6.37
European Geriatric Medicine	5	60	12.52	Gerontology	2	56	4.13
Medicina Clinica	5	100	4.83	International Journal of Environmental Research and Public Health	2	10	3.33
Australian and New Zealand Journal of Medicine	4	29	1.12	Journal of the American Medical Directors Association	2	208	17.32
Frontiers in Nutrition	4	31	6.5	International Journal of Food Sciences And Nutrition	2	8	0.3

Table 2. The top 20 most cited articles on geriatric malnutrition according to total citations (PY: Publication year, TC: Total citation count, AC: Average citations per year)

No	Article	Author Journal	PY	TC	AC
1	Identifying the elderly at risk for malnutrition - The Mini Nutritional Assessment	Guigoz, Y et al. Clinics in Geriatric Medicine	2002	611	29.1
2	Protein and energy supplementation in elderly people at risk from malnutrition	Milne, Anne C. Cochrane Database of Systematic Reviews	2009	356	25.4
3	Malnutrition in the elderly: A narrative review	Agarwal, E. Maturitas	2013	256	25.6
4	'Malnutrition Universal Screening Tool' predicts mortality and length of hospital stay in acutely ill elderly	Stratton, RJ British Journal of Nutrition	2006	230	13.5
5	Malnutrition in the elderly and its relationship with other geriatric syndromes	Saka, Bulent Clinical Nutrition	2010	199	15.3
6	A concept analysis of malnutrition in the elderly	Chen, CCH Journal of Advanced Nursing	2001	191	8.68
7	Malnutrition in institutionalized elderly - how and why	Keller, HH Journal of The American Geriatrics Society	1993	175	5.83
8	Outcome of protein-energy malnutrition in elderly medical patients	Cederholm, T American Journal of Medicine	1995	172	6.14
9	Prevalence of malnutrition and analysis of related factors in elderly patients with COVID-19 in Wuhan, China	Li, Tao European Journal of Clinical Nutrition	2020	157	52.3
10	Protein-energy malnutrition in elderly medical patients	Constans, T Journal of The American Geriatrics Society	1992	151	4.87
11	Malnutrition and depression among community-dwelling elderly people	Sarria Cabrera, Marcos Aparecido Journal of The American Medical Directors Association	2007	139	8.69
12	Sarcopenia and malnutrition in acutely ill hospitalized elderly: Prevalence and outcomes	Cerri, Anna Paola Clinical Nutrition	2015	127	15.9
13	Undiagnosed malnutrition and nutrition-related problems in geriatric patients	Volkert, D. Journal of Nutrition Health & Aging	2010	117	9
14	Understanding the gastrointestinal tract of the elderly to develop dietary solutions that prevent malnutrition	Remond, Didier Oncotarget	2015	114	14.3
15	Malnutrition in elderly: social and economic determinants	Donini, L. M. Journal of Nutrition Health & Aging	2013	110	11
16	Effects of food fortification on nutritional and functional status in frail elderly nursing home residents at risk of malnutrition	Smoliner, Christine Nutrition	2008	108	7.2
17	Prevalence and determinants for malnutrition in geriatric outpatients	van Bokhorst-de van der Schueren, Marian A. E. Clinical Nutrition	2013	106	10.6
18	Evaluation of the efficacy of six nutritional screening tools to predict malnutrition in the elderly	Poulia, Kalliopi-Anna Clinical Nutrition	2012	103	9.36
19	Malnutrition and associated factors in elderly hospital patients: A Belgian cross-sectional, multicentre study	Vanderwee, Katrien Clinical Nutrition	2010	102	7.85
20	Malnutrition in the hospitalized geriatric-patient	Bienia, R Journal of The American Geriatrics Society	1982	97	2.37

DISCUSSION

Malnutrition is described as a deficit, excess, or imbalance of energy, protein, and other nutrients that produce observable detrimental consequences on tissue shape and function, as well as clinical outcomes. Malnutrition is a geriatric syndrome that is frequently seen in up to 50% of the geriatric population (15). Geriatric malnutrition is associated with increased morbidity and mortality, and early identification of individuals at risk is favorable for minimizing morbidity and mortality, hospitalization requirements, and expenses (16,17).

Malnutrition in geriatric patients is a crucial healthcare problem, especially in developed and aging countries. However, our research data shows that between 1980 and 2005, there were not many publications on malnutrition in the aging population. Especially compared to other similar research areas like total parenteral nutrition, geriatric malnutrition has a small body of knowledge even of this day (18). There has been an upward trend in the publications about geriatric nutrition since 2005, with the sole decrease being in 2022. We attribute this decrease to the pandemic of 2020 and 2021. Evaluation of non-linear regression analysis reveals that the number of publications will continue to increase exponentially in the years to come. With an average citation count of 24.62 citations per article, geriatric nutrition shows its importance even though the total number on this subject is relatively low.

When analyzing the distribution of publications by country, the top 10 countries with the most publications on geriatric malnutrition were all developed nations. This study's correlation analysis shows a substantial link between article productivity and economic development indicators, revealing that economic development level affects geriatric nutrition publication output. In addition, bibliometric studies on various medical topics have been shown in the literature to increase publishing activity (11,19). GDP and GDP per capita are correlated with publication count, but interestingly the correlation is much more robust with GDP than GDP per capita; this suggests that a country's income is more critical than a household's income for scientific publications about geriatric malnutrition.

When the density map was created based on collaboration between nations, the countries with the highest level of cooperation were Spain, Italy, USA, China, and Germany. When the co-authorship of nations on geriatric malnutrition is investigated, it seems that most countries collaborated based on their geographical location (Malaysia-China-Singapore/Germany-Austria-Netherlands/Italy-Switzerland). However, also there were curious clusters like USA-Iran-Norway-Sweden-Taiwan and England-France-Canada-Belgium-Japan-Lebanon. Turkey, South Korea, and Poland were not in cooperation with any other country but had significantly contributed to research and publication.

Clinical Nutrition was the journal with the most published articles to date, followed by Journal of Nutrition Health & Aging, Nutrients, Nutricion Hospitalaria, Nutrition, European Journal of Clinical Nutrition, Asia Pacific Journal of Clinical Nutrition, Journal of the American Geriatrics Society, respectively. When the average number of citations per article for journals was investigated, Clinical Nutrition was again the first journal with the most citations per article (148.18 citations per article). Nutrients, European Journal of Clinical Nutrition, Journal of Nutrition Health & Aging, British Journal of Nutrition, Nutrition, Nutricion Hospitalaria, Journal of the American Geriatrics Society, Journal of the American Medical Directors Association, and BMJ Open were the other nine journals in the top ten most cited journals per article, respectively.

The most cited study was "Identifying the elderly at risk for malnutrition - The Mini Nutritional Assessment" published in Clinics in Geriatric Medicine in 2022 by Guigoz, Y., and had 611 total citations and an average of 29.1 citations per year (20). The second most cited study was "Protein and energy supplementation in elderly people at risk from malnutrition" by Milne, Anne C. in the Cochrane Database of Systematic Reviews, with 356 total citations and an average of 25.4 citations per year (21). The third was "Malnutrition in the elderly: A narrative review" by Agarwal, E., published by Maturitas in 2013, with 256 total citations and an average of 25.6 citations per year (2). However, interestingly, "Prevalence of malnutrition and analysis of related factors in elderly patients with COVID-19 in Wuhan, China" by Li, Tao in European Journal of Clinical Nutrition was the publication with the highest average citation count with 52.3 citations per year after it published (22), we attribute this to the relevancy of issues in the elderly population infected with Covid-19 in the pandemic era.

When the keyword analysis findings were examined, it was found that the clustering analysis classified geriatric malnutrition subjects into nine distinct clusters. Malnutrition, elderly, nutritional status, aged, mini nutritional assessment, mortality, sarcopenia, depression, nutrition, and older adults were the most frequently used keywords. According to the data, after our search keywords were excluded from the list, the terms studied in recent years were Geriatric Nutritional Risk Index, malnutrition risk, stroke, heart failure, prognosis, GLIM, cancer, and prevention. Protein-energy malnutrition, cachexia, quality of life, geriatric assessment, validity, hospital, aging, anthropometry, sarcopenia, and mini nutritional assessment were the most frequently cited terms.

Only one bibliometric research was discovered while evaluating the literature on geriatric nutrition (12). While it had more publications in analysis, it included meeting abstracts and letters to the editor, and some search criteria were not precisely specific to the issue at hand, so we believe this focused and concise investigation supplements that work. Also, as a critical difference from other similar work, this article's time scope was between 1980 and 2022. Since citation and co-citation analyses could not be done in the PubMed and Scopus databases, they were left out of the analysis. WoS is favored over competing databases because it includes citation analysis and indexes articles from higher-quality publications.

CONCLUSION

Malnutrition in the elderly population is a severe problem globally, notably in aging countries. Early diagnosis, prevention, rehabilitation, and, most importantly, knowledge are vital to reducing malnutrition's effects on the geriatric population. Geriatric malnutrition is one of the current trending research topics and seems more relevant every year in the aging world. We believe this article will lead to more research and publications on this critical topic.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethics committee approval is not required in this bibliometric study.

Informed Consent: Our research is a retrospective worldwide data analysis. Thus, informed consent is not required.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the manuscript, and they have approved the final version.

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Original Article

MEDICINE PALLIATIVE CARE

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J Med Palliat Care 2023; 4(2): 158-162

Are the correlation results of HPV positive cases with cervical smear always consistent?

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ABSTRACT:

Aim: Cervical cancer is a type of genital cancer which come second after breast cancer in women and may cause death. However, it can be prevented with screening tests by ensuring early diagnosis. Most of cervical cancers (99.7%) are associated with Human Papilloma Virus (HPV) and it is known that HPV must be present for the generation of cervical cancer. Thus, 70% of the patients have been found to be positive for HPV-16 and HPV-18. Both the association with cervical cancer and HPV and data related to development of cancer and dysplasia was researched retrospectively in this study. It was aimed to analyze and use the results by examine if the smear results of the patients and the HPV results are compatible in all HPV positive cases.

Material and Method: 1050 patients who were examined by gynecologist and taken Pap smear test at the end of the examination during July 2020 and March 2022, were included in our study. In all cases the Pap test was re-evaluated by the same pathologist using the 2014 Bethesda System. High-risk HPV (HR HPV) DNA (HPV types 16,18,31,33,35,39,45,51,52,56,58,59,66,68) tests results, applied to the patients at an external center, were reviewed. Results of patients diagnosed as LSIL, HSIL and cervical cancer by Pap smear test were evaluated again beside HPV DNA analyses and their clinical information. Chi-square test was used for statistical analysis. $p<0.05$ values were considered statistically significant.

Results: Of 1050 patients, 139 had LSIL, 170 had HSIL, and 112 had cervical cancer. The highest incidence of LSIL, HSIL and cancer was observed in the 30-39 age group, while the rate of these diseases was lower in the 50-59 age group compared to other groups. In addition, all patients with SIL and cervical cancer had smoking history. HR HPV DNA test was positive in 240 of 1050 patients. 56 patients diagnosed as LSIL and 89 patients diagnosed as HSIL by Pap smear had positive HR HPV DNA test results. HR HPV DNA positivity was reported in 74 of 112 patients with cervical cancer. In 21 patients who had normal smear test were detected HR HPV DNA positivity. 17 of these patients were in the 30-39 age group and 4 of them were in the 40-49 age group.

Conclusions: Because of all 112 patients with cancer were not HR HPV positive and the smear results of 21 HR HPV positive patients were normal, our study serves an example for studies to show that the results of smear and HPV DNA in cervical cancer are not always compatible.

Keywords: Cervix, cancer, HPV, screening

INTRODUCTION

Cervical cancer is ranked as the 4th most cancer among women worldwide. Its incidence and mortality have been gradually decreasing due to the development of early diagnosis and treatment methods and becoming widespread of cytological screening programs (1-5).

Pap smear test, which is used in early diagnosis, has high sensitivity and is easy to apply. It is low-cost and innocuous test, which also reduces the treatment burden, morbidity and mortality. Studies to prevent cervical cancer by using different screening methods are gaining importance in worldwide. Screening programs and strategies vary among countries (6-8,9).

In USA screening is started within the first three years following the age of onset of sexual intercourse or at the age of 21 at the latest. The screening begins at the age of 20 in Germany, for UK this age is 25 years. Screening is maintained until the age of 70 years. In Finland, which can be given as a more successful example, screening begins at the age of 30 and ceases at the age of 60 (9,10-12). Considering the conditions of our country, the achievable target is population-based screening, which starts at the age of 30 and ends at the age of 65 in women. Studies are going on to develop cervical cancer screening programs with various methods such as HPV DNA screening and to spread the screenings to the general population (13,14).

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The HPV DNA testing is the most objective and reproducible one among the current cervical screening tests. Evaluation of cervical cytology and simultaneous HPV DNA analysis is named as co-test. It is the most accepted screening method in women over the age of 30 (15,16).

Primary HPV DNA screening provides earlier detection of cervical lesions compared to cytology, but its effect on treatment options and adverse obstetric outcomes has not been comprehensively studied (16-18). It is expected to reduce both the risk of cancer and potential complications associated with cervical cancer screening by starting HPV DNA screening at the age of 20 (18,19).

MATERIAL AND METHOD

Research Design and Case Selection

This descriptive, retrospective study was conducted after the approval of the Kırıkkale University Non-invasive Clinical Researches Ethics Committee (Date: 29.06.2022, Decision No: 2022.06.33). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. 1050 of 2410 patients between the ages of 20 and 59 applied in the period of July 2020 and March 2022 to the Department of Obstetrics and Gynecology of Kırıkkale University Faculty of Medicine with complaints of abnormal vaginal bleeding and abdominal pain were selected as study group. Patients were divided into four age groups as follows: 20-29, 30-39, 40-49 and 50-59. Medical records of patients was searched and for each age group number of pregnancy and parity and whether they smoked were investigated.

Cases whose gynecological examinations and smear test sampling were performed were included in the study.

In addition, although not considered as a definite risk factors for cervical cancer, blood pressure measurement values in the file information and Hemogram and blood cholesterol levels measurements in biochemical analyzes were evaluated and large data sets were created.

In each age group, according to the results of the smear test the number of patients diagnosed with Low grade squamous intraepithelial lesion (LSIL), High grade squamous intraepithelial lesion (HSIL) and cervical cancer was determined, and the cases that were positive and negative in the HPV DNA test were analyzed. The data of the selected patients for the analysis and the results were checked by the pathologist. Statistical analyzes and calculations were performed by means of IBM SPSS Statistics 21.0 program (IBM Corp. Released 2012. IBM SPSS Statisticsfor Windows, Version 21.0. Armonk, NY: IBM Corp.). Categorical variables were compared with the Chi-Square Test. A p-value below 0.05 were considered statistically significant.

Analysis of Smear and HR HPV DNA

For cytological analysis, the previously diagnosed cases taken with the conventional method and stained by applying normal Pap test staining procedures were removed from the archive and re-evaluated and interpreted based on the 2014 Bethesda System by the same pathologist. All datas were noted by forming groups as inflammation, LSIL, HSIL and cancer. By reviewing the tests for HPV DNA, two groups were recorded as positive and negative.

In high-risk HPV DNA (HR HPV DNA) analyzes, measurements were made for HPV types 16,18,31,33 ,35,39,45,51,52,56,58,59,66,68 and specific genotypic data were obtained with the qualitative multiplex assay method. Analyses were performed at Cancer Early Diagnosis Screening and Training Center.

Reassessment with physical examination findings was performed for the cases who had negative smear result with positive HPV DNA for any type. In addition, the cases diagnosed as LSIL, HSIL, and cancer without Hr HPV DNA were reanalyzed. There were no significant physical examination and biochemical analysis findings that would affect the results. The distribution of patients with or without cervical cancer was shown in **Figure 1**.

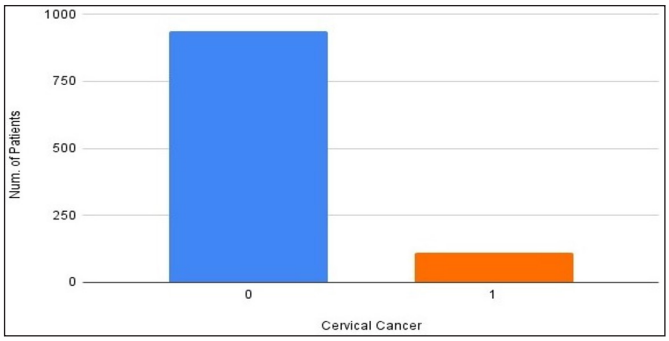

Figure 1: The distribution of cases according to having cancer (112 of 1050 had cervical cancer)

RESULTS

Considering the distribution of 1050 patients included in our study by age groups; There were 300 patients in the 20-29 age group, 360 patients in the 30-39 age group, 264 patients in the 40-49 age group and 126 patients in the 50-59 age group.

For the study group, the mean age was 37.23 ± 9.26 years. When the number of pregnancies of the patients was examined, the maximum number of pregnancies was five. However, the number of women who gave birth twice was the highest. In terms of distribution by age groups, it was highest in the 30-39 age group (n=162). In addition, the number of patients giving birth twice was higher in all age groups (n=364).

The least number of pregnancies was detected in the 20-29 age group. While there were 147 patients with one pregnancy, there was no patient with a fourth pregnancy in this group.

At the same time 20-29 age group had the lowest birth rate in the number of births. While 84 of 300 patients in this group gave birth twice, there was not found any patient being pregnant for four times.

Pregnancy and birth numbers by age groups were given in **Tables 1** and **2**.

Table 1. Number of pregnancies by age groups of patients

		Number of pregnancies					
Age range	Number (n)	0	1	2	3	4	5
20- 29	300	41	147	92	20	-	-
30-39	360	10	60	162	109	17	2
40-49	264	4	27	102	98	32	1
50-59	126	2	2	16	53	51	2

Table 2. Number of births by age groups of patients

		Number of birth				
Age range	Number (n)	0	1	2	3	4
20-29	300	41	145	84	13	-
30-39	360	10	60	162	109	17
40-49	264	4	27	102	96	30
50-59	126	2	2	16	50	51

There did not seen birth in any of the women who were pregnant for five times.

In addition, in cases where pregnancies in other age groups did not end with delivery and in some inconsistencies in the number of pregnancies and births, certain information about the possible termination of these pregnancies before delivery could not be reached.

Patients diagnosed as LSIL and HSIL in Pap test and HPV DNA results are shown in Tables 3 and 4 in **Figures 2** and **3**).

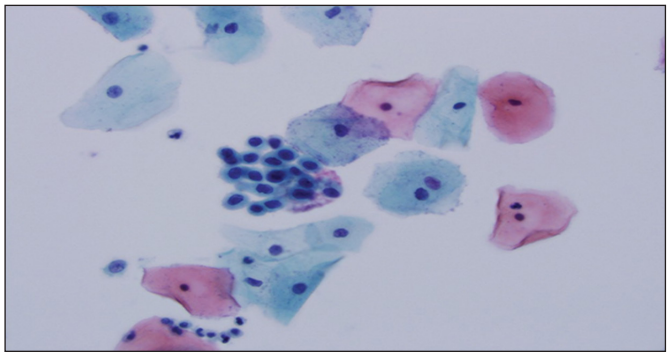

Figure 2: Low Grade Squamous Intraepithelial Lesion conventional Pap test (PAP x20)

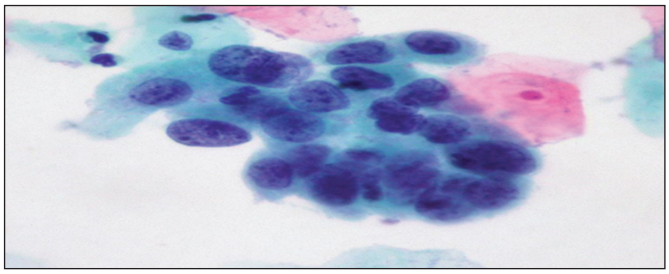

Figure 3: High Grade Squamous Intraepithelial Lesion conventional Pap test (PAP x40)

LSIL was detected in 139 patients. While the highest incidence of LSIL was detecetd in the 30-39 age group (n=47) the lowest incidence was detected in the 50-59 age group (n=22). HSIL was seen in 170 patients. HSIL was observed in 62 patients in the 30-39 age group at most (**Table 3** and **4**).

Table 3. Patients diagnosed with LSIL in Pap test and HPV DNA positivity rates

LSIL (*HPV DNA positive cases) p= 0.704			
Age range	Number n (%)	Pap test LSIL(+) HPV DNA(+) (n- %)*	Pap test LSIL (-) n
20-29	300 (31.50%)	34 (18-52.9%)*	266
30-39	360 (28.5%)	47 (20-42.5%)*	313
40-49	264 (25.1%)	36 (10-27.7%)*	228
50-59	126 (12%)	22 (8-36.3%)*	104

The rates and numbers given in black are calculated for patients diagnosed with LSIL in Pap test and HPV DNA positivity number and rates are given in red.

Table 4. Patients diagnosed with HSIL in Pap test and HPV DNA positivity rates

HSIL (*HPV DNA positive cases) p= 0.376			
Age range	Number n (%)	Pap test HSIL (+) HPV DNA (+) (n-%) *	Pap test HSIL (-) n
20-29	300 (31.50%)	38 (30-78.9%)*	262
30-39	360 (28.5%)	62 (35-56.4%)*	298
40-49	264 (25.1%)	50 (18-36%)*	214
50-60	126 (12%)	50 (18-36%)*	116

The rates and numbers given in black are calculated for patients diagnosed with HSIL in Pap test and HPV DNA positivity number and rates are given in red.

Cervical cancer was found in 112 of 1050 patients according to smear test results. While the highest incidence for cancer was detected in 30-39 age group with 45 patients and the lowest incidence was seen in 50-59 age group with 16 patients (**Table 5**).

Table 5. Patients diagnosed with cervical cancer in Pap test and HPV DNA positivity rates

Cervical Cancer (*HPV DNA positive cases) p=0.047			
Age range	Number n (%)	Pap test cancer (+) HPV DNA (+) (n-%)*	Pap test cancer (-) n
20-29	300 (31.50%)	13 (10-7.69%)*	287
30-39	360 (28.5%)	45 (40-88.8%)*	315
40-49	264 (25.1%)	38 (20-52.63%)*	226
50-59	126 (12%)	16 (4-25%)*	110

The rates and numbers given in black are calculated for patients diagnosed with cervical cancer in Pap test and HPV DNA positivity number and rates are given in red.

Considering that smoking is a risk factor in cervical cancer, the number of patients had history of smoking was investigated and it was observed that 478 patients were smoker. It was determined that 139 patients diagnosed with LSIL, 170 patients diagnosed with HSIL and 112 patients diagnosed with cervical cancer were all smokers.

HPV DNA test results of all patients were grouped for each age groups as negative and positive. HPV DNA positivity was seen in 240 of 1050 patients. Distribution of positivity by age groups was as follows: 58 in 20-29, 112 in 30-39, 52 in 40-49 and 18 in 50-59.

In 56 of 139 patients diagnosed with LSIL by Pap test, in 89 of 170 patients diagnosed with HSIL, in 74 of 112 patients diagnosed with cancer; HR HPV test was positive in 219 patients in total. There was a significant relationship between cervical cancer age groups and HR HPV DNA positivity (p=0.047).

Pap test results were normal in the repeat controls of 21 patients with positive HR HPV DNA tests.

In addition, the HR HPV DNA test was found to be negative in 38 patients diagnosed with cervical cancer. The percentage values of the data are shown in Table.3.

HR HPV DNA test was negative in 810 patients in total. The distribution of HR HPV DNA negative patients by age group is as follows: 242 patients in the 20-29 age group, 148 patients in the 30-39 age group, 212 patients in the 40-49 age group and 108 patients in the 50-59 age group.

DISCUSSION

Cervical cancer is the second most common cancer in women after breast cancer, causing a woman death every two minutes in the world (1,2). There are more than 400,000 cases of cervical cancer in the world annually. Approximately 250,000 patients die from cervical cancer each year (2,4,6). It is most common in the 50-59 age group. It is known that dysplastic changes in the cervix begin at an earlier age, in the 30-39 age group. Developing technologies, changes in lifestyles, the younger population being freer and changing partners frequently, the prevalence of viral infections cause a decrease in the age of dysplasia in the cervix (5,7).

The role of HPV in etiology is becoming increasingly important. The rate of cancer development in women infected with the virus in the high-risk group is higher than in other groups. So, HR HPV DNA analyzes are also included in cancer screening programs along with pap test (9-11).

In the study of Clavel et al. (12) they investigated the risk of developing LSIL over time in normal HPV negative smears and the potential of HR HPV types to develop LSIL. They reported that it would be correct to use Pap smear test and HR HPV DNA analyzes together.

There can be cases who have normal Pap smear results with HR HPV DNA positive. Contrary to this, there may be cases who have lesion detected by colposcopy or Pap smear and not infected HR HPV. In the literature, there are studies in which HR HPV DNA negativity was detected mostly in postmenopausal women (13,16).

In our study, there were patients (21 patients) whose HR HPV DNA analyses were positive and pap test smear results were normal for years.

Zergeroğlu et al. (18) reported that it was not appropriate to establish a screening program by performing HPV analysis alone in their study on menopausal patients among 5180 patients. They also showed that correlating Pap test and HR HPV DNA was practical to increase sensitivity and specificity and to prevent false positive and false negative results.

Öztürk et al. (16) emphasized that cervical cancer may develop in HPV-negative cases in their study. In our study, 38 of 112 cases with cervical cancer were found to be HR HPV DNA negative.

In addition, it is a fact that Pap test intake inadequacies to mislead in screening results. Therefore, diagnostic options with different methods are needed. Hosono et al. (15) reported in their study that inadequate pap test screenings in Japanese women affected the results.

In our study, it is important that only 74 of 112 patients diagnosed as cervical cancer had a positive HR HPV DNA test, and that the results of 21 patients with positive HPV analyses were normal after regular Pap test and colposcopic analyses. These results show that Pap test and HR HPV DNA analysis are not always correlated.

Sharif performed DNA analysis with PCR test to detect HR HPV type, in patients with suspected cervical neoplasia in his study. He showed that neoplasia detection rates increased in cases which was correlated with Pap test results. In addition, in his study, he found that this rate increased even more in cases in which the presence of neoplasia was supported in the biopsy as a result of colposcopic analysis performed (20).

In the retrospective study Song et al. (21) they analyzed the records of 4117 women who were selected from 33,531 Korean women who were performed Pap test, HPV analysis, cervicography, and colposcopic biopsy. They found the prevalence of cervical intraepithelial neoplasia 2 (CIN 2) cases to be 10.8% and the rate of HR HPV positive cases to be 61.0% by Pap test. With the

application of cervicography in addition to Pap test for the detection of CIN 2 cases, this rate increased to 97.5%, while the HR HPV positivity rate was 93.7%. These results support that it is not appropriate to use only one test alone for the diagnosis of cervical neoplasia.

In another study, Song et al. (22) showed that when Pap test and HPV tests were used together, they achieved excellent performance in detecting CIN or cervical cancer, and the combined use of the tests significantly reduced false negative errors.

CONCLUSION

In our study, similar to these studies in the literature, we concluded that it is not appropriate to perform Pap test or HR HPV DNA analysis alone in the detection of cervical neoplasia. We suggest that it would be more accurate to evaluate HR HPV DNA analysis and Pap test together in the detection of cervical neoplasia.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of KKU Faculty of Medicine Hospital Clinical Research Non-invasive Clinical Researches Ethics Committee (Date: 29.06.2022, Decision No: 2022.06.33).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the manuscript, and they have approved the final version.

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Original Article

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Protective ileostomy in rectal cancer surgery-is it really temporary?

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ABSTRACT

Aim: This single-center retrospective study aimed to evaluate the rate of protective ileostomy closure in patients with rectosigmoid junction/rectal cancer and to investigate the factors that prevent ileostomy reversal.

Material and Method: Patients with rectal cancer treated with/without neoadjuvant chemoradiotherapy were included in this study. All were treated with anterior rectal resection and temporary protective ileostomy creation. Decision for ileostomy closure was brought upon predefined ileostomy closure protocol.

Results: Total number of 115 patients (17 with rectosigmoid junction and 98 with rectal cancer) were operated. Neoadjuvant chemoradiotherapy was conducted in 90 of them. Ileostomy closure rate was 73.9%. Mean time for stoma closure in patients with chemoradiotherapy conduction was 227.8 days, while in the rest, time was shorter (168.3 days), without statistical difference. Multivariate analysis revealed that endoscopic examination of the anastomosis during its creation was independent prognostic factor that affected ileostomy closure.

Conclusion: More than one quarter of the patients with protective ileostomy experienced non-closure of their stoma due to various events after index rectal cancer surgery. Endoscopic examination of the anastomosis during its creation presented as independent factor affecting ileostomy closure.

Keywords: Loop ileostomy, protective ileostomy, ileostomy reversal, ileostomy closure, rectal cancer

INTRODUCTION

Temporary enteric diversion with loop ileostomy in patients treated with sphincter-sparing rectal surgery for rectal cancer reduces the devastating septic consequences from eventual anastomotic leakage and the need for reoperation (1, 2). It also reduces significantly the postoperative mortality rates after the index surgery for rectal cancer (3). Protective ileostomy existence has certain negative impact on the quality of life and is associated with stoma-related morbidity (skin irritation, stoma-dressing leakage, dehydration, renal function alteration with subsequent chronic renal failure) (4-7). On contrary, the stoma closure caries risk with serious postoperative morbidity and mortality rates no matter the timing for closure (8-10). Significant number of the patients with "temporary" diverting ileostomy never experience their stoma closure due to various reasons (9). This study aimed to investigate the rate of non-closure for temporary ileostomy and the factors affecting this undesirable outcome.

MATERIAL AND METHOD

The study was carried out with the permission of İstanbul Prof. Dr. Cemil Taşcıoğlu City Hospital Clinical Researches Ethics Committee (Date 14.11.2022; Decision No: 322). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients and Index Surgery Protocol

Patients treated for rectal cancer with and without prior neoadjuvant chemoradiotherapy (CRT) were included in this retrospective single-center study in the period of 2017-2022. Inclusion criteria were set for patients with created protective "loop" ileostomy at index surgery for rectal cancer and the ones that were subsided to ileostomy closure in the same institution. Depending on the tumor localization, all patients were operated with anterior or low anterior rectal resection (open and laparoscopic). Splenic flexure was not routinely mobilized and the decision was made based on the length of the colon and localization of tumor. After

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colon resection, anastomosis creation with double stapled technique followed. Linear single use reloadable stapler was used for distal resection of the specimen. Circular stapler was employed for the anastomosis creation. All of the created anastomoses were tested with air-bubble test. In part of the cases, on surgeons' demand, rectoscopy with flexible rectosigmoidoscope was performed for the confirmation of the viability of bowel mucosa, patency of anastomosis and possible anastomotic hemorrhage presence. Creation of protective "loop" ileostomy followed (11).

Ileostomy Closure Protocol

Prior to ileostomy closure surgery, routine colonoscopy was performed by the surgeon. In cases of anastomotic stenosis, endoscopic balloon-dilatation was indicated. The ones with successful post dilatation outcome were subsided to ileostomy closure. Ileostomy reversal was done on ileostomy site with standard elliptical excision of the skin (12). In some patients, median laparotomy was forced due to heavy intestinal adhesions. The intestinal continuity was performed with side to side linear stapled anastomosis or with end to end hand-sewn technique.

Data Collection and Statistics

Patient and surgery data were collected (age, gender, conduction of neoadjuvant CRT, preoperative endoscopy findings, distance of anastomosis from the anal verge, postoperative complications and length of stay for the ileostomy closure admission period). Part of the patients were excluded from the study due to the COVID-19 pandemic obstacles and due to ileostomy reversal surgery performed in other centers. IBM SPSS, version 25 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Variable distribution normality was tested with Kolomogorov-Smirnof test. Chi-square test was used for two categorical and Student's T test for two numerical variables comparison. Multivariate logistic regression analysis were performed to test the relation between the variables in order to point on the factors affecting the non-closure of ileostomy. P value of less than 0.05 was considered significant.

RESULTS

Total number of 115 patients with rectal/rectosigmoid junction cancer were operated during the study period and ended with the construction of temporary protective ileostomy. Mean age of the patients was 61. Majority were male patients (83), and the rest 32 were females. According to tumor localization, rectosigmoid junction cancer presented in 17 cases, while the rest 98 were rectal cancer cases subdivided due to tumors' distance from the anal verge (upper rectum, middle rectum and low rectum). Preoperative clinical magnetic resonance imaging (MRI) stage I was established in 4 patients, and in 5 patients with Stage IV. The rest of them (106) presented with Stage II/III. In 90 (78.3%) patents, long-course neoadjuvant chemoradiotherapy was conducted. No statistically significant difference was noted between the patients' gender according to tumor localization, preoperative tumor stage and the use of neoadjuvant CRT (**Table 1**).

Table 1. Demographics and tumor characteristics

Mean age, years	61
Female, no (%)	32 (27.8%)
Male, no (%)	83 (72.2%)
Cancer localization, no (%)	
Rectosigmoid junction	17 (14.8)
Upper rectum	36 (31.3)
Mid rectum	45 (39.1)
Low rectum	17 (14.8)
Preoperative cancer stage, no (%)	
Stage I	4 (3.5)
Stage II	19 (16.6)
Stage III	87 (75.6)
Stage IV	5 (4.3)
Use of neoadjuvant CRT according to cancer localization, no (%)	
Rectosigmoid junction	6 (6.7)
Upper rectum	30 (33.3)
Middle rectum	41 (45.6)
Low rectum	13 (14.4)
Use of neoadjuvant CRT according to stage, no (%)	
Stage II	12 (13.3)
Stage III	74 (82.2)
Stage IV	4 (4.5)

no=number; CRT=chemoradiotherapy

Complications after index surgery with protective ileostomy followed with overall complication rate of 17.4%. In 6 patients anastomotic dehiscence occurred with a rate of 5.2%. Eight patients developed anastomotic stenosis (6.9%). In 5 patients, postoperative mechanical obstruction due to adhesions developed. In one patient, twist of the created Ileostomy occurred, forcing re-laparotomy with re-creation of the stoma. One abdominal wall abscess was noted due to perforation of the terminal end of afferent ileostomy loop.

Ileostomy reversal was performed in 85 patients with ileostomy closure rate of 73.9%. In 70 of them, neoadjuvant CRT was conducted. In the group treated with upfront surgery (without neoadjuvant CRT), 15 patients experienced closure of their stoma. The difference between these two groups of patients presented without statistical difference. The group with CRT conduction had mean time of their stoma closure of 227.8 days (SE: 19.8), while the group with no neoadjuvant CRT use had shorter mean time of ileostomy reversal of 168.3 days (SE: 46.02). This difference was not statistically significant (**Table 2**).

Table 2. Neoadjuvant CRT use and timing of ileostomy closure

	Neoadjuvant CRT conducted	Neoadjuvant CRT not conducted	p value
Ileostomy			0.073[a]
closed	70	15	
non-closed	20	10	
Mean time of stoma closure (days)	227.8	168.3	0.186[b]
Total	90	25	

CRT= chemoradiotherapy; a Pearson Chi-Square Test; b Student's T Test

Before ileostomy closure, 10 patients died. In 7 patients, distant metastases developed in liver, brain and lungs. Local recurrence occurred in 5 patients. Prior to the decision for stoma closure, patients with anastomotic stenosis were treated with endoscopic balloon dilatation. In 4 of them, after satisfactory endoscopic stenosis treatment, ileostomy was closed. In the rest 4, the reversal procedure was contraindicated. In other 6 patients, endoscopy revealed partially disturbed anastomotic integrity as a consequence of subclinical dehiscence after the index surgery. In 2 of them, ileostomy closure followed. Two patients presented with anal sphincter insufficiency and were not suitable candidates for ileostomy reversal and one patient rejected ileostomy reversal procedure due to present comorbidities and increased operative risk (**Table 3**). Mean duration of hospital stay for the ileostomy reversal surgery was 6.5 days (range 3-28; SD±3.5).

Table 3. Complications and events after index surgery

Complication / event	no (%)
Anastomotic dehiscence	6 (5.2)
Postoperative intestinal mechanical obstruction	5 (4.3)
Ileostomy twisting	1 (0.8)
Ileostomy site abscess	1 (0.8)
Stenosis of colo-rectal anastomosis	8 (6.9)
Anal sphincter insufficiency	2 (1.7)
Local recurrence	5 (4.3)
Deceased	10 (8.7)
Metastases occurrence (liver/brain)	7 (6.1)

No=Number

Multivariate analysis on the factors that prevent stoma closure was performed by the use of Logistic Regression Model. Patients' gender, tumor localization and stage and conduction of neoadjuvant treatment did not affect the ileostomy closure. On contrary, the endoscopic examination of the anastomosis during its creation was the only independent prognostic factor that affected ileostomy closure (p=0.02; 95% CI 1.343-29.601) (**Table 4**).

Table 4. Multivariate analysis on factors that affected ileostomy closure

	H.R.	S.E.	Wald	p value	95% C.I. for EXP(B)	
					Lower	Upper
Neoadjuvant CRT	1.838	0.557	1.197	0.274	0.617	5.474
Tumor localization	0.971	0.244	0.014	0.904	0.601	1.568
Tumor stage	1.536	0.412	1.082	0.298	0.684	3.445
Gender	0.753	0.507	0.315	0.575	0.279	2.031
Endoscopy	6.305	0.789	5.445	0.020	1.343	29.601
Constant	0.735	1.508	0.042	0.838		

H.R.=Hazard Ratio; S.E.=Standard Error; C.I.=Confidence Interval

DISCUSSION

Best way to avoid stoma-related complications including the ones after stoma reversal surgery is not to create one. Hence, the use of protective ileostomy is still widely present in patients operated for rectal cancer. Despite the proper training and meticulous operative technique, stoma-related morbidity is the reality (13).

In this study, majority of the patients in whom protective ileostomy was performed were with rectal cancer presentation. Still, patients with rectosigmoid cancer localization can be subsided for temporary fecal diversion and are not always excluded from this procedure. Possible reasons for ileostomy creation in these patients might depend on the tumor size, their preoperative status and intraoperative technical difficulties and anastomosis related issues.

When dealing with protective ileostomy closure, surgeon should keep in mind two key points: timing for stoma closure and risk factors that lead to complications after ileostomy reversal surgery. In the recent British multicenter, observational study CLOSE-IT, mean closure time of ileostomy following anterior rectal resection was around 9 months (14). In the study of Turner et al. (15) median duration with stoma was 237 days. Aktaş et al. (16) reported median interval between ileostomy creation and closure of 202 days. This study has median time for closure similar to the recent reports despite the delay for closure in part of the patients due to COVID-19 pandemic measures.

Patients in this series had average timing for closure of within the previous reports. As expected, the ones without adjuvant CRT conduction, the time for ileostomy closure was shorter. Still, this difference it this study showed no statistical difference. The optimal timing for temporary ileostomy closure is not defined. In the past decade accent was put on early ileostomy closure with certain advantages over the late closure. In the systematic review and meta-analysis of O'Sullivan et al. (10) six randomized controlled trials were analyzed. They showed no difference between early and late

ileostomy closure. Podda et al. (17) showed that early ileostomy closure presented with lower incidence of postoperative small bowel obstruction (P=0.02) and lower rate of stoma-related complications (P<0.00001). Identical advantages of early ileostomy closure regarding postoperative ileus/small bowel obstruction were drawn in the meta-analysis of Cheng et al. (18). They also confirmed shorter operative time duration for early stoma closure. Early closure (within 150 days) was associated with less complications (P<0.001) in the retrospective study of Werner (19). However, most of the recent meta-analyses advise patient selection for the early ileostomy closure strategy (18-20).

Unfortunately, not every patient will experience his protective ileostomy closure. Local recurrence, distant metastases development and patients' death were major factors for non-closure in this study. Disturbed anastomotic integrity and stenosis and the anal sphincter insufficiency were also obstacles that prevented ileostomy reversal procedure conduction in part of this series.

The reported rate of non-closure of the temporary protective ileostomy ranges between 15.1-41.3% (9,14, 19,21,22). In this study, the ileostomy non-closure rate (26.1%) was within the reported ranges.

Other reported factors that prevent stoma closure can be classified as patient related and other medical factors (cancer stage and localization, the use of neoadjuvant/ adjuvant therapy, anastomosis integrity) (21,22). According to Gustafsson, high level of patient education has higher chance of timely stoma-reversal. At the same time, advanced rectal cancer stage carries high risk for non-reversal (21). The multivariate analysis of the study of da-Fonseca points on the anastomotic fistula, presence of metastases and stoma closure during chemotherapy as factors that prevent stoma closure (22). Another risk factor for non-reversal of the temporary ileostomy is preoperative radiotherapy. Namely, in the study of Zhu et al. (1) patients without preoperative radiotherapy conduction had ileostomy closure rate of 100% contrary to the ones with radiotherapy conduction (P=0.004). The anastomotic stenosis and colon stiffness proximal to colorectal anastomosis caused by preoperative radiotherapy were pointed as risk factors for stoma permanence. The multivariate analysis in the present study pointed the anastomotic stenosis and intraoperative endoscopic examination of the created colo-rectal anastomosis as factors that affect ileostomy closure.

Limitations

This is retrospective single-center study with small number of patients.

CONCLUSION

This study showed that more than ¼ of patients with created protective ileostomy will never experience its closure. Even the ones with closed ileostomy suffer from certain postoperative complications, some of them requiring additional operative interventions. The performance of intraoperative endoscopy examination is independent factor affecting the protective ileostomy closure. Surgeon must think twice; primarily whether to create protective ileostomy, and at the second time, whether to close it. Temporary protective ileostomy is not always temporary.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of İstanbul Prof. Dr. Cemil Taşcıoğlu City Hospital Clinical Researches Ethics Committee (Date 14.11.2022; Decision No: 322).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: No conflict of interest was declared by the authors.

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Original Article

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A novel inflammation indicator of acute stent thrombosis and in-hospital mortality in acute coronary syndrome: multiple inflammation index

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ABSTRACT

Aim: The inflammatory milieu plays a triggering role in the development of acute stent thrombosis (ST), which occurs as a catastrophic complication following percutaneous coronary intervention (PCI) in patients with acute coronary syndrome (ACS). This study aimed to investigate the prognostic role of multi-inflammatory index (MII), a powerful new marker of inflammation, in predicting of high SYNTAX score, acute ST and in-hospital mortality in patients with ACS undergoing PCI.

Material and Method: This retrospective study included 1488 consecutive patients with ACS undergoing PCI, and definitive ST was determined according to Academic Research Consortium criteria. Inflammation indices were calculated as follows: Systemic immune inflammation (SII)=neutrophil×platelet/lymphocyte ratio, CAR=CRP/albumin ratio, MII-1=platelet×CRP/lymphocyte ratio, MII-2=neutrophil×CRP/lymphocyte ratio, MII-3=SII×CRP.

Results: The incidence of acute ST was 3.6%. All inflammation indices was higher in the acute ST group and high SYNTAX score group. Multivariable regression analysis showed that MII-3 independent predictors of acute ST and high SYNTAX score. MII-3 exhibited better diagnostic performance than other inflammatory indices. The threshold value of MII-3 in predicting acute ST was >9084 (AUC=0.842, sensitivity=87.3%, specificity=%77.8) and patients with MII-3 >9084 had a 3.73-fold greater risk of mortality.

Conclusion: MII-3 is a stronger predictor of acute ST following PCI and it is associated with an increased risk of mortality. MII may be an essential prognostic screening tool for identifying high-risk patients prior to procedure.

Keywords: Acute coronary syndrome, inflammation, stent thrombosis, SYNTAX score

INTRODUCTION

In acute coronary syndrome (ACS), which is one of the leading causes of death globally, Percutaneous coronary stent implantation, known as primary percutaneous coronary intervention (PCI), is often used for treatment (1). Acute stent thrombosis (ST) is a catastrophic complication that occurs following PCI and is associated with myocardial infarction and sudden cardiac death (2). Its incidence is about 2.4% and has a mortality rate of up to 34% (2, 3). Acute ST processing may occur depending on the patient, lesion, stent characteristics, and efficacy of antiaggregant treatment. However, pre-procedural indicators are not well defined yet (2, 4).

Increasing evidence suggests that the inflammatory milieu plays a vital role in the development of acute ST (5, 6). This could potentially point to microvascular and molecular mechanisms involving ischemia, oxidative stress, endothelial damage, and innate immune cells (7, 8). Previous studies have reported that the systemic immune inflammation index (SII) derived from inflammatory immune cells is a superior predictor of cardiac events (9, 10). Recent studies in different diseases have suggested that multi-inflammatory indices (MII) obtained from the combination of inflammatory immune cells and C-reactive protein (CRP), an acute phase reactant, are a better prognostic indicator (11-13). However, the diagnostic performance of MII in cardiovascular disease or events has not been investigated yet.

This study aimed to investigate the prognostic role of MII in predicting high SYNergy between Percutaneous Coronary Intervention with TAXus and cardiac surgery (SYNTAX) score, acute ST and in-hospital mortality in patients with ACS undergoing PCI.

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MATERIAL AND METHOD

This retrospective study was performed on ST-segment elevation myocardial infarction (STEMI) patients who underwent primary PCI from a single-center Cardiology Clinic between January 2018 and January 2021. The study followed the revised Declaration of Helsinki (2013, Brazil) and all ethical procedures and was approved by the Ankara City Hospital Ethics Committee (Date: 30.11.2022, Decision No: E1-22-3056). The need for informed consent was waived under the approval of the Local Ethics Committee due to the retrospective design.

Patient Selection

2684 consecutive patients diagnosed with STEMI who underwent PCI were evaluated retrospectively. STEMI was defined following the fourth universal definition of MI (14) with management procedures being aligned with the latest guidelines of the European Society of Cardiology (15). Angiographic data were analyzed in the cardiac catheterization laboratory. At the operator's discretion, ticagrelor (180 mg) or prasugrel (60 mg) was loaded in addition to aspirin (300 mg). 1196 patients who did not meet the inclusion criteria were excluded. Exclusion criteria were a history of inflammatory disease or active inflammatory conditions, kidney or liver disease, autoimmune disease, cancer, history of anti-inflammatory or chronic corticosteroid or nephrotoxic drugs, heart valve disease, dilated cardiomyopathy, decompensated heart failure, previous revascularization history, oral anticoagulant use, persistent coronary dissection, undersized stent, attempt bifurcation, loading clopidogrel as antiaggregant, intraprocedural stent thrombosis, residual thrombus or stenosis >50%, no reflow during PCI (thrombolysis in myocardial infarction [TIMI] flow grade <3), pregnant or had delivered within the last 90 days, and missing data on clinical measurements. After the exclusion, 1488 patients were included in this study (**Figure 1**).

All patients' demographic, comorbid diseases and clinical data were obtained from the hospital's electronic information system and patient files.

Definitions

Acute ST was defined as ST occurring within the first 24 hours after percutaneous coronary stent implantation. Definitive ST was evaluated according to the following Academic Research Consortium criteria: (1) the Presence of a thrombus that originates from the stent or the segment 5 mm proximal or distal to the stent (occlusive or not), and (2) at least one of the following: Acute ischemic symptom onset at rest and/or new ischemic electrocardiogram changes suggestive of acute ischemia and/or typical increase and decrease in cardiac biomarkers. In repeated measurements, blood pressure >140/90 mmHg or antihypertensive drugs was defined as hypertension, and fasting plasma glucose (FPG) level ≥126 mg/dL or using antidiabetic drugs was defined as diabetes mellitus.

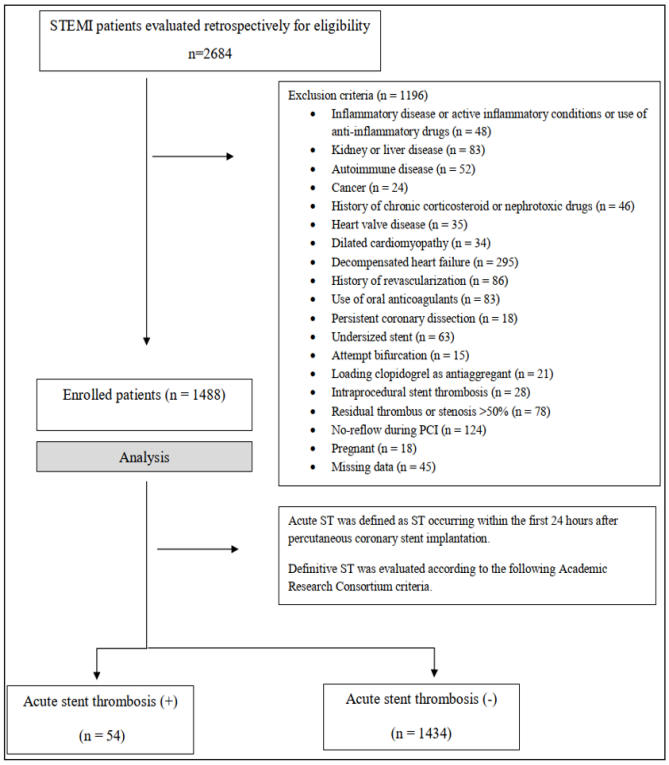

Figure 1. Flow diagram of the cohort study

Laboratory Analysis

Blood samples were taken at the time of admission and during the follow-up and were measured using Beckman Coulter LH 780 (Mervue, Galway, Ireland). The levels of hemoglobin (photometrically), platelets (impedance method), CRP (immunoturbidimetric method), albumin (bromine cresol green method), triglycerides, and total cholesterol (enzymatic colorimetric method) and HDL (homogeneous enzymatic colorimetric method) were determined. Low-density lipoprotein (LDL) levels were calculated using the Friedewald formula. Inflammation indices were calculated as follows: PLR=platelet to lymphocyte ratio, NLR=neutrophil to lymphocyte ratio, SII=neutrophil count×platelet count/lymphocyte count, CAR=CRP to albumin ratio, MII-1=PLR×CRP, MII-2=NLR×CRP, MII-3=SII×CRP. Cardiac troponin I (cTnI) levels were measured intermittently up to the peak level using a Roche Diagnostics Cobas 8000 c502 analyzer (Roche Diagnostics, Indianapolis, IN, USA).

Coronary Angiography

Coronary arteries were visualized with the standard Judkins technique, and cine-angiographic images were recorded (AXIOM Artis, Siemens AG, Munich, Germany). At least two orthogonal plan images were

taken for each segment. Based on the baseline coronary angiograms, the SYNTAX score was calculated by two cardiologists blinded to the patients data. The SYNTAX score was evaluated for all lesions with a >50% diameter stenosis in a vessel greater than 1.5 mm according to the SYNTAX score calculator 2.1 (www.syntaxscore.org). Accordingly, all patients were divided into 2 groups as low (<23) and high (≥23) SYNTAX scores. In 200 randomly selected patients, the kappa (k) value was 0.94 at intra-observation reliability and 0.92 at interobserver reliability. Echocardiographic data were measured with a 2.5 MHz phased array transducer (Vingmed GE, Horten, Norway), and left ventricular ejection fraction (LVEF) was calculated using the modified Simpson's method.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows 20.0 (IBM Corp., Armonk, NY, USA). The normality distribution of numerical data was evaluated with the Kolmogorov-Smirnov test. Normally distributed variables were presented as mean±standard deviation, and non-normally distributed variables were presented as median (25^{th} and 75^{th} percentiles). For comparisons between groups, the Student T-test and Mann-Whitney U test were used according to normality distribution. Categorical variables were expressed as numbers and percentages, and comparisons between groups were evaluated with Chi-square and Fisher's Exact tests. Spearman's correlation analysis links inflammation indices and the SYNTAX score. Potential confounding factors for acute ST and high SYNTAX score were identified by multivariable regression analysis. Components of inflammatory indices were not included in the regression analysis due to multi-collinearity. A multivariate regression model (Model I) was constructed with potential confounding factors and SII and CAR inflammation indices but not MII. Next, a new multivariate regression model (Model II) was created in which MII-3 was included in Model I, but SII was omitted due to multi-collinearity. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of the inflammation indices to predict acute ST. $P < 0.05$ was considered statistically significant.

RESULTS

The mean age of 1488 patients included in the study was 58.4±11.2 years, the majority of them were male (75.2%), and the incidence of acute ST was 3.6%. The demographic and clinical characteristics of patients were reported in **Table 1**. Demographic findings did not differ between groups with and without acute ST ($p > 0.05$). Mean LVEF levels were lower in the acute ST group than without the acute ST group, while the median SYNTAX score and mean number of severely diseased vessels were higher ($p < 0.05$). NLR, PLR SII, CRP, CAR, and MII levels were higher in the acute ST group than without the acute ST group (**Table 1**).

Potential confounding factors associated with acute ST were determined as LVEF, stent length, number of SDV, SYNTAX score, cTnI, leukocytes, CRP, albumin and inflammatory indices. Model I regression analysis showed that SII (OR=1.10, $p < 0.001$) and CAR (OR=1.15, $p < 0.001$) were independent predictors of acute ST, while Model II regression analysis showed MII-3 (OR=1.06, $p < 0.001$). In both models, stent length, number of SDV, and SYNTAX score were common independent predictors of acute ST. However, Model II regression analysis improved the variance in explaining acute ST compared to Model 1 regression analysis (Nagelkerke R2=0.508 for Model II vs. Nagelkerke R2=0.415 for Model I) (**Table 2**).

Table 2. Independent predictors of acute stent thrombosis.

Variables	OR (95% CI)	p value
Univariable		
LVEF	0.97 (0.95-0.99)	0.045
Stent length	1.13 (1.07-1.21)	< 0.001
Multivessel disease	1.75 (1.01-3.04)	0.047
Number of SDV	2.30 (1.55-3.42)	< 0.001
SYNTAX score	1.09 (1.06-1.12)	< 0.001
cTnI	1.02 (1.01-1.03)	< 0.001
WBC	1.12 (1.04-1.19)	0.043
NLR	1.16 (1.08-1.25)	< 0.001
PLR	1.09 (1.06-1.12)	< 0.001
SII, $\times 10^2$	1.06 (1.03-1.10)	< 0.001
CAR	1.12 (1.06-1.18)	< 0.001
MII-1	1.08 (1.04-1.12)	< 0.001
MII-2, $\times 10^2$	1.03 (1.02-1.05)	< 0.001
MII-3, $\times 10^2$	1.05 (1.03-1.06)	< 0.001
Model I Multivariable		
Stent length	1.12 (1.06-1.20)	< 0.001
Number of SDV	2.26 (1.48-3.43)	< 0.001
SYNTAX score	1.06 (1.02-1.10)	0.006
SII, $\times 10^2$	1.10 (1.08-1.21)	< 0.001
CAR	1.15 (1.08-1.21)	< 0.001
	Nagelkerke R2=0.415, p<0.001	
Model II Multivariable		
Stent length	1.15 (1.08-1.22)	< 0.001
Number of SDV	2.27 (1.50-3.45)	< 0.001
SYNTAX score	1.05 (1.01-1.09)	< 0.001
MII-3, $\times 10^2$	1.06 (1.04-1.08)	< 0.001
	Nagelkerke R2=0.508, p<0.001	

Abbreviations: CAR, C-reactive protein to albumin ratio; CI, confidence interval, LVEF, left ventricular ejection fraction; MII, multi-inflammation index; NLR, neutrophil to lymphocyte ratio; OR, odds ratio; PLR, platelet to lymphocyte ratio; SII, systemic immune-inflammation index; SDV, severely diseased vessels; SYNTAX, SYNergy between Percutaneous Coronary Intervention with TAXus and cardiac surgery; WBC, white blood cell.

Table 1. The demographic and clinical characteristics.

Variables	Study population n=1488	Acute ST (+) n=54	Acute ST (-)	p value
Age, years	58.4±11.2	58.6±9.4	58.4±11.3	0.901
Male gender, n (%)	1119 (75.2)	39 (72.2)	1080 (75.3)	0.630
Smoking, n (%)	577 (38.8)	26 (48.1)	551 (38.4)	0.157
Diabetes mellitus, n (%)	318 (21.4)	15 (27.8)	303 (21.1)	0.239
Hypertension, n (%)	640 (43.0)	25 (46.3)	615 (42.9)	0.675
LVEF, %	48.9±8.2	46.4±10.1	49.3±8.1	0.022
Stent length, mm	23.5±4.7	26.1±4.0	23.4±4.7	< 0.001
Stent diameter, mm	3.0±0.4	3.1±0.3	3.0±0.4	0.725
IRA, n (%)				
LAD	931 (62.6)	35 (64.8)	896 (62.5)	0.776
LCX	638 (42.9)	24 (44.4)	614 (42.8)	0.889
RCA	676 (45.4)	28 (51.9)	648 (45.2)	0.404
Multivessel disease, n (%)	683 (45.9)	32 (59.3)	651 (45.4)	0.044
Number of SDV	1.5±0.4	1.7±0.5	1.4±0.4	< 0.001
SYNTAX score	19.3 (13-25)	25.2 (21-32)	18.7 (13-24.5)	< 0.001
Tirofiban administration, n (%)	162 (10.8)	5 (9.3)	157 (10.9)	0.711
Medications, n(%)				
RAS blocker	511 (34.3)	19 (35.2)	492 (34.3)	0.885
Diuretics	330 (22.2)	11 (20.4)	319 (22.2)	0.868
β-blocker	383 (25.7)	12 (22.2)	371 (25.9)	0.636
CCB	330 (22.2)	13 (24.1)	317 (22.1)	0.739
Antiaggregant	409 (27.5)	13 (24.1)	396 (27.6)	0.643
Statin	365 (24.5)	12 (22.2)	353 (24.6)	0.750
OAD	302 (20.3)	14 (25.9)	288 (20.1)	0.302
cTnI, ng/mL	3.8 (1.6-21.8)	5.2 (2.8-20.7)	3.4 (1.7-8.9)	< 0.001
FBG, mg/dL	117.7±45.8	117.6±44.1	117.7±45.8	0.986
WBC, $10^3/mm^3$	8.6 (7.0-10.6)	9.1 (8.0-12.1)	8.6 (7.0-10.5)	0.032
Neutrophil, $10^3/mm^3$	5.3 (4.1-7.1)	6.6 (5.4-9.4)	5.3 (4.1-7)	< 0.001
Lymphocyte, $10^3/mm^3$	2.2 (1.7-2.8)	1.9 (1.6-2.4)	2.2 (1.7-2.8)	0.008
Platelet, $10^3/mm^3$	254.8±71.4	322.1±93.1	252.3±69.2	< 0.001
Hemoglobin, g/dL	14.2±1.5	14.1±1.6	14.2±1.5	0.922
Hematocrit, %	43.0±4.8	42.8±4.8	43.1±4.7	0.777
C-reactive protein, mg/L	7.2 (3.6-14.2)	14.3 (8.8-23)	7 (3.5-14)	< 0.001
Albumin, g/dL	3.9±0.4	3.7±0.6	3.9±0.4	0.006
Creatinine, mg/dL	0.9±0.3	0.9±0.2	0.9±0.3	0.483
Total cholesterol, mg/dL	192.4±78.5	192.7±45.5	192.4±79.5	0.983
LDL- cholesterol, mg/dL	121.9±38.3	119.8±41.8	122±38.2	0.670
HDL- cholesterol, mg/dL	40.2±9.7	41.6±9.2	40.1±9.8	0.240
Triglyceride, mg/dL	170 (120-231)	187.5 (127-255)	170 (120-230)	0.452
NLR	2.3 (1.7-3.5)	3.5 (2.6-5.3)	2.3 (1.7-3.5)	< 0.001
PLR	110.4 (83.9-151)	156.3 (112-215.9)	109.1 (83.5-150)	< 0.001
CAR	1.9 (0.9-3.8)	4 (3.2-6.7)	1.8 (0.9-3.7)	< 0.001
SII, $\times10^2$	5.8 (4.0-9.6)	10.4 (6.5-17.0)	5.6 (3.9-9.2)	< 0.001
MII-1	17.8 (8.2-35.8)	47.1 (28.4-88.4)	17.1 (8.1-33.8)	< 0.001
MII-2, $\times10^2$	8.5 (3.9-16.2)	22.0 (14.0-32.6)	8.3 (3.8-15.5)	< 0.001
MII-3, $\times10^2$	45.0 (19.6-90.6)	145.0 (103.3-232.1)	42.4 (19.1-83.4)	< 0.001

Numerical variables were shown as mean±standard deviation or median (min-max). Categorical variables were shown as number (%). Abbreviations: CAR, C-reactive protein to albumin ratio; CCB, calcium channel blocker; cTnI, cardiac troponin-I; FBG, fasting plasma glucose; HDL, high density lipoprotein; IRA, infarct-related artery; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; LDL, low density lipoprotein; LVEF, left ventricular ejection fraction; MII, multi-inflammation index; NLR, neutrophil to lymphocyte ratio; OAD, oral antidiabetic drug; PLR, platelet to lymphocyte ratio; RAS, renin-angiotensin system; RCA, right coronary artery; SII, systemic immune-inflammation index; SDV, severely diseased vessels; SYNTAX, SYNergy between Percutaneous Coronary Intervention with TAXus and cardiac surgery; ST, stent thrombosis; WBC, white blood cell.

The diagnostic performance of inflammatory indices in predicting acute ST is shown in **Figure 1**. The threshold value of MII-3 in predicting acute ST was > 9084 with 87.3% sensitivity and 77.8% specificity and it exhibited better diagnostic performance than other inflammatory indices (**Figure 2A**). The rate of in-hospital mortality was 7.6% (n=113). The acute ST group had a higher in-hospital mortality rate than without acute ST group (24.1% vs. 7.0%, p < 0.001). The threshold value of MII-3 (> 9084) determined to predict acute ST was associated with a 3.73-fold increased risk of mortality (**Figure 2B**).

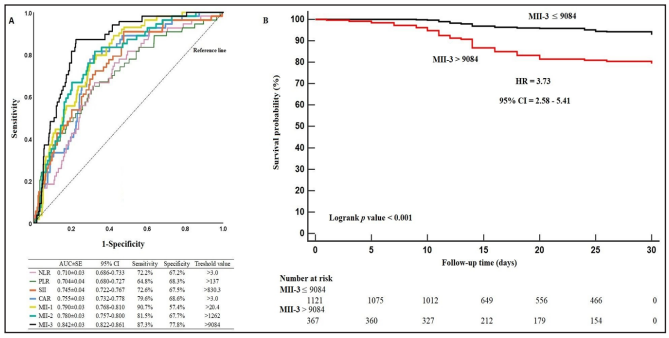

Figure 2. Diagnostic performance of inflammatory indices in predicting acute stent thrombosis (A) and in-hospital mortality risk according to the threshold value of MII-3 in predicting acute ST (B)

There was a positive correlation between the SYNTAX score and MII indices (r=0.405, p < 0.001 for MII-1; r=0.414, p < 0.001 for MII-2; r=0.426, p < 0.001 for MII-3) (**Figure 3**). Demographic and clinical findings associated with a high SYNTAX score are shown in Table (**Table 3**), and potential confounders for univariable regression analysis are presented in (**Table 4**). Model I regression analysis showed that SII (OR=1.05, p < 0.001) and CAR (OR=1.43, p < 0.001) were independent predictors of high SYNTAX score, while Model II regression analysis showed MII-3 (OR=1.10, p < 0.001). Model II explained the SYNTAX score with a higher variance than Model 1 (Nagelkerke R2=0.522 for Model II vs. Nagelkerke R2=0.433 for Model I).

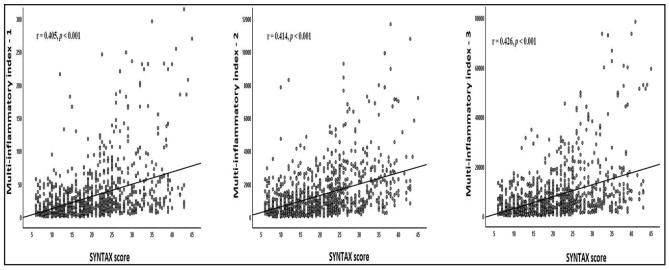

Figure 3. Correlation analysis between SYNTAX score and multi-inflammatory indices.

Table 3. Relationship between demographic and clinical characteristics and SYNTAX score.

Variables	High SS n=509	Low SS n=979	p value
Age, years	59.7±10.7	57.8±11.4	< 0.001
Male gender, n (%)	379 (74.5)	740 (75.6)	0.633
Smoking, n (%)	195 (38.3)	382 (39.0)	0.790
Diabetes mellitus, n (%)	124 (24.4)	194 (19.8)	0.042
Hypertension, n (%)	241 (47.3)	399 (40.8)	0.015
LVEF, %	46.9±8.5	50.0±7.9	< 0.001
cTnI, ng/mL	3.2 (1.8-12.1)	2.6 (1.4-10.0)	0.082
FBG, mg/dL	122.6±54.5	115.2±40.3	0.007
WBC, 10^3/mm^3	9.3 (7.1-10.1)	8.7 (7-10.8)	0.048
Neutrophil, 10^3/mm^3	6.3 (4.8-8.3)	5.1 (4.1-6.8)	< 0.001
Lymphocyte, 10^3/mm^3	2.1 (1.6-2.7)	2.3 (1.8-2.9)	< 0.001
Platelet, 10^3/mm^3	263.3±77.2	250.4±67.9	0.001
Hemoglobin, g/dL	13.9±1.7	14.4±1.4	< 0.001
Hematocrit, %	43.0±5.2	43.2±4.5	0.441
C-reactive protein, mg/L	12.3 (6.5-21.3)	5.6 (2.7-10.4)	< 0.001
Albumin, g/dL	3.7±0.4	3.9±0.4	< 0.001
Creatinine, mg/dL	1.0±0.3	0.9±0.3	0.001
Total cholesterol, mg/dL	197.1±121.5	190.0±41.1	0.200
LDL- cholesterol, mg/dL	124.2±41.9	120.7±36.3	0.112
HDL- cholesterol, mg/dL	38.8±10.4	41.0±12.8	0.001
Triglyceride, mg/dL	187 (127-257)	164.5 (119-216)	0.001
NLR	2.5 (1.8-4)	2.3 (1.6-3.4)	< 0.001
PLR	121 (93.3-168.2)	105 (81.4-144.7)	< 0.001
CAR	3.4 (1.6-6.1)	1.4 (0.7-2.7)	< 0.001
SII, ×10^2	6.3 (4.4-10.8)	5.5 (3.8-9.1)	< 0.001
MII-1	28 (15.1-58.5)	13.6 (6.3-25.8)	< 0.001
MII-2, ×10^2	14.6 (7.2-27.0)	6.1 (2.9-12.0)	< 0.001
MII-3, ×10^2	75.4 (38.7-15.5)	32.8 (14.4-67.9)	< 0.001

Numerical variables were shown as mean±standard deviation or median (min-max). Categorical variables were shown as number (%). Abbreviations: CAR, C-reactive protein to albumin ratio; CCB, calcium channel blocker; FBG, fasting plasma glucose; HDL, high density lipoprotein; IRA, infarct-related artery; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; LDL, low density lipoprotein; LVEF, left ventricular ejection fraction; MII, multi-inflammation index; NLR, neutrophil to lymphocyte ratio; OAD, oral antidiabetic drug; PLR, platelet to lymphocyte ratio; RAS, renin-angiotensin system; RCA, right coronary artery; SII, systemic immune-inflammation index; SDV, severely diseased vessels; SYNTAX, SYNergy between Percutaneous Coronary Intervention with TAXus and cardiac surgery; ST, stent thrombosis; WBC, white blood cell.

Table 4. Independent predictors of high SYNTAX score

Variables	OR (95% CI)	p value
Univariable Regression		
Age	1.02 (1.01-1.03)	0.002
Diabetes mellitus	1.30 (1.01-1.68)	0.043
Hypertension	1.31 (1.05-1.62)	0.015
LVEF	0.95 (0.94-0.97)	< 0.001
cTnI		
FBG	1.04 (1.01-1.09)	0.003
WBC	1.03 (1.01-1.08)	0.050
Hemoglobin	0.84 (0.78-0.90)	< 0.001
HDL-cholesterol	0.98 (0.97-0.99)	< 0.001
Triglyceride	1.02 (1.01-1.03)	< 0.001
NLR	1.07 (1.03-1.12)	0.001
PLR	1.05 (1.03-1.07)	< 0.001
SII, x102	1.03 (1.02-1.05)	< 0.001
CAR	1.42 (1.35-1.50)	< 0.001
MII-1	1.03 (1.01-1.05)	< 0.001
MII-2, $\times 10^2$	1.07 (1.05-1.09)	< 0.001
MII-3, $\times 10^2$	1.11 (1.09-1.13)	< 0.001
Model I Multivariable Regression		
Age	1.03 (1.01-1.05)	< 0.001
LVEF	0.96 (0.94-0.98)	< 0.001
cTnI		
HDL-C	0.97 (0.95-0.99)	< 0.001
SII, $\times 10^2$	1.05 (1.03-1.07)	< 0.001
CAR	1.43 (1.35-1.51)	< 0.001
	Nagelkerke R2=0.433. p< 0.001	
Model II Multivariable Regression		
Age	1.03 (1.01-1.05)	< 0.001
LVEF	0.96 (0.94-0.98)	< 0.001
HDL-C	0.97 (0.95-0.99)	< 0.001
cTnI	2.27 (1.50-3.45)	< 0.001
MII-3, $\times 10^2$	1.10 (1.08-1.13)	< 0.001
	Nagelkerke R2=0.522. p < 0.001	

Abbreviations: CAR, C-reactive protein to albumin ratio; CI, confidence interval, FBG, fasting plasma glucose; HDL, high density lipoprotein; LVEF, left ventricular ejection fraction; MII, multi-inflammation index; NLR, neutrophil to lymphocyte ratio; OR, odds ratio; PLR, platelet to lymphocyte ratio; SII, systemic immune-inflammation index; WBC, white blood cell.

DISCUSSION

To our best knowledge, this is the first study to evaluate the prognostic role of MII in ACS patients. The main consequences are: 1) MII-3 was an independent marker of acute ST and improved the model predicting acute ST. 2) MII-3 had better diagnostic performance than other inflammatory markers in predicting acute ST. 3) MII-3 was an independent predictor of higher SYNTAX scores. 4) The threshold value of MII to predict acute ST was an important risk factor for in-hospital mortality.

ST, a catastrophic complication of percutaneous coronary stent implantation, can occur acutely (first 24 hours after stent placement), early (first month), late (first year), or very late (after one year) (16). Despite the advances in technology and procedural techniques, the emergence of new generation stents, and dual antiplatelet therapy strategies (DAPT), it still has a significant incidence (17). The pooled analysis of multicenter coronary stent clinical trials reported that more than 80.0% of ST cases occurred within two days of PCI (18). In addition to patient characteristics such as hronic kidney disease, comorbid inflammatory conditions, advanced age, decompensated heart failure and early discontinuation of DAPT, reduction in stent size, coronary dissection, post-PCI TIMI flow <3, clopidogrel resistance, and bifurcation lesions increase the risk of acute ST (16, 19). On the other hand, there is growing evidence that inflammation contributes to the development of acute ST (5, 6). Therefore, we excluded patients with the above risk factors that might affect the relationship between inflammation and acute ST.

The SYNTAX score, which is a guide for revascularization in coronary artery disease, is a prognostic indicator for CV events (20). It also offers predictive value in acute ST (21). The immune system generates an inflammatory response in acute cardiovascular events, and it plays a role in smooth muscle cell proliferation, endothelial regeneration, oxidative stress, and platelet activation (8). These mechanisms are involved in the pathogenesis of acute ST and restenosis, in addition to being associated with higher SYNTAX scores (22). It can be used as a guide in the early prognosis prediction since inflammatory parameters provide an essential predictive value in cardiovascular events, including acute ST. However, inflammatory parameters offer different predictive values in cardiovascular events (23) as demonstrated in the current study. Therefore, simple and easily obtained stronger signals are needed to evaluate inflammation. A combined index derived from inflammatory parameters may exhibit superior diagnostic performance than its components. Previous studies have shown that MII offers a stronger prognostic value over old and new indicators of inflammation, including CRP, NLR, PLR, SII, and CAR in different patient groups (11-13). However, it has not yet been investigated in ACS patients. In this study, we evaluated MII, which is suggested to be a more power indicator of inflammation.

Acute phase reactants or CAR had a significant association with high SYNTAX score and acute ST, consistent with previous limited studies (24-26). The potential mechanism by which these acute phase reactants accelerate the development of plaque and thrombosis is that an increased release of CPR in circulation triggers the complement system, inducing leukocyte activity, platelet aggregation, lipid accumulation, and apoptosis (27), and decreasing albumin levels negatively affect anti-platelet aggregation, anti-inflammatory, antioxidant or anticoagulant activity

and disruption of vascular integrity (28). However, the effect of acute phase reactants on leukocyte activation causes increased accumulation of macrophages (29). It is known that increased platelet reactivity significantly increases the risk of acute ST (30). Therefore, a combined index containing acute phase reactants and inflammatory immune cells may provide superior diagnostic performance.

There are rare studies evaluating the relationship between SII or CAR and ST in patients with CAD undergoing PCI (24, 31). Ocal et al. (31) reported that high SII levels were associated with ST and that SII was an independent predictor of in-hospital and long-term mortality. Akboga et al. (24) evaluated the predictors of acute ST in patients with ACS undergoing PCI, and they found that increased levels of SII and CAR were independent predictors. In their study, CAR levels were a stronger indicator than SII. The present findings both support and extend previous studies. Firstly, Model I regression analysis showed that CAR and SII were independent predictors of acute ST. Secondly, ROC curve analysis showed that SII and CAR levels exhibited better diagnostic performance than NLR and PLR. However, the diagnostic performance of CAR and SII was similar. The diagnostic performance of SII compared to NLR and PLR in acute ST has not been evaluated previously. Thirdly, Model 2 regression analysis improved the variance in explaining acute ST. In contrast, ROC curve analysis showed that MII-3 had better diagnostic performance than other inflammatory indices.

This study was also the first to evaluate the relationship between MII and in-hospital mortality in ACS patients. The rate of in-hospital mortality in the acute ST group was consistent with the higher cumulative mortality rate reported in previous studies (2-4). The cut-off value of MII-3 for predicting acute ST was associated with a higher risk of mortality. Previous studies in patients with metastatic colorectal cancer and critically ill have shown that MII from leukocyte and CRP levels is an independent predictor of mortality and has better diagnostic performance than other markers of inflammation (11, 12). In addition, MII exhibited strong diagnostic performance in distinguishing between massive and non-massive pulmonary embolism patients (13). Considering the predictive and diagnostic performance value of MII in different patient groups, especially MII-3, it may be an essential prognostic screening tool in ACS patients.

Although this study had a prominent sample representative of the ACS cohort, its single-center, and retrospective design was the main limitation. Second, intravascular imaging techniques were not used to assess stent apposition or expansion. Third, early ST, late ST or very late ST evaluation was not performed. Finally, the levels of microRNA and cytokines that play a role in inflammation were not examined. These could better explain the contribution of inflammation in the development of acute ST.

CONCLUSION

MII-3, a powerful new indicator of inflammation, is a simple, inexpensive, and practical biomarker in predicting both high SYNTAX score, acute ST and in-hospital mortality in ACS patients. Moreover, MII-3 exhibited higher diagnostic performance than other inflammatory parameters. Therefore, it may be an essential prognostic screening tool for identifying high-risk patients prior to procedure in ACS patients undergoing PCI.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara City Hospital Ethics Committee (Date: 30.11.2022, Decision No: E1-22-3056).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the manuscript, and they have approved the final version.

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Original Article

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Cardiovascular risk assessment with pulse wave velocity, intima media thickness, and flow-mediated dilatation in patients with idiopathic pulmonary fibrosis

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ABSTRACT

Aim: The underlying mechanism of fibrotic lung diseases predisposing to coronary artery disease is not yet clear. Chronic inflammation may contribute to atherosclerosis and play a role in increased cardiovascular risk. To study investigate subclinical atherosclerosis by measuring carotid femoral pulse wave velocity (PWV), carotid intima media thickness (CIMT), and flow-mediated dilatation (FMD) in patients with idiopathic pulmonary fibrosis (IPF).

Material and Method: This cross-sectional study consisted of 55 newly diagnosed IPF patients and 55 healthy controls between September 2019 and September 2021. Cardiovascular Risk Assessment was evaluated by endothelial function measured by FMD, CIMT measured by carotid doppler ultrasonography, and arterial stiffness measured by PWV.

Results: In multivariable regression models, the presence of IPF was common independent predictor of CIMT (β±SE=0.18±0.05, p=0.002), log(FMD) (β±SE=−0.15±0.04, p<0.001) and log(PWD) (β±SE=0.16±0.03, p<0.001). An increase log(PWV) levels were common independent predictors of CIMT and log(FMD). The levels of CRP were positively correlated with CIMT (r=0.359, p=0.009) and PWV (r=0.338, p=0.018) levels, while it was negatively correlated with FMD levels (r=-0.372, p=0.004).

Conclusions: IPF patients have elevated risk of endothelial dysfunction and atherosclerosis. A sustained inflammatory response may have play an important role in the process of atherosclerosis.

Keywords: Cardiovascular disease, coronary artery disease, pulmonary fibrosis, atherosclerosis

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a chronic and progressive lung disease of unknown etiology that is associated with significant morbidity and mortality, and characterized by an abnormal accumulation of fibrotic tissue in the lung parenchyma (1). IPF may present with nonspecific symptoms, such as dyspnea, cough, and low exercise capacity. Many of these symptoms can be similar to those of heart failure, and therefore, it requires a multidisciplinary approach (2). Recent epidemiological evidence has suggested that patients with IPF are at increased risk of cardiovascular disease (CVD) (3, 4). The mechanisms between IPF and CVD are still unclear. However, chronic inflammatory processes may contribute to the formation of atherosclerosis.

Atherosclerosis is a complex inflammatory-fibroproliferative response that develops against the accumulation of atherogenic lipoprotein originating from the blood plasma in the arterial intima (5). The carotid intima-media thickness (CIMT) test is a simple and inexpensive technique to evaluate the cumulative effect of atherosclerotic risk factors (6). However, endothelial dysfunction is observed in the early phase of atherosclerosis (7). Endothelial dysfunction refers to impaired nitric oxide (NO) production and/or an imbalance in relaxation and contraction factors, such as endothelium-derived endothelin1 (ET-1), angiotensin, and oxidants. Flow-mediated dilation (FMD) is a good ultrasonographic

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marker of early atherosclerotic changes that is used to measure endothelial function, as it demonstrates the vasodilation response of peripheral arteries to physical stimuli. Endothelial dysfunction is a well-known response to cardiovascular risk factors (8).

Previous studies have suggested that fibrotic lung disorders predispose to coronary artery disease (CAD) (9,10). To the best of our knowledge, in the literature, we did not identify a study in which subclinical atherosclerosis was detail evaluated by cardiovascular risk tests in IPF patients. Therefore, in the present study, we aimed to investigate cardiovascular risk assessment by FMD, CIMT and pulse wave velocity (PWV), which marker for subclinical atherosclerosis, in patients with IPF compared to and age and sex and smoking matched healthy controls.

MATERIAL AND METHOD

The study was carried out with the permission of İstanbul Training and Research Hospital Ethics Committee (Date: 13.09.2019, Decision No: 1985). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Population

This research was conducted as a cross sectional study between September 2019 and September 2021. Written informed consent was obtained from all of the participants.

Fifty-five consecutive patients with newly diagnosed IPF, who were over 18 years of age, in the Department of Chest Diseases and referred for evaluation of cardiac symptoms were included in the study. The diagnosis of IPF was made according to the 2018 international IPF guideline (1). All patients had pathological usual interstitial pneumonia or patern on chest high resolution computed tomography. While selecting the healthy control group, we evaluated the patients presenting with general examination (ICD code: Z00.8) between September 2019 and September 2020. We identified 460 patients without any health problems in the 12-month period. Afterwards, 1:1 matching method was performed between the control group and IPF patients in terms of age and sex and smoking.

Patients with a history of coronary artery disease, pulmonary arterial hypertension, kidney disease (defined as patients with an estimated glomerular filtration rate (eGFR) of<15 ml/min/1.73 m2, or who require hemodialysis or peritoneal dialysis treatment), liver diseases (including active hepatitis and liver cirrhosis), documented sleep apnea, thyroid diseases, asthma, malignancy, any inflammatory diseases were excluded from the study.

Demographic, laboratory and clinical findings were recorded in patient files at the time of admission to the hospital.

Biochemical Parameters

Venous blood samples were taken in first admission, and analyzed for a complete blood count and lipid and cardiac biomarkers. Collected blood samples were centrifuged at 1500 rpm for 10 minutes to measure the determined parameters. Triglycerides and total cholesterol were measured using the enzymatic colorimetric method, high-density lipoprotein (HDL) cholesterol was measured using the homogeneous enzymatic colorimetric method, and albumin was measured using the brom cresol green method on a Beckman Coulter AU681-10 autoanalyzer (Danaher Corp., CA, USA). Low-density lipoprotein (LDL) was measured using the Friedewald formula. Thrombocytes were measured using the impedance (resistance) method, and the other hematological parameters were measured using the Sysmex XE 2100 hematology analyzer (Roche Diagnostic Corp., IN, USA). Hemoglobin was measured photometrically. Kidney function test were measured by colorimetric method (Cobas 8000, Roche, Germany), C – reactive protein (CRP) was measured turbidimetric method on a Beckman Coulter AU 5800 autoanalyzer (Danaher Corp., CA, USA).

Echocardiography

Echocardiography procedures were performed using a Philips Affiniti 70G Ultrasound 2.5-MHz transducer echocardiography device (Koninklijke Philips N.V., Eindhoven, Netherlands) by a cardiologist who had no knowledge about the study. Parasternal long- and short-axis views, and apical 2- and 4-chamber views were obtained. The left ventricular diameters were measured from the M-mode images in parasternal long axis view. The modified Simpson method was used to calculate the left ventricle ejection fraction using the apical 4-chamber views. Tricuspid regurgitation was accepted as jet area 5 cm2 and above.

Carotid Doppler Ultrasonography

The CIMT was measured with the patient in the supine position with both hands under his or her head. The measurements were performed using a GE LOGIQ S8 high-resolution B-mode ultrasound device (Gyeonggi-do, Korea) by a radiologist who had no knowledge about the clinical statuses of the patients.

In these measurements, the right and left main carotid arteries were evaluated with an automated system using a linear probe. The measurements were performed from 3 points: right and left main carotid arteries, bifurcation, and first 2-cm part of internal carotid arteries. Longitudinal measurements were performed from the distances defined between the vascular lumen echogenicity and media adventitia echogenicity. The CIMT was calculated by taking the average of the 3 measurements made for both carotid arteries.

Flow-Mediated Dilation

The FMD technique was used to evaluate the endothelial functions in the brachial artery. The patients were placed in a comfortable position on their backs. A 10-Mhz transducer was placed on the right brachial artery trace at 4–5 cm above the elbow, and was imaged longitudinally along the arterial trace, where the best image was obtained. The projection of the edge of the transducer was marked on the skin using a pencil by keeping the transducer fixed where the appropriate image was obtained. The brachial artery diameter (intima-to-intima) was measured 3 times and the average of these 3 measurements was recorded as the basal diameter. These measurements taken from the brachial artery were taken at the end of the diastole according to the ECG trace. After the basal brachial artery diameter was recorded, the cuff of the sphygmomanometer was tied to the arm. It was inflated at an average pressure of 200 mmHg and kept in this way for 5 min. The cuff was then abruptly lowered and the transducer was properly placed on the skin at the point that had been previously marked using a pencil. In order to evaluate the hyperemic response, the brachial artery image was taken for 90 second and the artery diameter at first minute was measured at the end of diastole. The percentage change in the FMD value with respect to the basal vessel diameter was calculated according to the formula below.

FMD%=[(peak diameter–baseline diameter)/ baseline diameter]×100

Pulse Wave Velocity

The pulse wave velocity (PWV) was calculated using the SphygmoCor system (AtCor Medical, West Ryde, NSW, Australia). Patients were monitored primarily with 3-channel ECG. Then, after resting for 10 minutes in the supine position, the ultrasound probe was placed in the left supraclavicular fossa and angulated medially to target the subclavian artery exit from the aorta, and the right femoral artery was used as the distal measurement point. In the Doppler spectral recording taken from the aorta and femoral artery using a continuous-wave doppler, the systolic deflection starts were taken as the reference point and the distance differences between the R wave on the ECG recordings were recorded as the time between the reference points [transit time (T)] of the PWV. Next, the distance between the reference points (D) was determined in meters with the surface measurement. Accordingly, it was calculated as PWV=D/T (m/s).

Statistical Analysis

Normality testing was performed with the Kolmogorov-Smirnov test. Normal distributions were shown as mean±standard deviation and non-normal distributions as median (interquartile range (IQR): 25–75). Categorical variables were expressed as numbers and percentages. Differences between groups of numerical variables were evaluated with Student T-test or Mann-Whitney U test according to normality distribution. Comparison of categorical variables were performed Chi-square, Yates correction, and Fisher exact tests. The correlation between numerical variables were tested by Pearson and Spearman correlation analysis. Stepwise multivariable linear regression analyses were conducted to establish any possible independent predictors of CIMT, FMD and PWV. All statistical data were analyzed by STATA (StataCorp, Texas, ABD), and $p<0.05$ was considered to be statistically significant.

RESULTS

The IPF group consisted of 40 male (72.7%) and 15 female (27.3%) patients (mean age 65.0±9.8 years). The mean age, gender distribution and smoking rate were similar between the IPF group and the control group. The demographic and clinical findings are shown in detail in **Table 1**. The mean CIMT (1.1±0.4 mm vs. 0.8±0.2 mm; p=0.002), median PWV (16.4 vs. 11.4 m/s, p<0.006), mean leukocyte (9.6±2.2 vs. 7.2±2.1 ×103/μL, p<0.001), mean HCT (42.6±4.8 vs. 39.8±3.2 %, p=0.002), and median CRP (5.4 vs. 2.7 mg/L, p<0.001) levels were higher in IPF group compared to the control group, and median FMD was lower (8.7 vs. 14.7 %, p=0.010) (**Table 1**).

There was a positive correlation between the CIMT and PWV levels (r=0.536, p<0.001). There was negative correlation between FMD and CIMT (r=–0.544, p<0.001) and PWV levels (r=–0.419, p<0.001). The CRP levels were positively correlated with CIMT (r=0.359, p=0.009) and PWV (r=0.338, p=0.018) levels, while it was negatively correlated with FMD levels (r=-0.372, p=0.004) (**Table 2**).

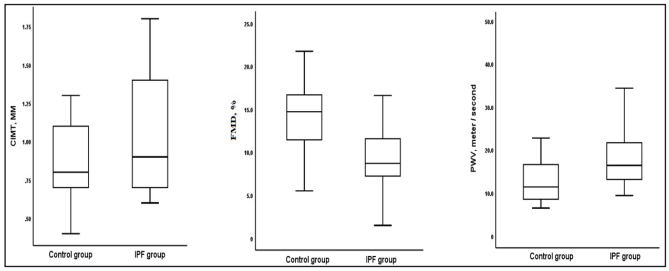

Figure 1. Cardiovascular risk indicators in IPF patients

Abbreviations: IPF: Idiopathic pulmonary fibrosis, PWV: Pulse wave velocity, FMD: Flow-mediated dilation, CIMT: Carotid-intima media thickness.

Table 1. Distribution of the demographic and clinical findings in study population.

Variables	Control group	IPF group	p
	n=55	n=55	
Demographic findings			
Age, years	63.6±9.5	65.0±9.8	0.449
Gender, n(%)			0.536
Male	36 (65.5)	40 (72.7)	
Female	19 (34.5)	15 (27.3)	
BMI, kg/m²	23.8±2.6	24.6±3.5	0.176
Smoke, n(%)	14 (25.5)	16 (29.1)	0.831
Diabetes mellitus, n(%)	-	11 (20.0)	-
Hypertension, n(%)	-	18 (32.7)	-
Gastroesophageal reflux, n(%)	-	15 (27.3)	-
SBP, mm Hg	118.1±12.6	122.3±11.8	0.074
DBP, mm Hg	70.1±8.6	72.8±11.3	0.161
Drugs, n(%)			
Drug-free or steroid	-	10 (18.2)	-
Pirfenidon	-	32 (58.2)	
Nintedanib	-	13 (23.6)	
Echocardiographic findings			
EF, %	59.5±2.4	58.6±3.2	0.149
Tricuspid regurgitation, n(%)	3 (5.5)	5 (9.3)	0.716
PAB, mmHg	27.8±6.8	32.7±11.3	0.055
Laboratory findings			
Hemoglobin, g/dL	13.6±1.1	13.9±1.7	0.267
Leukocyte, ×10³/μL	7.2±2.1	9.6±2.2	<0.001
Platelet, ×10³/μL	229.5±51.6	251.1±63.8	0.053
HCT, %	39.8±3.2	42.6±5.6	0.002
Triglycerid, mg/dL	147 (97-184)	123 (97-152)	0.202
HDL, mg/dL	50.1±11.2	49.4±15.8	0.797
LDL, mg/dL	138 (97-163)	132 (103-151)	0.722
Albumin, g/dL	42.1±7.7	41.2±3.3	0.424
UREA, mg/dL	32 (26-45)	33 (27-40)	0.914
Creatinine, mg/dL	0.8±0.2	0.9±0.4	0.124
Sodium, mmol/L	140.6±2.4	136.5±19	0.113
Potassium, mmol/L	4.4±0.3	4.5±0.4	0.362
CRP, mg/L	2.7 (0.9-5.6)	5.4 (2.9-13.3)	<0.001
Vascular parameters			
CIMT, mm	0.8±0.2	1.1±0.4	0.002
FMD, %	14.7 (11.4-16.7)	8.7 (7.1-11.9)	0.010
PWV, meter / second	11.4 (8.4-16.6)	16.4 (13-21.9)	<0.001

Categorical variables are expressed as the number (%), while numerical variables are expressed as the mean±standard deviation or median (IQR: 25–75).
Abbreviations: EF: Ejection fraction, PAB: Pulmonary artery pressure, CIMT: Carotid-intima media thickness, FMD: Flow-mediated dilation, PWV: Pulse wave velocity, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, HCT: Hematocrit, CRP: C-reactive protein.

Table 2. Parameters associated with the CIMT, FMD and PWV levels.

Variables	CIMT		FMD		PWV	
	r	p	r	p	r	p
CIMT	-	-	-0.544	<0.001	0.536	<0.001
FMD	-0.544	<0.001	-	-	-0.419	<0.001
Age	0.436	<0.001	-0.308	0.013	0.291	0.020
BMI	0.218	0.096	0.182	0.090	0.136	0.164
EF	-0.137	0.154	0.114	0.236	-0.053	0.581
PAB	0.179	0.101	-0.154	0.164	0.147	0.157
Hemoglobin	-0.118	0.222	-0.012	0.899	0.081	0.404
Leukocyte	0.281	0.048	-0.361	0.006	0.313	0.025
Platelet	0.131	0.174	-0.180	0.060	0.063	0.513
HCT	0.020	0.833	-0.129	0.179	0.152	0.126
Triglycerid	-0.131	0.171	-0.020	0.834	0.046	0.632
HDL	-0.319	0.016	0.310	0.013	-0.312	0.035
LDL	-0.149	0.191	-0.065	0.500	-0.045	0.644
Albumin	-0.111	0.250	0.184	0.084	-0.255	0.007
UREA	0.188	0.129	-0.065	0.502	0.075	0.439
Creatinine	0.133	0.160	-0.111	0.247	0.176	0.096
Sodium	0.012	0.904	0.120	0.201	-0.165	0.106
Potassium	0.155	0.146	-0.112	0.246	-0.098	0.469
CRP	0.359	0.009	-0.372	0.004	0.338	0.018

Abbreviations: EF: Ejection fraction, PAB: Pulmonary artery pressure, CIMT: Carotid-intima media thickness, FMD: Flow-mediated dilation, PWV: Pulse wave velocity, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, HCT: Hematocrit, CRP: C-reactive protein.

In multivarible regression models, the presence of IPF was common independent predictor of CIMT (β±SE=0.18±0.05, p=0.002), log(FMD) (β±SE=–0.15±0.04, p<0.001) and log(PWD) (β±SE=0.16±0.03, p<0.001). Also, increasing log(PWV) values were common independent predictors of CIMT and log(FMD) (**Table 3**).

DISCUSSION

In this cross-sectional study was showed that subclinical atherosclerosis is increased in IPF patients without cardiovascular risk factors. The relationship between cardiovascular risk indicators and CRP levels supports that the inflammatory process may play a pathological role in atherosclerosis. In addition, PWV was found to be a common independent predictor of both CIMT and FMD.

Although the fibrotic process is limited to the lungs in IPF, cardiovascular comorbidities are frequently observed (11). Despite this frequency, the relationship has not yet been clarified. One of the prominent hypotheses is that IPF promotes atherosclerosis (12). Decreased lung function in patients with IPF can cause chronic hypoxemia, and the imbalance between oxygen demand and supply in the arterial wall may play a key role in the development of atherosclerotic lesions (13). In the process of atherosclerosis, specific conditions (anoxia, inflammation, oxidative stress) induce angiogenic factors and predispose the patient to

the formation of atherosclerotic plaques (14). Abundant angiogenic chemokine has been detected in tissue samples from animal models and patients with IPF (15). Cytokines of interleukin (IL)-4, tumor necrosis factor-α, and IL-13, which show high levels in pulmonary fibrosis patients, can lead to atherogenesis in various ways (16). A circulating angiogenic factor may arise from the systemic vascular endothelium and affect the lungs (15, 17).

Data collected from the TOMORROW and INPULSIS studies confirmed a history of atherosclerotic CVD in approximately 20% of IPF patients (18). In the literature, subclinical atherosclerosis in IPF patients had mostly studied with a single cardiovascular risk indicator. Consistent with previous studies, we showed that an increase CIMT and a decrease FMD levels in IPF patients (19, 20). Abnormal endothelial physiology plays a role in the early stage and formation of atherosclerosis as well as in dynamic plaque control in the late stage. This suggests that the increase in CIMT may be after the deterioration of endothelial function in the arterial vessel wall (21). On the other hand, the presence of IPF was an independent predictor for increased indicators of cardiovascular risk. This finding suggested that IPF may cause endothelial dysfunction and result in CVD by accelerating the atherosclerosis process. There are several mechanisms that support this hypothesis. Firstly, strong nitric oxide expression was observed in the macrophages, neutrophils, and alveolar epithelium in the lungs of the patients with IPF, and increased nitric oxide production is responsible for oxidative damage (22). Secondly, increased oxidative damage plays a role in the development of endothelial dysfunction (23). Thirdly, activation of inflammatory cells may contribute, or trigger, to atherosclerosis (24). In atherosclerosis, lipid accumulation and activation of inflammatory cells in the arterial intima play an important role (25). When tissue damage occurs, macrophages accumulate in the damaged tissue due to the inflammatory response, and CRP expression is induced and increases with the progression of atherosclerosis (26). A previous study demonstrated that a positive correlation between CRP and carotid plaque in IPF patients (19). This may explain that the association between cardiovascular risk indicators and high CRP and low HDL.

Table 3. Independent predictors of CIMT, FMD, and PWV levels.

Variables	Univariable Regression			Multivariable Regression		
	β±SE	95% CI lower; upper	p	β±SE	95% CI lower; upper	p
CIMT						
Age	0.02±0.01	0.01; 0.02	<0.001	0.09±0.02	0.05; 0.14	<0.001
Male gender	0.11±0.07	-0.30; 0.24	0.123	-	-	-
IPF presence	0.21±0.06	0.09; 0.33	0.001	0.18±0.05	0.07; 0.28	0.002
Leukocyte	0.08±0.01	-0.02; 0.03	0.529	-	-	-
HDL	-0.06±0.02	-0.10; -0.01	0.016	-	-	-
CRP	0.12±0.06	0.01; 0.24	0.011	-	-	-
log(PWV)	1.05±0.13	0.78; 1.31	<0.001	0.83±0.13	0.57; 1.09	<0.001
log(FMD)	-0.84±0.14	-1.11; -0.58	<0.001	-0.55±0.12	-0.81; -0.31	<0.001
				Adjusted R2= 0.568; p<0.001		
log(FMD)						
Age	-0.05±0.01	-0.09; -0.02	0.005	-0.04±0.02	-0.07; -0.01	0.030
Male gender	0.07±0.04	-0.08; 0.09	0.863	-	-	-
IPF presence	-0.19±0.03	-0.26; -0.13	<0.001	-0.15±0.04	-0.23; -0.08	<0.001
Leukocyte	-0.02±0.01	-0.03; -0.02	0.026	-	-	-
HDL	0.01±0.01	-0.01; 0.04	0.347	-	-	-
CRP	-0.06±0.04	-0.14; 0.12	0.096	-	-	-
log(PWV)	-0.39±0.09	-0.57; -0.20	<0.001	-0.17±0.04	-0.33; 0.01	<0.001
				Adjusted R2= 0.436; p<0.001		
log(PWV)						
Age	0.04±0.02	0.01; 0.07	0.049	-	-	-
Male gender	0.05±0.04	-0.28; 0.13	0.203	-	-	-
IPF presence	0.17±0.03	0.10; 0.23	<0.001	0.16±0.03	0.10; 0.23	<0.001
Leukocyte	0.02±0.01	0.01; 0.03	0.034	-	-	-
HDL	-0.03±0.01	-0.06; -0.01	0.013	-0.03±0.01	-0.05; -0.01	0.018
CRP	0.08±0.04	0.02; 0.16	0.016	0.11±0.04	0.04; 0.18	0.023
				Adjusted R2= 0.397; p<0.001		

Comorbidites and antifibrotics treatment effects were adjusted in all analyses.
Abbreviations: IPF: Idiopathic pulmonary fibrosis, HDL: High-density lipoprotein, PWV: Pulse wave velocity, FMD: Flow-mediated dilation, CIMT: Carotid-intima media thickness, β: Regression coefficient, SE: Standart error, CI: Confidence interval

Previous studies have shown the relationship between the PWV and coronary atherosclerosis (27, 28). The degree of atherosclerotic changes in the arterial system is significantly correlated with the PWV, and increased PWV, as a reflection of arterial stiffness, is an indicator of atherosclerosis. In addition, there is a positive correlation between PWV and endothelial dysfunction (24). To the best of our knowledge, we could not find any study evaluating arterial stiffness in IPF patients. However, it has been reported that the arterial stiffness increases in patients with chronic lung disease (29). In the current study, the PWV values were found to be higher in the IPF patients when compared to those in the control group. In addition, increased PWV values were found to be an independent predictor associated with decreasing FMD values and increasing CIMT values. In light of these findings, it was determined that increased arterial stiffness was associated with impaired endothelial function in patients with IPF and can contribute to the atherosclerosis process. Therefore, determining endothelial dysfunction in terms of both atherosclerotic process and cardiovascular risk may be important for prognosis in patients with IPF.

The main limitation of this study was that it did not allow for the establishment of the cause-effect relationship between IPF and atherosclerosis as a result of its cross-sectional nature. There may be a tight link between IPF and endothelial dysfunction; however, contrary to studies that have shown that IPF causes endothelial damage, it has also been shown that endothelial microparticles (30), and microvascular endothelial cell damage, and antiendothelial cell antibodies may play a role in the pathogenesis of IPF (31). Therefore, prospective controlled studies are needed on larger populations. Other important limitations included the low number of patients, as this was a single-center study, not evaluating atherosclerosis with coronary angiography, and not measuring the biochemical markers of the endothelial functions, such as asymmetric dimethyl arginine.

CONCLUSION

IPF patients without traditional or additional cardiovascular risk factors have elevated risk of endothelial dysfunction and atherosclerosis. A sustained inflammatory response may have play an important role in the process of atherosclerosis. Evaluating CIMT and FMD for subclinical atherosclerosis is technically difficult, requires highly skilled operators, and is expensive, and difficult to use as a readily available screening tool. Therefore, both endothelial dysfunction and subclinical atherosclerosis can be easily detected with PWV in patients with IPF.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of İstanbul Training and Research Hospital Ethics Committee (Date: 13.09.2019, Decision No: 1985).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: No conflict of interest was declared by the authors.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the manuscript, and they have approved the final version.

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