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REVIEW ARTICLE

Telemedicine/telehealth in Preventive Medicine

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Abstract

Telemedicine describes the remote medical support that the patients receive from physicians for their health. Telehealth, on the other hand, covers all subjects such as patient education, diagnosis, treatment, raising awareness about health issues, and includes mobile health as well as telemedicine. Preventive medicine describes practices and approaches to prevent undesirable situations and complications before, during, or after the occurrence of diseases.

Primary care providers, who practice preventive medicine most intensively, also frequently exercise telehealth practices. Cost-effectiveness, data security, addressing the lack of education of patients and doctors, redesigning computer systems in terms of ease of use, making necessary legal regulations, and simplifying bureaucratic duties create concerns for physicians and users.

Since physical contact with the patient is not possible, communication between the doctor and the patient should be maintained simultaneously through technological methods. Therefore, the existing infrastructure, internet network, and hospital data system should be both fast, and near-perfect. Telemedicine may be a very good alternative for patients, assuming that healthcare institutions are largely concerned with pandemic patients, or that the risk of Covid-19 has not yet been eliminated in hospitals.

Keywords: Telehealth, Telemedicine, Preventive Medicine, Covid-19, Mobile Health.

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INTRODUCTION

With the introduction of the coronavirus pandemic (Covid-19) into our lives, both remote working and its principles have become widespread and gained prominence in the new world order. The success of remote working practices in many areas brought up the widespread usage of these practices in the healthcare sector. In this review, the use of telemedicine/telehealth in preventive medicine practices and new developments that emerged with the Covid-19 pandemic will be discussed in light of the current literature.

Telemedicine describes the remote medical support that the patients receive from physicians for their health. Telehealth, on the other hand, covers all subjects such as patient education, diagnosis, treatment, raising awareness about health problems, and includes mobile health as well as telemedicine (1, 2, 3).

It is known that there are many approaches to telemedicine. It is stated that the first use of telemedicine was a warning system based on smoke communication regarding an epidemic disease. To give an example from the recent period, it is stated that in 1999, a patient in Antarctica shared the lump in her breast via satellite, she was diagnosed with cancer, and then chemotherapy agents parachuted to the station (4).

On behalf of telemedicine, for the first time in our country, it was ensured that the images of radiological examinations were on a web environment that could be accessed continuously, that these images were reported and that they could be accessed by citizens or physicians via the e-Nabiz application. Later, laboratory results were integrated into this system. In this way, physicians' work has been facilitated and repetitive examination requests have been prevented (5). Recently, the web-based application *'Neyim Var'* developed by the Ministry of Health within the scope of mobile use was made available to patients (6).

One of the topics to be discussed within the framework of Telemedicine/Telehealth is the billing issue. In Turkey, departments such as Gastroenterology, General Surgery, Psychiatry, and Family Medicine under Kocaeli University Faculty of Medicine, already provide telemedicine services under the name of "web clinics". However, there is no clear data on how these examinations will be billed or how they will be controlled by health institutions (7).

Another important issue is how much medical malpractice insurance will be included in this system. As the recently - increased malpractice cases and the high compensations have often led physicians to defensive medicine, telemedicine can raise new questions. The "Framework for the Implementation Procedures and Principles of TeleHealth Service" issued in 2015 specifies the procedures and principles for medical services only for aircraft and sea vehicles cruising within the Turkish Search and Rescue Area. In February 2021, the General Directorate of Health Information System of the Ministry of Health attempted to create a system called "dr.e.nabız" and even a user guide was published. However, due to unknown reasons, the system was not implemented. Therefore, although new steps have been taken in this regard, there are uncertainties in terms of both applicability and establishing a legal basis (7).

Table 1. WHO has identified five specific categories of telemedicine practices (8)

Teleradiology	Use and interpretation of digital radiology.
Teledermatology	Conveying and consulting medical information and images related to the skin.
Telepathology	Diagnostic consultation of pathology preparation image sections.
Telepsychiatry	Remote delivery of mental health services.
Remote patient monitoring (Monitorization)	Monitoring the health status of patients with restricted mobility or limited access with cameras, sensors, mobile applications, and various devices.

Preventive medicine describes practices and approaches to prevent undesirable situations and complications before, during, or after the occurrence of diseases (9). Prevention consists of levels called primordial, primary, secondary, tertiary, and quaternary prevention. Primordial prevention includes preventive services for the general

population. Water sanitation and tobacco control can be given as examples of this practice. Primary prevention refers to practices for the prevention of diseases for a particular risk group. Pneumococcal vaccination in adults is an example of this practice. Secondary prevention covers early diagnosis and treatment applications. Cancer screenings would be an example in this regard.

Tertiary prevention avoids undesirable situations and complications that may develop after the disease occurs. Rehabilitation of a stroke patient is an example of tertiary prevention. Quaternary prevention is "a practice to identify patients and communities at risk of over-medicalization, protect them from medical invasions, and provide them with scientifically and ethically acceptable care procedures". Avoiding exposing the person to excessive radiation for examination purposes is quaternary prevention (10). In this context, primary care providers who practice preventive medicine most intensively, also frequently exercise telehealth practices.

In Spain, telemedicine practices can also be carried out in primary care. In a study conducted here, it was concluded that the physicians are satisfied in terms of cost-effectiveness, but the lack of training of patients and physicians should be eliminated as well as the lack of data security, and computer systems should be redesigned to provide ease of use. In addition, participating physicians expect necessary legal regulations to be made and simplify their bureaucratic duties. Patients participating in the same study expressed their concerns about data security (11).

Again, in Australia, primary care physicians stated that they are in need of training and technical support regarding telehealth. In the study carried out in this region, the participants emphasized that there should be software integrated into their existing systems and that network connections should be developed. (12).

In Sweden, the experiences and care patterns of people receiving telemedicine services from primary health care providers were examined. According to this examination, the participants of the study conducted in Sweden stated that they are satisfied with the high accessibility. In addition, a decrease in consulting primary care and emergency departments was observed (13).

In a 2015 study conducted in the United Kingdom with 21 subjects from nursing homes without the telemedicine system and 27 more from ones with the system installed, it was found that in 20 months, the rate of consulting emergency departments decreased by 45%, and the costs of consulting healthcare providers decreased by 39% (14).

In a randomized controlled study conducted in the USA in 2020, it was found that medication compliance was 7 times higher in patients discharged from the hospital and followed up with a telehealth system for 12 months. No significant difference was observed between the rates of consulting emergency departments and hospitalization of the patients (15).

In a US-based study conducted with chronic obstructive pulmonary patients in which physical frailty was remotely monitored, patients admitted to the telehealth pulmonary rehabilitation clinic and the control group were examined based on elbow flexion and arm extension strength. Sensitivity was found to be high in monitoring physical frailty in both groups using the sensor-based system and camera-based telehealth system. It was seen that physical fragility could be monitored remotely by using a two-dimensional and high-resolution camera (16).

Society needs to use telehealth applications as well as health professionals. In the mobile health (mHealth) study conducted in the USA in 2019, the blood pressure and heart rate of the participants were measured for 12 weeks with the help of an application downloaded to their mobile phones and smartwatches. As a result of the study, an e-cohort identifies cardiovascular disease risk factors were defined. In addition, it was detected that the participants were highly compatible with the monitoring of cardiovascular parameters with a smartwatch (17).

The study conducted in Japan, in which patients with fatigue complaints were examined, is an alternative. Changes after personalized nutritional therapy based on remote blood data analysis were screened by the Anti-Aging QOL Common Questionnaire published by the Japanese Society of Anti-Aging Medicine. Ferritin, total protein, albumin, blood urea nitrogen, creatinine, total cholesterol, high-density lipoprotein cholesterol (HDL), triglyceride (TG), aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl

transpeptidase (γ-GTP), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), cholinesterase, creatine kinase (CK) and mean corpuscular volume (MCV) levels of patients were analyzed in the study. Before and after nutritional therapy, symptoms were followed up in 3-month periods using the questionnaire with telehealth application. After the treatment, a significant change was observed especially in the complaints of fatigue of the patients. Vitamin supplements and mineral supplements were used in nutritional therapy. Patients whose complaints did not regress were referred for medical treatment (18).

In cases where physical contact with the patient is not possible, the communication between the doctor and the patient should be maintained simultaneously through technological methods. Therefore, the existing infrastructure, internet network, and hospital data system should be both fast and near - perfect. Telemedicine may be a very good alternative for patients, assuming that healthcare institutions are largely concerned with pandemic patients, or that the risk of Covid-19 has not yet been eliminated in hospitals. For this reason, hospitals in many countries are trying to provide help for diseases that will require green zone examination through the telemedicine system (19).

Even if the entire infrastructure is complete, there will of course be communication problems. In a study conducted by Eberly et al. on the use of telemedicine during the Covid-19 pandemic, telemedicine has been found to be used at lower levels by elderly patients, Asian patients, and non-English speaking patients in the early days of Covid-19. Likewise, it was determined that telemedicine is used by female patients, African - American patients or patients of Hispanic origin, and patients with low socioeconomic status at lower levels (20).

Bolivia is one of the countries where remote monitoring of Covid-19 patients is carried out along with the pandemic. According to the data of the National Call Center, a low mortality rate was observed in patients who received teleconsultation. It could be seen in the data that the burden of the health system is alleviated when remote monitoring is done effectively (21).

Similar results were also obtained in Brazil. It was reported that as a result of the follow-up of Covid-19 patients using telehealth, resources are used effectively, and inequality of access is reduced. The biggest concern of Brazilian doctors when providing teleconsulting services was asymptomatic cases (22).

In Australia, the body temperature, heart rate, and oxygen saturation of Covid-19 patients without active comorbid disease and who can be treated at home or in other suitable places were monitored. No deaths were observed in the cases followed up. Telehealth applications have been effective in meeting health needs during the pandemic and have greatly prevented the healthcare systems from straining. Healthcare providers must anticipate problems with data transfer and develop strategies that can increase people's access to telehealth technologies (23).

CONCLUSION

Today, telehealth is generally used in the follow-up process of patients and is seen as a complementary rather than an alternative to physical rounds. In the light of these observations on Telehealth or Telemedicine, it has been seen that this system is useful. However, how and/or in which situations this system can be used needs to be discussed.

You will appreciate that taking advantage of this method, especially during the pandemic, will also alleviate the burden of the healthcare system. However, we believe that necessary legislative arrangements should be made in this regard, algorithms should be created for the follow-up of patients to be included in the telehealth system, information systems should be optimized and the necessary network infrastructure should be provided.

On the other hand, for the effective use and dissemination of these applications, the legal authorities and responsibilities of all healthcare professionals, especially physicians, regarding their transactions within the scope of telehealth, and also the rights and responsibilities of service recipients should be determined.

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ORIGINAL ARTICLE

Prognostic factors after pneumonectomy in non-small cell lung cancer

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Abstract

Background: This study aims to evaluate the factors affecting survival and mortality in patients who underwent pneumonectomy for non-small cell lung cancer.

Methods: The study included 241 pneumonectomy patients. Demographic data, mortality, histopathological characteristics, tumor stages, and 5-year survival rates were analyzed.

Results: The study included nine women (3.7%) and 232 men (96.3%). The patients' mean age was 58.4±8.0 (34–81) years. Forty-five patients (18.7%) were 65 years of age or older, and 196 patients (81.3%) were less than 65 years of age. The 30-day postoperative mortality rate was 7.9% (n=19). The only factor affecting mortality was determined as age 65 and over ($p = 0.012$). The median survival time was 52 months, and the 5-year survival rate was 49.4%. In multivariate analysis, advanced age, pN2 status, not receiving neoadjuvant treatment, performing sampling lymph node dissection, and not receiving adjuvant treatment were poor prognostic factors.

Conclusion: Age, pN2 status, neoadjuvant and adjuvant therapy, and lymph node dissection technique were determined as the most important prognostic factors affecting survival in patients who underwent pneumonectomy for non-small cell lung cancer. Age was the most important factor affecting mortality.

Keywords: Prognosis, Pneumonectomy, Survival Rate, Carcinoma, Non-Small-Cell Lung.

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INTRODUCTION

Lung carcinomas are currently the leading cause of cancer-related deaths. In non-small cell lung carcinoma, surgical treatment in the early stage is the gold standard. Although lobectomy is the most common resection performed for lung cancer, extended lung resections are required in some cases due to invasion of surrounding tissues.

Despite advances in surgical techniques, pneumonectomy still has higher morbidity and mortality rates than other anatomic resections. As it is associated with higher morbidity and mortality, compared to other lung resections, the effect of pneumonectomy on long-term survival is still controversial (1).

This study aims to evaluate the factors affecting survival and mortality in patients who underwent pneumonectomy for non-small cell lung cancer.

MATERIALS AND METHODS

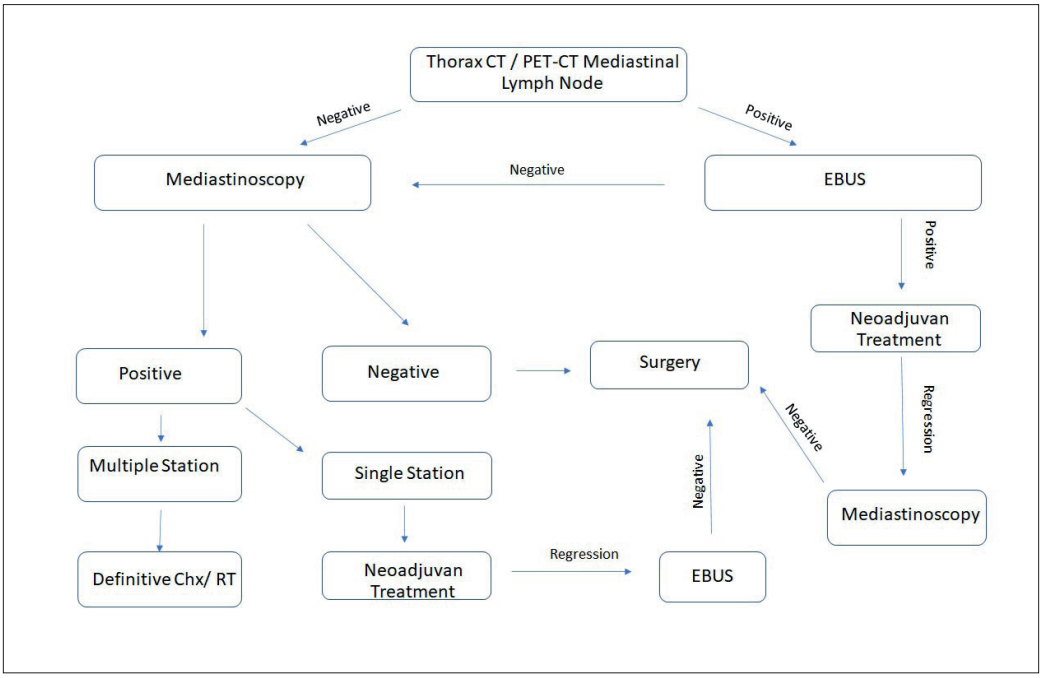
This study involved a retrospective analysis of data pertaining to patients who underwent pneumonectomy due to non-small cell lung carcinoma between January 2008 and December 2016. A total of 351 pneumonectomy patients were initially evaluated for the study. Of these, 11 patients whose data could not be accessed, eight patients who underwent incomplete resection, 32 patients who underwent completion pneumonectomy, 51 patients who underwent carinal sleeve pneumonectomy, and eight patients who underwent pneumonectomy due to complication were excluded. Histopathologic results other than squamous cell carcinoma and adenocarcinoma cell type were excluded in order to include homogeneous groups in the study. Consequently, the study included 241 patients. 9 of 29 patients received neoadjuvant treatment for N2 disease, 20 patients received neoadjuvant treatment for tumor size.

This study was approved by the clinical research ethics committee of the Health Sciences University, İstanbul Training and Research Hospital (Date: 28.06.2019 number: 1883).

Preoperative Evaluation

Preoperative thoracic computed tomography (CT) was ordered for all patients. In addition, positron emission tomography (PET-CT) and cranial magnetic resonance imaging (MRI) were requested for all patients to evaluate for distant metastases. Pulmonary function tests were done to assess pulmonary reserve. Patients with a history of cardiac disease and those 60 years of age and older were evaluated with echocardiography in the cardiology department. Fiberoptic bronchoscopy was performed preoperatively to evaluate endobronchial lesions. The preoperative mediastinal staging was performed in accordance with ESTS and ATS guidelines (2). Seven patients who received neoadjuvant due to N2 disease were evaluated by invasive staging (mediastinoscopy or EBUS) before resection. Resection was planned for patients who were found pN0. The preoperative lymph node evaluation algorithm is shown in Figure 1.

Figure 1 . Preoperative lymph node evaluation algorithm



All operations were performed with posterolateral thoracotomy incision. The surgical resections were classified as standard and extended. Extended resections were done in patients with invasion of the pericardium, main pulmonary artery, or chest wall.

In the study, the lymph node dissection technique was divided into sampling and Systematic nodal dissection as defined by ESTS (3).

Postoperative Follow-Up

Patients were reanimated in the operating room, then monitored in the surgical intensive care unit until their general condition was stable. Intravenous analgesic treatment was used for pain management. The patients' thoracic drains were removed when daily drainage volume was less than 300 ml.

The patient's demographic data, length of hospital stay, morbidity and mortality, histopathological characteristics, relapses, and 5-year survival rates were analyzed. In addition, data regarding the patients' age, comorbidities, histopathology results, tumor stage, adjuvant, neoadjuvant therapies received, and survival were obtained from hospital records and the national survival database. Pathologic staging was based on the 8th edition of the TNM classification system. There were 195 patients who received adjuvant therapy during the postoperative period.

Patients were followed with thoracic CT and physical examination in collaboration with oncologists every three months for the first two years, every six months between 2 and 5 years, and once a year after five years.

Statistics:

The patients' demographic and clinical data were evaluated using descriptive statistics. Chi-square (χ^2) test or Fisher's Exact test were used to demonstrate relationships between categorical data. Survival was evaluated by Kaplan–Meier analysis, while log-rank analysis was performed to compare factors. A p-value less than 0.05 was considered statistically significant. All statistical tests were performed using SPSS software (Version 22.0, SPSS Inc., Chicago, IL, USA).

RESULTS

The study included nine women (3.7%) and 232 men (96.3%). Twenty-nine patients (12.0%) received neoadjuvant therapy. The patients' mean age was 58.4±8.0 (range=34–81) years. Forty-five patients (18.7%) were 65 years of age or older, and 196 patients (81.3%) were less than 65 years of age. Left pneumonectomy was performed on 161 patients (66.8%), while right pneumonectomy was performed on 80 patients (33.2%). 62 (25.7%) underwent extended pneumonectomy and 179 patients (74.3%) underwent standard pneumonectomy. Fifty-four patients (22.4%) had adenocarcinoma, 187 (77.6%) had squamous cell carcinoma. Adjuvant therapy was given to 195 patients (80.9%). The demographic characteristics of the patients are shown in Table 1.

Table 1. Comparison of patients' demographic information and histopathological features

Variables		(n)	%
Gender	Male	232	96.3
	Female	9	3.7
Age (Year)	<65	196	81.3
	>65	45	18.7
CCI	0-2	137	56.8
	>2	104	43.2
Side	Right	80	33.2
	Left	161	66.8
Resection Type	Standard	179	74.3
	Extended	62	25.7
Lymph Node Dissection	Sampling	146	60.6
	Systemic	95	39.4
Histopathology	Adenocarcinoma	54	22.4
	Squamous	187	77.6
Tumor Diameter (cm) (Mean±SD)		5.24±2.9	
pN Status	N0	60	24.9
	N1	157	65.1
	N2	24	10
p-Stage	0	8	3.3
	1	14	5.8
	2	90	37.3
	3	129	53.5
Neoadjuvant Therapy	No	212	88
	Yes	29	12
Adjuvant Therapy	No	46	19.1
	Yes	195	80.9

CCI: Charlson Comorbidity Index, SD: Standard Deviation

The 30-day postoperative mortality rate was 7.9% (n=19). Gender, Charlson comorbidity index, operation side, histopathology, tumor stage, and neoadjuvant treatment did not affect mortality (p>0.05). The only factor affecting mortality was determined as age 65 and over (p=0.012). In patients 65 years and older mortality rate was %42.1 (n=8). Table 2 includes factors affecting mortality.

Table 2. Factors Affecting Mortality

Variables		Mortality (-)		Mortality (+)		p-value
		(n)	%	(n)	%	
Gender	Male	215	96.8	17	89.5	0.104
	Female	7	3.2	2	10.5	
Age (Year)	<65	185	83.3	11	57.9	0.012
	≥65	37	16.7	8	42.1	
CCI	0-2	128	58.1	8	42.1	0.176
	>2	93	41.9	11	57.9	0.176
Side	Right	77	34.7	3	15.8	0.093
	Left	145	65.3	16	84.2	
Resection Type	Standard	164	73.9	15	78.6	0.788
	Extended	58	26.1	4	21.1	
Histopathology	Adenocarcinoma	49	22.1	5	26.3	0.774
	Squamous	173	77.9	14	73.7	
Tumor Diameter (cm) (Median)		5		5		0.641
Tumor Diameter	<7 cm	203	91.4	17	89.5	0.675
	≥7 cm	19	8.6	2	10.5	
Neoadjuvant Therapy	No	194	87.4	18	94.7	0.484
	Yes	28	12.6	1	5.3	

CCI: Charlson Comorbidity Index, SD: Standard Deviation, Bold values indicate statistical significance (p<0.05)

The mean follow-up time was 53 months. The median survival time was 52 months, and the 5-year survival rate was 49.4%. In patients 65 years and older, the median survival was 28 months (31.1%) (p=0.002). The 5-year survival rate was 50.7% in patients with pN0-N1, while the survival rate was 37.5% in patients with pN2 (p=0.027). In patients who received neoadjuvant therapy, the average rate of 5-year survival was 65.5%, while the survival rate was 47.2% in patients who did not receive neoadjuvant treatment. (p=0.020). The mean 5-year survival rate was 62.1% in pneumonectomy patients who underwent systematic lymph node dissection, while the 5-year survival rate was 41.1% in patients who underwent sampling. The 5-year survival rate was 53.6% in patients who received adjuvant therapy, while the 5-year survival rate was 30.4% in patients who did not receive adjuvant therapy (Table 3).

Table 3. Factors Affecting Survival in Patients Undergoing Pneumonectomy

Variables		5 Year Survival (%)	Median Survival (Months)	%95 (CI)	Univariate Analysis p-Value
Age (Year)	<65	53.6	69	47-90	0.002
	>65	31.1	28	9-46	
Gender	Male	48.3	47	26-67	0.310
	Female	77.8	132	37-226	
Side	Right	51.3	61	39-82	0.520
	Left	48.4	41	17-64	
Histopathology	Squamous	51.3	65	45-84	0.456
	Adenocarcinoma	42.6	33	7-58	
N Status	pN0- pN1	50.7	61	41-80	0.027
	pN2	37.5	19	0-43	
Tumor Diameter	< 7cm	47.6	52	32-71	0.853
	> 7cm	49.5	33	0-115	
Resection Type	Standard	66.5	65	41-88	0.229
	Extended	45.2	38	9-66	
Neoadjuvant Therapy	No	47.2	41	22-59	0.020
	Yes	65.5	96	80-126	
Lymph Node Dissection	Sampling	41.1	35	25-44	0.005
	Systemic	62.1	92	58-125	
Adjuvant Therapy	No	30.4	13	0-26	0.001
	Yes	53.8	69	49-88	

CCI: Charlson Comorbidity Index. Bold values indicate statistical significance (p<0.05), CI: Confidential Interval

In multivariate analysis, advanced age, pN2 status, not receiving neoadjuvant treatment, performing sampling lymph node dissection, and not receiving adjuvant treatment were poor prognostic factors. In Table 4, a multivariate analysis of factors affecting survival is included.

Table 4. Multivariate analysis of factor affecting survival

Variables	HR	%95 CI		p-Value
		Lower	Upper	
Age	0.59	0.39	0.88	0.010
N Status	2.09	1.26	3.45	0.004
Neoadjuvant Therapy	0.48	0.27	0.86	0.014
Lymph Node Dissection	0.643	0.45	0.90	0.012
Adjuvant Therapy	0.48	0.32	0.72	<0.001

HR: Hazard Ratio, CI: Confidential Interval, Bold values indicate statistical significance (p<0.05)

DISCUSSION

Shapiro et al. stated ages 65 years and older, gender, comorbidities, and steroid use were predictors of mortality (4). In our study, the overall 30-day postoperative mortality rate was 7.9%. In our study, the only factor affecting mortality rate was determined as age. Pneumonectomy is considered a technique that surgeons avoid due to its high risk of perioperative complications and higher morbidity and mortality rates compared to limited anatomic resections. Pneumonectomy is still practiced today when complete surgical resection is required. Many studies have reported higher mortality rates in pneumonectomy than in limited resections (4–8). However, there is still no clear consensus on the perioperative approach for these patients. The prevailing view is to perform either sleeve resections or complex resections that cause less parenchymal loss than pneumonectomy to avoid high mortality rates.

In our study, the most important factors affecting survival were age, N2 disease, and receiving neoadjuvant and adjuvant therapy. In patients 65 years of age and older, the mean survival time was 28 months, while the 5-year survival rate was 31.1%. For patients under 65 years of age, these values were 69 months and 53.6%, respectively ($p<0.001$). Cusumano et al. reported that N2 status was a factor associated with poor prognosis (9). In our study, the mean survival times among patients with and without N2 lymph node involvement were 19 months and 61 months, respectively ($p=0.027$). Consistent with the literature, nodal involvement was one of the factors associated with poor prognosis (10). This emphasizes the importance of preoperative mediastinal staging in patients planned for pneumonectomy. In a 2010 report of a randomized phase 3 trial, Pisters et al. reported that neoadjuvant therapy increased survival rates but that the difference did not reach statistical significance (11). In the same study, it was also reported that adjuvant chemotherapy provided a significant survival benefit. In our study, adjuvant therapy was found to be the factor that provided a significant survival benefit. Patients who received adjuvant therapy survived for a mean of 69 months, compared to 13 months for those who did not ($p=0.001$). The 5-year survival rate of patients who received adjuvant therapy was 53.8%, significantly higher than the 5-year survival rate of those who did not (30.4%). Similar studies also reported that adjuvant therapy administered after complete resection significantly increased survival rates (12).

There are many studies on the role of neoadjuvant therapy in resectable lung cancer, but there is still controversy regarding its survival benefit (13). Some randomized trials and meta-analyses indicate that neoadjuvant therapy improves survival (14). However, other studies have suggested that it does not confer any survival benefit and in some single- and multicenter prospective randomized studies, performing pneumonectomy after neoadjuvant therapy was reported to have an adverse effect on mortality and morbidity (15–17).

Systematic lymph node dissection is the standard procedure in resection for lung cancer, but the value of this approach for survival and nodal staging is still uncertain. Adachi et al. found no significant differences between nodal sampling groups and systematic dissection patients' overall survival (18). Handa et al., in their study about segmentectomy patients, stated that performing mediastinal lymph node dissection was found to provide more appropriate pathological staging by harvesting more lymph nodes and the mediastinal lymph node dissection group tended to have a better prognosis (19). In this study, performing systemic lymph node dissection group has a better prognosis than the sampling group.

Potential sources of bias in the present study include its retrospective design, the inclusion of operations performed by different surgeons, and the small number of women in the patient sample. Moreover, the patients' lack of disease-free survival data is a source of bias in the results of the geriatric patient group.

In conclusion, age, pN2 status, neoadjuvant and adjuvant therapy, and lymph node dissection technique were determined as the most important prognostic factors affecting survival in patients who underwent pneumonectomy for non-small cell lung cancer. Age was the most important factor affecting mortality. Further investigation is needed to clarify the value of prognostic factors.

Declarations

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

This study was approved by the clinical research ethics committee of the Health Sciences University, İstanbul Training and Research Hospital (Date: 28.06.2019 number: 1883).

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ORIGINAL ARTICLE

The effects of lymph node dissection techniques on the survival of geriatric patients with non-small cell lung cancer

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Abstract

Background: Lymph nodes are the most important prognostic factors in lung cancer. Controversy still continues on lymph nodes prognosis. This study aims to evaluate the effects of lymph node dissection techniques on survival in geriatric patients.

Methods: The study was conducted retrospectively in patients who were operated on for non-small cell lung cancer (NSCLC) between 2007 and 2016. Lobe-specific lymph node dissection (LsLND) was performed in 77 patients, while complete (systematic) lymph node dissection (SLND) was performed in 206 patients.

Results: A total of 283 patients were included in the study, of which 258 were male (91.2%) and 25 were female (8.8%). The median age of the patients was 69 years (IQR: 65-84). The mean survival time of the patients was 46 months, and the 5-year survival rate was 38.9%. The survival rate in pN2 disease was 15.6%, while the survival rate in pN0 disease was 46%. While the 5-year survival rate was 34.4% in patients who underwent lobe-specific lymph node sampling, it was 40.5% in patients who underwent systematic lymph node dissection (p=0.147).

Conclusions: As a result of our study, no difference was found in terms of survival between lobe-specific lymph node dissection or systematic lymph node dissection in the geriatric age group. Especially pN2 disease, histopathological, and resection width were observed among the most important prognostic factors affecting survival. Therefore, we think lobe-specific lymph node sampling may be preferred instead of performing complete-systematic lymph node dissection in advanced ages because of less morbidity.

Keywords: Carcinoma, Non-Small-Cell Lung, Survival Rate, Prognosis, Lymph Nodes.

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INTRODUCTION

Lung cancers remain the leading cause of cancer-related mortality (1,2). In therapy, surgery has been accepted as the main procedure for the early stages. Surgical treatment is particularly avoided in elderly patients with lung cancer. The fragility of vascular structures of the elderly, the loss of elasticity of lung parenchyma, and high comorbidities are the main reasons for surgeons to avoid surgical treatments. However, patients over 75 years old are compared with younger ages, and it is seen that curative lung resection has been performed 22% less than elderly patients(3).

Today, there have been ongoing debates about lymph nodes which are one of the most crucial prognostic factors in lung cancer. It can be seen that there are different views and approaches in the literature related to the issue. There has not been a clear consensus about lymph node dissection, especially in the geriatric age group yet (4–6). While some suggest that it increases the complications and does not have an effect on survival and due to this reason, they offer simple lymph node dissection; some others think that complete lymph node dissection will increase the chance of survival of the patient.

In this study, our aim was to evaluate the effects of lymph node dissection techniques on the survival of geriatric patients.

MATERIALS AND METHODS

This study has been retrospectively conducted with patients who had operations due to non-small cell lung cancer (NSCLC) between 2007 and 2016. Patients with mortality, patients who received neoadjuvant therapy, and patients whose data cannot be reached have been excluded from the study. Two hundred eighty-three patients with NSCLC are evaluated in this study. The geriatric group is defined as over 65 years old in the study. All patients in the study are required a thoracic CT in order to evaluate the preoperative tumor localization. Positron emission tomography and cranial magnetic resonance imaging have been used to evaluate distant metastases. Respiratory function tests and carbon monoxide diffusion capacity (DLCO) have been used so as to evaluate respiratory capacities. As all the patients are geriatric, they have been examined by cardiology pre-operatively.

The lymph node dissections of the patients in the study are evaluated in two groups. While lobe-specific lymph node dissection has been performed in 77 patients (LN1), complete (systematic) lymph node dissection has been performed in 206 patients (LN2). The lymph node dissection techniques have been accepted as defined by Watanabe (7).

This study was approved by the clinical research ethics committee of the Health Sciences University, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital (Date: 29.07.2021 number: 2021/141) and written consent was obtained from all patients participating in the study.

Statistical Method:

Statistical analyses were done by using IBM SPSS Windows 22.0. While numeric variables were determined by mean±standard deviation and median (min-max), categorical variables were determined by number and percentage. Kaplan Meier analysis was used to evaluate the survival rate, and log-rank analysis was used to compare factors. In this study, the level of significance was accepted as $p<0.05$.

RESULTS

In the study, 258 male (91.2%) and 25 female (8.8%) patients were included. The median age of the patients was 69 years (IQR: 65-84). While pneumonectomy was performed on 61 patients (21.6%), lobectomy was performed on 222 patients (78.7%). Also, while right resection was performed on 155 patients (54.8%), left resection was performed on 128 patients (45.2%). The mean diameter of the tumors was found to be 4.5±2.3 centimeters. Systematic (complete) lymph node dissection was performed in 206 patients, and lobe-specific lymph node dissection was performed on 77 patients (27.2%). There were 124 (72.1%) patients with pN0, 58 (73.4%) patients with pN1, and 24 patients (75%) with pN2, who underwent systematic lymph node dissection. Forty-eight (27.9%) patients with pN0, 21 (26.6%) patients with pN1, and 8 patients (25%) with pN2 underwent lobe-specific lymph node dissection ($p=0.934$). Demographic, surgical, and histopathologic properties of the patients are shown in Table 1.

Table 1. Demographic and surgical characteristics of the patients

Variables		n	%
Gender	Male	258	91.2
	Female	25	8.8
Age (Median)	Year	69	
Side	Right	155	54.8
	Left	128	45.2
Operation	Lobectomy	222	78.4
	Pneumonectomy	61	21.6
pN Status	pN0	172	60.8
	pN1	79	27.9
	pN2	32	11.3
Histopathology	Adenocarsinoma	112	39.6
	Squamous Cell Carsinoma	158	55.8
	Other	13	4.6
Stage	I	88	31.1
	II	100	35.3
	III	95	33.6
Lymph Node Dissection Technique	LN1	77	27.2
	LN2	206	72.8

LN-1: lobe-specific lymph node dissection, LN-2: systematic lymph node dissection

The average survival time of the patients were 46 months, and the five-year survival rate was found to be 38.9%. While the five-year survival rate was 26.2% in the pneumonectomy patients, it was 42.4% in lobectomy patients (p=0.005). The survival rate was 41.6% in right-operated patients; on the other hand, it was determined as 54.6% in left-operated patients. It was determined that there was no statistically significant difference (p=0.057). While pN2 patient survival was 15.6%, pN0 patient survival was detected as 46%. The five-year survival rate was 34.4% in the patients for whom lobe-specific lymph node dissection has been done. On the other hand, the survival rate was determined to be 40.5% in patients for whom systematic lymph node dissection was performed (p=0.147). In the analysis of survival performed by excluding pN2 and pneumonectomy patients, the 5-year survival rate in the LN1 group was 40.7%, while the 5-year survival rate in the LN2 group was 47%. There was no statistically significant difference between the groups (p=0.135). Prognostic factors that affect the survival rate are shown in Table 2.

Table 2. Prognostic factors affecting survival

Variables		5 Year Survival (%)	Median Month	%95 CI	p-Value
Gender	Male	39.2	48	39-52	0.873
	Female	36	46	28-67	
Side	Right	41.6	52	45-58	0.057
	Left	54.6	37	22-51	
Operation	Lobectomy	42.4	50	42-57	0.005
	Pneumonectomy	26.2	26	11-40	
Histopathology	Adeno Carsinoma	35.3	41	32-49	0.008
	Squamous Cell Carcinoma	43.4	52	42-61	
	Other (Large Cell and Adenosquamous cell carcinoma)	15.4	12	0-28	
Lymph node	pN0	46	55	45-64	0.002
	pN1-pN2	27.9	37	25-48	
Lymph Node Dissection Technique	LN1	34.4	40	21-58	0.147
	LN2	40.5	47	39-52	

CI: Confidence Interval, LN-1: lobe-specific lymph node dissection, LN-2: systematic lymph node dissection

Based on the multivariate analysis of factors affecting survival, pN1-N2 status and large cell and adenosquamous cell carcinomas were found as poor prognostic factors. Multivariate analyses of prognostic factors affecting survival rate are shown in Table 3.

Table 3. Multivariate analysis of prognostic factors affecting survival

Variables		HR	%95 CI	p-Value
Operation	Pneumonectomy	1.34	0.9-1.9	0.123
Histopathology	Adenocarsinoma			0.004
	Squamous Cell Carcinoma	0.77	0.5-1.0	0.102
	Other (Large Cell and Adenosquamous cell carcinoma)	2.01	1.1-3.6	0.021
Lymph node	pN1-pN2	1.45	1.0-2.0	0.023

CI: Confidence Interval

DISCUSSION

The situation of the lymph node is one of the most important prognostic factors in lung cancers. Today, systematic lymph node dissection is one of the standard procedures in lung resections. European Society of Thoracic Surgeons (ESTS) suggests systematic lymph node dissection for complete resection to all patients(8). ESTS recommend at least three mediastinal lymph node (at least one of them subcarinal), and at least six lymph node must dissect for systematic lymph node dissection. However, in early lung cancers, radical dissection occurs more complications to the patients. Previous studies have shown that lobe-specific lymph node dissections have been foreseen as more practical than systematic lymph node dissections in lung cancers.

Sugi et al. have stated that among the patients for whom systematic lymph node dissection has been performed, the morbidity is higher than the ones for whom sampling has been done, and they also notified that a longer time is required intraoperatively (9). Particularly, they have stated that the operation time has been prolonged in systematic lymph node dissections on the left. There have been many publications from Japan that report that the best way to detect the metastasis rate (N-positive) in cancers is performed systematic lymph node dissection. Especially in peripheral tumors, it is a 10-25% possibility to see lymph node metastasis, and for this reason, systematic lymph node dissection is required to correct staging (9,10).On the other hand, Gajra et al.(11) have detected a difference between random sampling lymph node dissection and systematic lymph node dissection related to the survival of the patients. While the five-year survival rate is 56.4% in random sampling lymph node dissections, it has been 83.3% in systematic lymph node dissections. Besides, the selective lymph node dissection technique has been a more prioritized choice in minimally invasive surgeries (12,13). Especially, there have been some approaches that support using this technique not to increase morbidity among elderly patients. However, this approach is not accepted as a standard technique. Also, Hokage has stated that the survival rates of subcarinal lymph node metastasis positive upper lobe tumors have a worse course than isolated upper mediastinal lymph node metastasis. For this reason, Aokage does not recommend a selective lymph node dissection technique (14). Similarly, Ichinose and Okada have also determined that subcarinal lymph nodes have a worse course than superior mediastinal lymph nodes related to survival rates (15,16). Tulay et al. (17), they stated that intraoperative sentinel lymph node mapping would provide better information about the lymphatic drainage of the tumor, assist the surgeon in performing a better lymphadenectomy, and enable the detection of occult and micrometastatic disease for non-small cell lung cancer. Also, Turna et al.(18) mentioned sentinel lymph node is also defined as the most common involved of mediastinal lymph node station or stations for each pulmonary lobe. 96.5% of the patients of the right upper lobe tumors have lower paratracheal lymph nodes. In our study, we recommend removing sentinel lymph nodes at the lob-specific lymph node dissection.

In this study, a statistical difference has not been detected between systematic lymph node dissection technique and lobe-specific lymph node dissection technique. While the five-year survival rate has been 40.5% in systematic lymph node dissection, it has been 34.4% in lobe-specific lymph node dissection technique.

In this study, it has been found out that the most important factor that affects the survival of geriatric patients is the width of resection, large cell carcinoma, and pN2. While the five-year survival rate of the patients for whom pN0 is detected is 46%, this rate is 27.9% for whom pN1-2 is detected. In their study, Sezen et al. have not been found out a relation between the resection type and survival rates(19). It has been found out that while the five-year survival rate of the patients with lobectomy is 44.6%, it is 23.4% in the patients with pneumonectomy. It is thought that there has been a statistically non-significant result in this study due to the low number of patients. Besides, Li et al. have been detected that the survival rate of patients with lobectomy

is higher than the ones with pneumonectomy. It has been observed that the five-year survival rate is 25.7% for the patients with lobectomy, and it is 7.3% for the patients with pneumonectomy($p<0.001$, HR:1.96) (4).

This is a retrospective study by definition, and also there might be a bias due to the low number of patient groups that are included in the study. The limitation increases because the number of women patients is also low. Moreover, it is a single-center study, and a lack of disease-free survival analysis might cause limitations.

In this study, the lack of clinical staging data also creates bias. In our clinical practice, we don't have any consensus about systematic lymph node dissection and lobe-specific lymph node dissection techniques. The surgeons' preference for the lymph node dissection technique can cause heterogeneity in the study. Also, in this study, our aim is to evaluate the long-term results of the lymph node dissection. However, we didn't evaluate short-term outcomes in this study; for this reason, this increases the selection bias of the study.

In this study, as a result, it has been found out that there is no difference between lobe-specific lymph node dissection and systematic lymph node dissection in geriatric patients in terms of survival rates. It has been observed that pN2 disease, histopathology, and the type of resection are the most important prognostic factors that affect the survival rates. Although ESTS recommended systematic lymph node dissection for lung cancer; we think that both surgical techniques can be applied to elderly patients since there is no difference in survival rates between lymph node dissection techniques. However, multi-centered and prospective studies are still required.

Declarations

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This study was approved by the clinical research ethics committee of the Health Sciences University, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital (Date: 29.07.2021 number: 2021/141) and written consent was obtained from all patients participating in the study.

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ORIGINAL ARTICLE

A comparison of clinical results of transtibial and transportal anatomical techniques in the arthroscopic reconstruction of anterior cruciate ligament

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Abstract

Background: The present study aims to compare the clinical outcomes of patients who underwent arthroscopic anterior cruciate ligament (ACL) reconstruction with Transtibial (TT) and Transportal Anatomical (TA) techniques with the diagnosis of ACL rupture.

Methods: A total of 56 patients who underwent arthroscopic ACL repair in the Orthopedics and Traumatology Clinic of Menemen State Hospital between 2015 and 2020 were included in the study. The mean age of the patients was 25 years, and follow-up period was 31 months. Of the patients, 53 were male, 3 were female, and 43 had ACL ruptures in the right knee and 13 in the left knee. ACL reconstruction was performed using the TT technique in 29 patients and the TA technique in 27 patients. Patients were evaluated using the Lysholm Assessment score, the Modified Cincinnati Rating System Questionnaire, the Tegner Activity Level Scale, and the International Knee Documentation Committee scoring.

Results: There was a significant difference in pre and postoperative controls ($p<0.05$) and while normal and near-normal results were obtained with the TT (89%) and TA (87%) techniques, there was no statistically significant difference between the two techniques when the postoperative data were compared ($p>0.05$).

Conclusions: In this study, there was no significant difference between the two techniques in terms of clinical outcome and patient satisfaction. Although there are studies in the literature showing that the TA technique is superior in terms of knee stability, good results are obtained with both techniques.

Keywords: Anterior Cruciate Ligament, Transtibial, Transportal Anatomical, Femoral Tunnel.

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INTRODUCTION

The anterior cruciate ligament (ACL) is the primary stabilizer that limits the anterior translation of the tibia from the femur and has a mechanical function to prevent tibial torsion, valgus, and varus stresses (1,2). Due to its important function in knee kinematics, ACL insufficiency causes instability, pain and osteoarthritis in the knee, resulting in deterioration of the patient's quality of life (3,4). The success of ACL reconstruction depends on patient selection, surgical technique, and post-operative rehabilitation.

While the opening of the tibial tunnel in single-bundle arthroscopic reconstruction surgery in anterior cruciate ligament ruptures are the same in both transtibial and transportal anatomical methods, the opening of the femoral tunnel in both methods are different. In the transtibial technique, the femoral guide is passed through the tibial tunnel and placed on the medial surface of the lateral femoral condyle. The femoral tunnel is opened at 10:30 in the right knee and at 1:30 in the left knee, leaving 1-2 mm of the posterior cortex. In the transportal anatomical method, the femoral tunnel is opened using the medial portal or the accessory medial portal. The femoral guide is passed through the medial or medial accessory portal, and the femoral tunnel is opened from the anatomical attachment of the anterior cruciate ligament on the medial surface of the lateral femoral condyle.

In terms of surgical technique, transtibial and transportal anatomical techniques are commonly used to open the femoral tunnel (5-7). The transtibial technique has been used by orthopedic surgeons for many years, and good results have been reported (8-10). However, there are also studies stating that the transtibial (TT) technique is not anatomical and does not provide rotational stability (11-14). The transportal anatomical (TA) technique, also known as the anteromedial technique, is the technique adopted and widely used by orthopedic surgeons. Various studies have shown that the anteromedial technique provides better knee stability (15-18). There are also studies in the literature showing that there is no statistically significant difference between TT and TA techniques (19-21).

This study aims to compare the clinical outcomes of patients who underwent ACL reconstruction using transtibial and transportal anatomical techniques with the diagnosis of ACL rupture and to determine whether the two techniques have any superiority over each other.

MATERIALS AND METHODS

Between January 2015 and September 2020 74 patients with the diagnosis of anterior cruciate ligament rupture underwent arthroscopic ACL reconstruction in the Department of Orthopedics and Traumatology of Menemen State Hospital. A total of 56 patients with adequate follow-up period were included in the study. Arthroscopic ACL repair was performed using autogenous hamstring tendon graft with the transtibial technique in 29 (52%) patients and the transportal anatomical technique in 27 (48%) patients (Figure 1, 2). The mean follow-up period of the patients was 31 (6 – 68) months.

Figure 1. ACL reconstruction with transportal anatomical technique. (Postoperative anteroposterior (A) and lateral (B) X-Ray view)

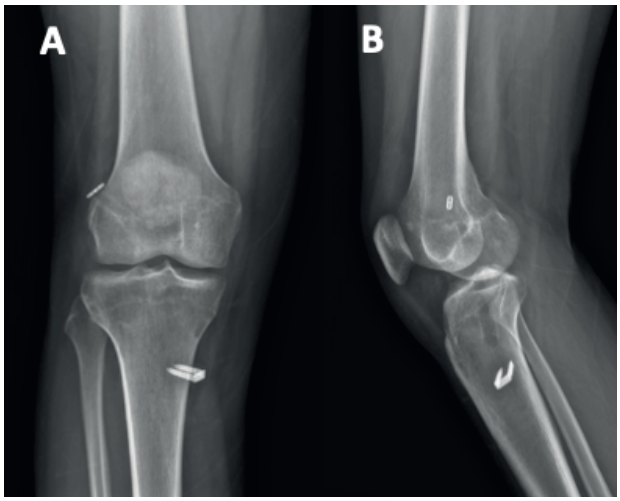
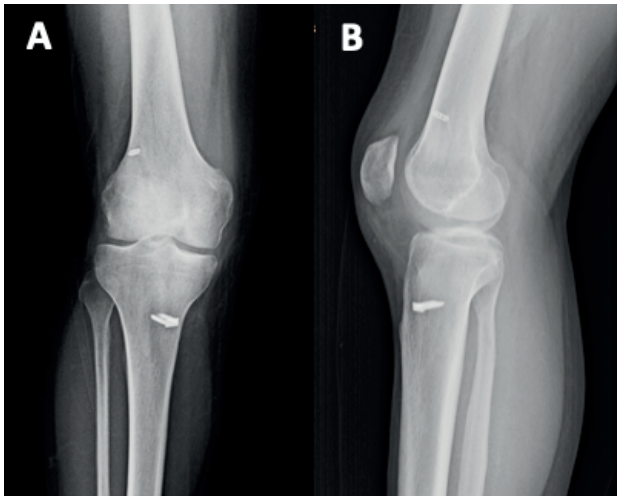


Figure 2. ACL reconstruction with transportal anatomical technique. (Postoperative anteroposterior (A) and lateral (B) X-Ray view)



The ethics committee approval was received for this study from the Ethics Committee of Izmir University of Health Sciences Tepecik Training and Research Hospital (Date: 17/05/2021. No: 2021/05-28). Of the patients treated with the TT technique, 27 (93%) were male and 2 (7%) were female. 21 (72%) patients had ACL rupture in the right knee and 8 (28%) in the left knee. The mean age was 25 (17-39) years. Of the patients treated with the TA technique, 26 (92%) were male and 1 (8%) was female. Twenty (74%) patients had ACL rupture in the right knee and 7 (26%) in the left knee. The mean age was 26 (18 -40) years (Table 1). The diagnosis was made according to the clinical examination and MRI findings of the patients.

Table 1. Patients demographics and baseline information.

	Transtibial	Transportal Anatomical
Number of patients	29 (%52)	27 (48%)
Age (years)	25 (17-39)	26 (18-40)
Male/Female	27 (93%) / 2 (7%)	21 (72%) / 8 (28%)
Right / left	21 (72%) / 8 (28%)	20 (74%) / 7 (26%)
Follow-up periods (month)	31 (6-68)	31 (6-68)

All patients were given 1 g first generation cephalosporin antibiotic prophylactically one hour before the operation. The graft removal and reconstruction were performed after the ACL rupture was arthroscopically confirmed.

Lysholm score, Tegner Activity Level score, Modified Cincinnati evaluation questionnaire and International Knee Documentation Committee (IKDC) evaluation form were filled in by all patients before the surgery and at the final checks.

All pre- and postoperative data of the patients in the study were recorded and statistical analyses were performed using the IBM SPSS Statistics 22.0 program. Significance level was accepted as p=0.05. The conformity of the variables to the normal distribution was tested with the Shapiro-Wilk test. Variables that did not fit the normal distribution were given with median (minimum-maximum) values, and the Mann-Whitney U test was used for comparisons between two independent groups, and the Wilcoxon test was used for comparison of two dependent groups. Categorical variables were given with frequency and percentage values (n (%)), and the Fisher's Exact Test and the McNemar-Bowker test were used for comparisons.

This study was approved by the clinical research ethics committee of the Health Sciences University Tepecik Training and Research Hospital (Date: 17.05.2021 number: 2021/05-28) and written consent was obtained from all patients participating in the study.

RESULTS

A significant difference was observed in the pre- and postoperative Tegner activity scores, Modified Cincinnati and Lysholm scores of the patients who underwent ACL reconstruction with the transtibial technique ($p<0.05$). Postoperative Tegner activity level, Modified Cincinnati and Lysholm scores were higher than preoperative scores (Table 2).

Table 2. Investigation of Tegner activity levels and Modified Cincinnati and Lysholm Scores before and after surgery in patients who underwent ACL reconstruction with the transtibial technique

	Before	After	Significance (p)
	Median (Min-Max)	Median (Min-Max)	
Tegner Activity Score	2(1-3)	7(5-8)	<0.001
Modified Cincinnati Score	40(16-50)	85(67-96)	<0.001
Lysholm Score	38(14-50)	85(68-95)	<0.001
p<0.05, Wilcoxon Signed-Rank Test			

There is a significant difference between IKDC scores in the transtibial technique ($p<0.05$). Patients treated with the transtibial technique show improvement in their postoperative IKDC scores compared to preoperative scores. (Table 3)

Table 3. Preoperative and postoperative IKDC scores of patients who underwent ACL reconstruction with the transtibial technique

Before	After				Significance (p)
	A	B	C	D	
A	0	0	0	0	0.010
B	1	2	0	0	
C	9	3	3	0	
D	7	3	1	0	
p<0.05, McNemar-Bowker Test					

(IKDC grade: A – normal, B – nearly normal, C – Abnormal, D – severely abnormal)

Preoperative and postoperative Tegner activity, Modified Cincinnati and Lysholm scores of patients who underwent ACL reconstruction with the transportal anatomical technique differ (p<0.05). Postoperative Tegner activity score, Modified Cincinnati and Lysholm scores of patients who underwent ACL reconstruction with the transportal anatomical technique were higher than preoperative scores. (Table 4)

Table 4. Preoperative and postoperative Tegner Activity Level, Modified Cincinnati and Lysholm Scores in patients who underwent ACL reconstruction with the transportal anatomical (TA) technique

	Before	After	Significance (p)
	Median (Min-Max)	Median (Min-Max)	
Tegner Activity Score	2(1-3)	7(5-8)	<0.001
Modified Cincinnati Score	42(30-53)	84(73-96)	<0.001
Lysholm Score	42(31-55)	85(68-96)	<0.001
p<0.05, Wilcoxon Signed-Rank Test			

There is a significant difference between the preoperative and postoperative IKDC scores of patients who underwent ACL reconstruction with the transportal anatomical technique (p<0.05). Patients undergoing ACL reconstruction with the transportal anatomical technique show an improvement in their postoperative IKDC scores compared to preoperative scores. (Table 5)

Table 5. Preoperative and postoperative IKDC scores of patients undergoing ACL reconstruction with the transportal anatomical technique

Before	After				Significance (p)
	A	B	C	D	
A	0	0	0	0	**0.004**
B	4	0	0	0	
C	8	4	2	0	
D	5	3	1	0	
p<0.05, McNemar-Bowker Test					

(IKDC grade: A – normal, B – nearly normal, C – Abnormal, D – severely abnormal)

There was no significant difference between transtibial and transportal anatomical techniques in terms of postoperative Tegner activity score, Modified Cincinnati and Lysholm scores (p>0.05). (Table 6)

Table 6. Postoperative Tegner activity level, Modified Cincinnati and Lysholm Scores of the Groups Included in the Study

	Post-operation		Significance (p)
	Transtibial	Transportal	
Tegner Activity Score	7(5-8)	7(5-8)	0.770
Modified Cincinnati Score	85(67-96)	84(73-96)	0.980
Lysholm Score	85(68-95)	85(68-96)	0.667
P<0.05, Mann-Whitney U Test			

There was no significant difference between the postoperative IKDC scores of patients who underwent ACL reconstruction with transtibial and transportal anatomical techniques (p>0.05). (Table 7)

Table 7. Postoperative IKDC Scores of the Groups Included in the Study

Postoperative IKDC Score	Transtibial	Transportal	Significance (p)
A	17(58.6)	17(63)	1.000
B	8(27.6)	7(25.9)	
C	4(13.8)	3(11.1)	
D	0(0)	0(0)	
p<0.05, Fisher's Exact Test			

(IKDC grade: A – normal, B – nearly normal, C – Abnormal, D – severely abnormal)

DISCUSSION

The ACL is the most injured ligament of the knee joint, and about 70% of tears occur during sports activities. Its incidence in the general population is approximately 1 in 3000 (22). Ligament reconstruction is widely used because of the low success rate in the conservative treatment of ACL injuries (23). The main goals of ACL reconstruction are to restore knee stability, restore pre-injury sports ability to the patient, and prevent joint degeneration in the long term (24-26). Transtibial and transportal anatomical techniques in ACL reconstruction are generally accepted by orthopedic surgeons, although debates continue regarding their superiority over each other (25,27,28). The success of ACL reconstruction surgery depends on many factors. Transtibial and transportal anatomical techniques are commonly used treatment modalities in ACL reconstruction (5-7).

In the present study, normal and near-normal results were obtained at a rate of 89% in the IKDC scores in ACL reconstruction performed with the transtibial technique, while this rate was 87% with the transportal anatomical technique. There was no statistically significant difference between the two techniques. There was no significant difference between transtibial and transportal anatomical techniques in terms of postoperative Tegner activity score, Modified Cincinnati and Lysholm scores.

Good results have been obtained for many years with the transtibial technique (8-10). It has been shown that the transtibial technique can generally lead to anteriorly located femoral tunnels (11,12,29). Kopf et al. suggested that although the transtibial technique prevents anterior translation of the knee, it does not provide rotational stability (30). Hefzy et al. reported that the most important cause of ACL graft failure is non-anatomical tibial and femoral tunnel location (31). There are studies showing that better results are obtained in terms of knee stability and functionality with the anatomical technique (15-18). Transportal drilling is considered the best option for anatomical placement of the ACL graft into the femur (32). Silva et al. stated that the anatomical technique placed the femoral and tibial tunnels in the center of the ACL footprint and provided better anteroposterior and rotational stability of the knee joint (29). Mirzatolooei et al. reported that the transportal anatomical technique achieved better short-term clinical results compared to the transtibial technique in ACL reconstruction (33). Alentorn-Geli et al. found a statistically significant difference in favor of the anatomical technique in their study including 1–2-year follow-up period. They reported that this was due to the more anatomical placement of the graft on the femoral side, but this difference was not observed between anatomical and transtibial techniques at 3-5 years and 6-10 years of follow-up (12). Metso et al. reported that there was no significant difference between the anteromedial and transtibial techniques in terms of maintaining knee stability (34). Jinzhong Zhao stated that an anatomical femoral tunnel will be created when the tibial tunnel is opened in accordance with the sagittal plane and tibial axis during the creation of the tibial tunnel (35, 36).

The limitations of our study are that it is retrospective, the number of patients included in the study is low, and there is no control group.

In conclusion, placement of the graft in accordance with the anatomy and tension, and fixation of the graft provide anterior-posterior and rotational stability of the knee joint in anterior cruciate ligament reconstruction. Although there are studies in the literature showing that the transportal anatomical technique is superior in knee stability, good results are obtained with both techniques. According to current study, it was considered that it could be achieved satisfactory results regardless to the technique if the tibial and femoral tunnels were opened appropriately according to the anatomy and the tension of the tendon graft.

Declarations

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

This study was approved by the clinical research ethics committee of the Health Sciences University Tepecik Training and Research Hospital (Date: 17.05.2021 number: 2021/05-28) and written consent was obtained from all patients participating in the study.

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ORIGINAL ARTICLE

Differences in the arthroscopic treatment of anterior and posterior shoulder instability in long-term follow-up

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Abstract

Background: Shoulder dislocations are frequent orthopedic injuries encountered in emergency services. Increasing the arthroscopic experience of physicians and developing technology has left the place of open surgical repair to arthroscopic reconstruction procedures. This study aimed to examine the results of arthroscopic reconstruction procedures for anterior and posterior shoulder instability.

Methods: In this study, 89 patients diagnosed with shoulder instability and treated arthroscopically in our clinic between January 1, 2013, and September 1, 2020, postoperative range of motion and functional results are evaluated with Rowe and WOSI scores.

Results: Fifty-seven of 89 patients had anterior, and 32 patients had posterior glenohumeral instabilities. In our study, 14 patients (15.7%) were under 20 years old, 55 patients (61.8%) between 21-30 years, 16 patients (18.0%) between 31-40 years, and 4 patients (4.5%) over 40 years. A total of 72 males (80.9%) were included in the study, with 17 females (19.1%). In the postoperative period, the mean shoulder joint flexion of all patients was recorded as 166.6 degrees, internal rotation 79.8 degrees, and external rotation was 79.9 degrees. The mean preoperative total WOSI score of all patients was 1062.6, whereas this score was 150.7 postoperatively. According to the Rowe score, there were poor results in all patients in the preoperative period, whereas the Rowe score of 70 patients was excellent; three patients were good, 11 patients were moderate, and five patients were poor in the postoperative period.

Conclusions: Arthroscopic treatment of glenohumeral instability could provide predictable success in unidirectional shoulder instability.

Keywords: Glenohumeral Instability, Arthroscopy, Shoulder, Dislocation.

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INTRODUCTION

Normal healthy shoulder function has been defined as the excellent harmony between mobility and stability (1). Shoulder mobility is primarily enabled by the glenohumeral joint, whereas its stability is provided through the complex interaction of anatomical structures that passively or actively stabilize the joint (2). The impairment of this mobility and stability balance in support of mobility is clinically reflected as a glenohumeral joint dislocation. Each year, about half of all major joint dislocations are glenohumeral joint dislocations (3).

Glenohumeral instabilities can be classified in several ways. If shoulder instability is classified as per the factor inducing it, it can be defined as traumatic or atraumatic. The direction of the movement can also characterize shoulder instability. Anterior and posterior instabilities are the most common types, while inferior, superior, and multidirectional instabilities have also been reported. To make a classification as per the degree of instability, two groups as dislocation and subluxation can be mentioned. When classified according to the time of injury, it can be defined as acute and chronic.

Approximately 80-90% of anterior shoulder dislocations typically occur after a trauma that applies excessive force on the shoulder in abduction and external rotation (4, 5). The incidence of traumatic anterior glenohumeral instability is 1.7% in the general population (6). When this traumatic event damages soft tissues or bone structures, such as the humeral head-glenoid, which contribute to shoulder stability, the risk for recurrent dislocation increases.

Posterior shoulder dislocation directly impacts the anterior shoulder or indirect forces when the arm is in abduction, internal rotation, and forward flexion (7). In general, indirect forces are electric shock and epileptic seizures. Compared to anterior instability, posterior shoulder instability is rarer and corresponds to 2-10% of all instability cases (8-10).

While it is assumed that immobilization for three to four weeks following the reduction of the first dislocation prevents recurrent dislocation, our current knowledge has indicated that immobilization for more than a week decreased the recurrence rate in cases with anterior dislocation for the first time (11). Recent studies have also shown that immobilization in internal rotation or external rotation does not provide superiority to each other in terms of recurrence rates (12).

Shoulder arthroscopy is an accepted method for treating many pathologies nowadays. The scope of injuries that can be treated with arthroscopic surgery has been broadened significantly owing to the technological developments in recent years and the increase in the skills and experiences of surgeons in arthroscopic intervention. Complex shoulder injuries have also been affected positively by these developments. Due to the possibility of early rehabilitation and minor damage to tissues, arthroscopic treatment has been widely accepted as preferred more than open surgery in instability surgery.

In our study, we aim to present the outcomes of our surgical technique by evaluating when patients could return to work and sports activities, whether they experienced the loss of workforce, at what level the shoulder joint ranges of motion were affected compared to the preoperative period, whether degenerative arthritis occurred clinically or radiologically in their glenohumeral joints after the surgery, whether their luxation or subluxation complaints continued after the surgery, and whether the direction of instability had an effect on the success of surgical treatment after arthroscopic instability surgery performed upon the physical examination and radiological evaluation of patients who presented with the complaints of shoulder instability.

MATERIALS AND METHODS

Patient Selection

This study included patients who presented to the clinic of orthopedics and traumatology in a university hospital with complaints of shoulder instability and underwent arthroscopic surgical repair between January 1, 2013, and September 1, 2020. The inclusion criteria of these patients were posttraumatic shoulder dislocation (at least once) and those who underwent arthroscopic anterior or posterior shoulder dislocation surgery. The study's exclusion criteria were non-traumatic voluntary dislocations and patients with multidirectional instability. This study included 89 patients who met these criteria. Of these 89 patients, 32 had posterior glenohumeral instability, and 57 had anterior glenohumeral instability.

Firstly, detailed medical history of patients who presented to our department with suspected instability was taken. It was questioned and recorded what patients' jobs were, whether they felt like their shoulders were dislocated, if they had dislocations before, what mechanism caused the dislocations, how many times they occurred, how old patients were when they had their first dislocations, when

they had their latest dislocations, whether the reduction procedure after dislocation was performed by a doctor under hospital conditions or they did it by themselves.

After questioning the medical history, sulcus, anterior-posterior drawer, Kim, anterior-posterior apprehension, and load and shift tests were routinely applied to patients to detect instability during physical shoulder examination and specify the type of instability, if any. Shoulder joint ranges of motion were checked and recorded.

The anteroposterior x-ray of the shoulder and shoulder arthro-MR were routinely requested from patients with a medical history and examination finding in favor of instability, and computed tomography images were additionally requested from patients with a suspected bone lesion.

After the plain x-rays, arthro-MR, and computed tomography images of the patients with instability were reviewed, an operation was planned for arthroscopic surgical repair for the patients for whom surgical fixation was deemed necessary.

Surgical Method

For arthroscopic repair, the patients were taken to the operating table in the beach chair position, their instability examinations were repeated under anesthesia, and then the arthroscopic procedure was initiated for their shoulder joints using posterior and anterior portals. We used a standard 30-degree angle scope. The posterior portal was opened 1.5 cm medial and inferior to the posterior corner of the acromion. Before the anterior portal was opened, the angle and position that would provide the best access to the glenoid labrum and anteroinferior capsule were determined with an epidural needle. The anterior portal was opened over the rotator interval, 1 cm lateral to the anterior corner of the acromion, under the guidance of the epidural needle, using the outside-in method. The presence of the anterior or posterior labral lesions was recorded. We decorticated the neck of the glenoid with a burr to reveal the bleeding bone necessary for tissue healing. The glenoid was drilled at a medial angle of 45 degrees to cover 2 mm of the glenoid lip, and a 2.9 absorbable or 3 mm metal anchor (Mitek 2.9 Lupine Ancor or 3 mm Fastin Threaded Anchor) was placed. The polydioxanone (PDS) was passed through the labrum and ligament, 5-7 mm inferior to the placed anchor with the help of a suture carrier system (Mitek, Ideal Suture Shuttle). Subsequently, the anchor threads were carried by this PDS and passed through the labrum and ligament. Afterward, sutures were placed with the sliding knot technique, and fixation was achieved.

Postoperative Management

In the postoperative follow-up, immobilization was ensured with a velpeau bandage for three weeks. Passive pendulum exercises were started immediately after surgery, and the patients were asked to do these exercises 5 times a day for 10 minutes. The stitches were removed on the 15th day. Physiotherapy was started in the 3rd week, and strengthening exercises were started between the 8th and 12th weeks. After the sixth month, they could return to sports activities.

In the third postoperative week, patients' ranges of motion were recorded without forcing them a lot. Until the sixth week, patients were recommended to do the described pendulum exercises to avoid carrying weight, internal-external rotation, and challenging stretching exercises.

In the sixth postoperative week, patients' ranges of motion were again checked and recorded. Patients were requested to perform the described abduction, adduction, flexion, extension, and internal-external rotation movements until the 10^{th} week.

At the postoperative 10^{th} week follow-up, patients' ranges of motion were re-checked, and patients were told that they could do all movements except contact sports and exposure to impact. They were explained that there would be no restriction in shoulder movements from the fourth month onward.

In addition to routine follow-ups, patients were called for follow-up in the second, fourth, and eighth months to evaluate their ranges of motion.

In the postoperative period, our treatment outcomes were assessed with the Rowe and WOSI scores. This study was approved by the clinical research ethics committee of the Atatürk University (Date: 08.12.2016 number: 19) and written consent was obtained from all patients participating in the study.

Statistical Analysis

SPSS 25.0 packaged software was used for data analysis. The distribution of data was assessed by the Shapiro–Wilk test. The Mann-Whitney U and Wilcoxon tests were applied since the data did not show a normal distribution. Data were evaluated at a significance level of 0.05.

RESULTS

When the patients in our study were divided into four groups as under 20 years of age, 20-30 years of age, 31-40 years of age, and over 40 years of age, 55 patients (61.8%) were in the 21-30 age group. A total of 14 patients (15.7%) under 20 years of age were determined. In total, 72 male (80.9%) and 17 female (19.1%) patients were included in the study. When the total number of dislocations in the shoulder joints that patients complained about were questioned, the mean total dislocation number was recorded as 5.1 (range: 1-12) in 89 patients (Table 1).

Table 1. Demographic data of the patients

Instability		Anterior (n: 57)	Posterior (n: 32)	Total (n:89)
Age		26.9 (SD: 6.9) [r: 18-45]	25.5 (SD: 5.7) [r: 18-39]	26.4 (SD: 6.5) [r: 18-45]
Total Number of Dislocation		6.3 (SD: 3.6) [r: 1-12]	2.9 (SD: 1.3) [r: 1-5]	5.1 (SD: 3.4) [r: 1-12]
Age categorical	<20	8 (14.0%)	6 (18.8%)	14 (15.7%)
	20-30	36 (63.2%)	19 (59.4%)	55 (61.8%)
	31-40	9 (15.8%)	7 (21.9%)	16 (18.0%)
	>40	4 (7.0%)	0	4 (4.5%)
Gender	Male	48 (84.2%)	24 (75.0%)	72 (80.9%)
	Female	9 (15.8%)	8 (25.0%)	17 (19.1%)
Side	Right	45 (78.9%)	16 (50.0%)	61 (68.5%)
	Left	12 (21.1%)	16 (50.0%)	28 (31.5%)
Dominance	Right	40 (70.2%)	23 (71.9%)	63 (70.8%)
	Left	17 (29.8%)	9 (28.1%)	26 (29.2%)
Trauma Mechanism	Falling	46 (80.7%)	2 (6.3%)	48 (53.9%)
	Sports injury	9 (15.8%)	11 (34.4%)	20 (22.5%)
	Epileptic attacks	2 (3.5%)	17 (53.1%)	19 (21.3%)
	Electrical accident	0	2 (6.3%)	2 (2.2%)
Dislocation Intervention	Doctor	44 (77.2%)	16 (50.0%)	60 (67.4%)
	Bonesetter	9 (15.8%)	10 (31.3%)	19 (21.3%)
	Patient	4 (7.0%)	6 (18.8%)	10 (11.2%)

SD: standard deviation; **r:** range

The degrees of shoulder joint flexion, extension, and internal-external rotation of patients were measured and recorded in the preoperative and postoperative 12th week. Preoperative and postoperative joint ranges of motion of patients in anterior and posterior groups are given in Table 2. Shoulder flexion range of motion was significantly higher in the patient group with anterior shoulder instability than in the patient group with posterior shoulder instability in both the preoperative period ($p<0.001$) and postoperative period ($p:0.012$) (Table 2).

Table 2. Preoperative and postoperative functional capacity of the patients' shoulder joints

		Anterior	Posterior	Total	p-value*
Shoulder Flexion	Preop	176.4 (SD: 3.9)	173.1 (SD: 3.7)	175.2 (SD: 4.2)	***<0.001***
	Postop	167.5 (SD: 11.5)	165.0 (SD: 6.2)	166.6 (SD: 9.9)	***0.012***
	Z	-5.427	-4.490	-7.033	
	p-value**	***<0.001***	***<0.001***	***<0.001***	
Shoulder Internal Rotation	Preop	86.0 (SD: 4.0)	85.9 (SD: 3.4)	86.0 (SD: 3.8)	0.690
	Postop	80.1 (SD: 3.4)	79.4 (SD: 8.2)	79.8 (SD: 7.0)	0.816
	Z	-5.504	-3.792	-6.644	
	p-value**	***<0.001***	***<0.001***	***<0.001***	
Shoulder External Rotation	Preop	86.9 (SD: 2.9)	85.6 (SD: 3.3)	86.5 (SD: 3.1)	0.070
	Postop	79.4 (SD: 11.2)	80.9 (SD: 3.9)	79.9 (SD: 9.2)	0.713
	Z	-5.336	-4.261	-6.774	
	p-value**	***<0.001***	***<0.001***	***<0.001***	

* Mann-Whitney U test to compare preoperative and postoperative results.

** Wilcoxon test to compare preoperative and postoperative results

SD: standard deviation

Patients' preoperative and postoperative 12th-week Rowe and WOSI scores were calculated and recorded. A significant difference was observed between the preoperative and postoperative Rowe and WOSI scores of the patients in anterior and posterior groups. However, no significant difference was identified between the scores when analyzed as per the type of instability variable (Table 3).

Table 3. Preoperative and postoperative Rowe and WOSI scores of the patients

		Anterior	Posterior	Total	p-value*
Rowe	Preop	31.6 (SD: 4.6)	30.9 (SD: 3.7)	31.3 (SD: 4.3)	0.501
	Postop	86.9 (SD: 15.1)	87.2 (SD: 16.1)	87.0 (SD: 15.4)	0.574
	Z	-6.613	-5.022	-8.259	
	p-value**	***<0.001***	***<0.001***	***<0.001***	
WOSI	Preop	1033.0 (SD: 181.1)	1115.3 (SD: 254.8)	1062.6 (SD: 212.9)	0.165
	Postop	189.0 (SD: 284.0)	82.6 (SD: 116.7)	150.7 (SD: 242.4)	0.252
	Z	-6.489	-4.941	-8.154	
	p-value**	***<0.001***	***<0.001***	***<0.001***	

* Mann-Whitney U test to compare preoperative and postoperative results.

** Wilcoxon test to compare preoperative and postoperative results

SD: standard deviation

Considering the Rowe score obtained in our study, all our patients had poor results in the preoperative period, whereas, out of 89 patients, 70 had excellent results, 3 had good results, 11 had moderate results, and 5 had poor results in the postoperative period.

DISCUSSION

In this study, falling was the primary cause of the patients with a history of anterior shoulder dislocation. At the same time, epileptic attacks were the primary cause of patients with posterior shoulder dislocation. In this study, the functional and clinical outcomes of patients with anterior or posterior shoulder instability after arthroscopic repair were similar. Arthroscopic surgery was successful in both patient groups.

Shoulder joint dislocations and instability are serious orthopedic problems influencing an individual's normal life and sports success. Acute anterior shoulder dislocation following trauma is a frequent injury that affects between 0.5 and 1.7% of people. Recurrence is reported in close to 90% of instances when it develops in young adults (13).

Anterior glenohumeral instability is the most observed type of glenohumeral instability (14). Of the 89 patients diagnosed with glenohumeral instability included in our study, 57 (64.0%) had anterior glenohumeral instability, and 32 (36.0%) had posterior glenohumeral instability.

Upon reviewing the literature in terms of etiology; Postacchini et al. (15) stated that 75% of anterior dislocations occurred due to trauma, while Robinson et al. (16) reported that posterior dislocations occurred after an accident-fall from a height by 67% and after epileptic seizures by 31.3%. In our study, of 57 patients with anterior instability, 46 described a history of shoulder dislocation after a fall, nine after a sports injury, and two after an epileptic seizure. Of 32 patients with posterior instability, 17 had a history of shoulder dislocation after an epileptic seizure and two after electric shock.

Open surgical repair, considered the gold standard in Bankart repair after a traumatic anterior shoulder dislocation, has been replaced by arthroscopic repair as a result of today's technological developments and increasing arthroscopy experiences (17). Cole and Romeo obtained similar Rowe score in open and arthroscopic Bankart repair and suggested higher score could be obtained as techniques were improved (18).

When the difference between the preoperative and postoperative joint ranges of motion in the anterior instability group was compared to that of the posterior instability group, the postoperative mean external rotation value in the anterior instability group was similar to the postoperative mean external rotation value in the posterior instability group. We believe that this difference, which does not lead to a subjective complaint in patients and does not have any statistical significance, results from the narrowing of the capsule in the direction of instability in the treatment of instability.

The restrictions in the joint movements of the patients in the postoperative period were not found significant when assessed in terms of functional life and subjective complaints. We anticipate that the degrees we obtained in present joint movement restrictions can be reduced to lower values when more effective rehabilitation programs are used, and patients are followed up closely by a specialist physiotherapist.

Raffaele et al. asserted that the Constant and Rowe scores had similar values to those of the contralateral shoulders in patients who underwent arthroscopic Bankart repair and were followed up for about 43 months (17). Yan H et al. found the mean Rowe score of 188 patients, whom they followed up for about 25.3 months, as 91.9 (19). Iwaso H et al., on the other hand, reported that the mean Rowe score increased to 82 in their study on 28 patients (20). In our study, preoperative and postoperative 12th-week Rowe scores of the patients were calculated and recorded. The preoperative mean Rowe score of 89 patients was 31.3, whereas the mean postoperative score was 87.0. A significant difference was observed between the preoperative and postoperative Rowe score of the patients ($p<0.001$). When these values are taken into account, the postoperative Rowe score obtained in our study seems to comply with the literature.

Because it is valid and widely acknowledged, the WOSI score was chosen as the most acceptable functional outcome score for enrolment. As reflected by the WOSI score, our arthroscopic stabilization outcomes were consistent with those of previous research (21-24).

There are several limitations of this study. The study was conducted in a single center and with a limited number of patients. The fixed study duration resulted in only 1 or 2 years of follow-up for some patients. Different results could be obtained in multicenter studies with large patient numbers.

Arthroscopic shoulder stabilization could provide predictable success in unidirectional shoulder instability without previous surgical intervention. Success rates may be lower in patients who have had previous surgery and in studies with large patient numbers with multiple instabilities.

Declarations

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

This study was approved by the clinical research ethics committee of the Atatürk University (Date: 08.12.2016 number: 19) and written consent was obtained from all patients participating in the study.

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ORIGINAL ARTICLE

The effects of the choice of the femoral head in hip hemiarthroplasty on radiological and clinical outcomes

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Abstract

Background: A displaced femoral neck fracture in patients over 70 years of age is a severe injury that affects the patient's quality of life. It is associated with increased morbidity and increased risk of mortality.

Methods: The cases were divided into a monopolar group (n=167) and a bipolar group (n=175). Data on age, gender, ASA scores, length of stay, and other diseases were obtained from the patients' files. Dislocation, infection and periprosthetic fracture rates were examined by examining the outpatient records of the patients in the postoperative period.

Results: The mean age of all patients included in the study was 79.7±8.16 years. 62.3% (n=213) of the patients were female and 37.7% (n=129) were male. There was no significant difference between the patients in the monopolar group and the bipolar group regarding complications (p=0.743). The 30-day mortality rates of the patients in the monopolar group were significantly higher than those in the bipolar group (p=0.041).

Conclusions: The use of the bipolar head in the surgical treatment of geriatric displaced femoral neck fractures with hemiarthroplasty may not provide any advantage in terms of functionality or complications.

Keywords: Femoral Neck Fracture, Geriatric, Hemiarthroplasty, Monopolar, Bipolar.

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INTRODUCTION

Femoral neck fractures (FNF) have a high incidence and it is a severe and life-threatening health problem with a 1-year mortality rate of 17 to 24% (1,2). A displaced FNF in patients over 70 years of age is a severe injury that affects the patient's quality of life and is associated with increased morbidity and increased risk of mortality (3,4). Open reduction internal fixation (ORIF) is rarely used in the elderly, given the chance of nonunion and worse patient outcomes after avascular necrosis and conversion to arthroplasty after a failed ORIF (3). In these patients, arthroplasty is now routinely performed (1,5).

Total hip arthroplasty (THA) or hemiarthroplasty (HA) are available as arthroplasty options in patients with geriatric FNF (6,7). HA is still considered the mainstay therapy for FNF in less active, elderly patients who do not impose high forces on the prosthetic joint; more than 75% of geriatric FNF are treated with HA (8-10).

Theoretically, bipolar head compared to monopolar head in the selection of femoral head in HA; it has the theoretical advantage of reducing acetabular cartilage wear and reducing the rate of dislocation thanks to its dual bearing system. In addition, the costs of the bipolar head are higher than the monopolar head (11). It is uncertain whether the benefits of the bipolar prosthesis justify its cost (1,11,12).

Our study hypothesis is that bipolar head use is not superior to monopolar head use in terms of complication and mortality rates in patients who have undergone hip HA. In light of this hypothesis, it was aimed to examine the effect of femoral head selection on these data by retrospectively looking at the postoperative data of the patients included in the study.

MATERIALS AND METHODS

The ethical committee approval of Health Sciences University Prof. Dr. Cemil Taşçıoğlu City Hospital was obtained for conducting the research (Date: 30/06/2020, decision no:293). This study was performed within the guidelines of the Helsinki Declaration. The files of patients who underwent HA with the diagnosis of FNF between January 2014 and December 2019 were reviewed. Patients with pathological fractures, patients who underwent THA, patients who underwent osteosynthesis, patients with neurovascular deficits, patients with neurologic disorders, patients younger than 65 years of age, and those who were missing follow-up were excluded from the study. The files of 342 patients aged 65 and over and diagnosed with femoral neck fracture who underwent HA were included in the study after the application of exclusion criteria. The cases were divided into two groups: a monopolar group (n=167) and a bipolar group (n=175) according to the characteristics of the applied femoral head.

All of the cases were operated under spinal or general anesthesia in the lateral decubitus position. Surgery was performed with a posterolateral approach. After the femoral head was excised, the femoral medulla was prepared by carving. After the application of the cemented femoral stem in appropriate sizes, the right size of the femoral neck and head was applied. Head selection (bipolar or monopolar) varied according to the surgeon's choice. After the prosthesis application, stability control was made by examination; then, a wound drain was placed, and the layers were closed anatomically.

The wound drain was removed within 48 hours postoperatively. If the cases did not have an exceptional situation to prevent them, they were mobilized with the help of a walker on the first postoperative day. The exercises that should be done and the movements that should not be done were explained to the patients by the physician. Enoxaparin 0.4 cc/day was administered to the patients postoperatively for the prophylaxis of venous thromboembolism, and anti-embolic stockings were worn.

Data on age, gender, American Society of Anesthesiology (ASA) score, length of stay, and other diseases were obtained from the files of the patients. INFINITT PACS (Picture Archiving Communication Systems) imaging program used in our hospital was used for radiographic evaluations. The surgical records of the patients included in the study were examined and divided into two groups according to the applied femoral heads. Dislocation, infection and periprosthetic fracture rates were analysed by reviewing the outpatient records of the patients in the postoperative period. Pelvic anteroposterior radiographs taken in the 6th month postoperatively of the survivors were evaluated for acetabular erosion. Again, the values of Harris hip scores were examined at the 6th-month outpatient controls. Using the hospital registry system, the death dates of the patients were reviewed to calculate the 30-day, 90-day and 1-year mortality. Then, the data of the bipolar and monopolar groups were compared statistically.

Statistical analyses were performed with SPSS version 25.0 software. The descriptive data were presented using mean, standard deviation, median and interquartile range (IQR) values. The compliance of the variables with normal distribution was examined with histogram graphs and the Kolmogorov–Smirnov test. The independent group t-test was used when evaluating the normally distributed (parametric) variables between the groups. The Mann–

Whitney U test and Kruskal Wallis H test assessed the non-normally distributed (non-parametric) variables between the groups. The Chi-square and likelihood ratio tests were used when determining the categorical data. Cases where the p-value was under 0.05 were accepted as statistically significant.

This study was approved by the clinical research ethics committee of the Health Sciences University, Prof. Dr. Cemil Taşcıoğlu City Hospital (Date: 30.06.2020 number: 2020/293) and written consent was obtained from all patients participating in the study.

RESULTS

The mean age of all patients included in the study was 79.7±8.16 years. 62.3% (n=213) of the patients were female and 37.7% (n=129) were male. There were fractures in the right hip in 45.9% (n=157) and left hip in 54.1% (n=185) of the cases. The mean age, gender, fracture types and distribution of ASA scores of the patients in both groups are shown in Table 1.

The distribution of complication and mortality rates obtained as a result of the collected data of the patients included in the study is shown in Table 2.

Table 1. Demographic data of the patients included in the study by groups

	Monopolar group (n=167)	Bipolar group (n=175)	p value
Age (Mean, SD)	81.57±7.56	77.99±8.34	***<0.001****
Gender (n, [%]) Female Male	 104 [62.3%] 63 [37.7%]	 109 [62.3%] 66 [37.7%]	0.998**
Side (n, [%]) Right Left	 77 [46.1%] 90 [53.9%]	 80 [45.7%] 95 [54.3%]	0.942**
ASA (n, [%]) I II III IV	 21 [12.6%] 49 [29.3%] 73 [43.7%] 24 [14.4%]	 18 [10.3%] 60 [34.3%] 70 [40%] 27 [15.4%]	0.707**
Number of comorbidity (n, [%]) 0-1 >2	 38 [22.8%] 129 [77.2%]	 22 [12.6%] 153 [87.4%]	**0.013****

* Student's t-test ** Pearson Chi-Square test

Table 2. Distribution of complications and mortality rates in patients according to groups

	Monopolar group (n=167)	Bipolar group (n=175)	p value
Complication (n, [%])	14 [8.4%]	13 [7.4%]	0.743*
Dislocation (n, [%])	10 [6%]	5 [2.9%]	0.158*
Periprostetic Joint Infection (n, [%])	4 [2.4%]	8 [4.6%]	0.274*
Periprostetic Fracture (n, [%])	1 [0.6%]	1 [0.6%]	0.739**
Acetabular erosion (n, [%])	5 [3%]	1 [0.6%]	0.11**
Harris Hip Score (mean, SD)	78.99±2.04	78.91±1.94	0.713***
Mortality (n, [%]) 30-day 90-day 1-year	 20 [12%] 25 [17%] 20 [16.4%]	 10 [5.7%] 19 [11.5%] 17 [11.6%]	 ***0.041**** 0.164* 0.262*

*Pearson Chi-Square test **Fisher's Exact test ***Student's t-test

DISCUSSION

Complication rates may increase with osteosynthesis treatment due to poor bone quality in elderly patients (12). Hemiarthroplasty for displaced femoral neck fractures in geriatric patients is an effective surgical treatment method that requires less revision surgery, less pain, higher satisfaction with the outcome of the operation, and a higher quality of life, without any difference in mortality (13,14). It has been produced with the theoretical design that the bipolar head can cause a decrease in acetabular wear and dislocation rates in hip hemiarthroplasty applications (9,15,16). However, the advantages in this regard are not clear, and there are results in the literature that even the bipolar head increases prosthesis dislocation compared to the monopolar head (9,11). In our study, there was no difference between the characteristics of the selected head component and the complication rates.

On the other hand, the mean age was significantly higher in the monopolar head group. Increased age may be associated with decreased activity. As a result of this situation, the similarity between the two groups in complication rates may have emerged. Perhaps in older patients with less activity, monopolar head selection may be the appropriate choice.

Functionally impaired patients have disadvantages such as occasional pain, acetabular erosion or implant loosening after HA, and the need for revision surgery as a result (7). The rates of acetabular erosion reported in the literature are variable and range from 0.6% to approximately 100% in long-term follow-up (17-19). At the same time, head selection may not affect revision rates due to this acetabular erosion (9). Although there was no relationship between acetabular erosion and its chief component in our study, it included early follow-up. For this reason, we believe that the selection of parts in the early period is not essential in need for premature acetabular erosion and the related revision.

Cemented HA may be associated with less pain and better functional scores (20,21). Also, cemented femoral stem may be related to lower re-operation rates (13,22). Although cemented stem was applied in all cases in our study; We believe that cemented femoral stem application is the application that should be preferred in geriatric patients due to reduced pain, early mobility advantage and reduced re-operation rates.

According to the results of a study comparing the functional results of bipolar and monopolar HA in femoral neck fractures, it seems that there is no advantage in using a bipolar endoprosthesis in the treatment of displaced FNF in the elderly. In addition, the extra cost of bipolar endoprostheses does not seem to warrant its use (11). Considering the results of our study, we also believe that the bipolar head does not provide a functional advantage. Perhaps the head choice in hemiarthroplasty is the result of the surgeon's belief in the theoretical advantages of bipolar treatments. On the other hand, the fact that the patients who underwent monopolar head in our study were older than the bipolar group may result from this belief. The fact that monopolar chief surgeons in older patients preferred it may have caused this situation.

The shortcomings of our study can be counted as being retrospective, inability to compare cemented and uncemented femoral stem applications, and short follow-up period. Another critical limitation of ours is that we could look at the acetabular erosions of the patients included in the study only with the 6th month postoperative radiographs. A prospective study can reveal these deficiencies, including different prosthesis selections and different groups with long-term follow-up.

In conclusion, using the bipolar head in the surgical treatment of geriatric displaced FNF with HA may not provide any advantage in terms of functionality or complications. Perhaps the choice of the femoral head in HA is simply a result of the surgeon's theoretical belief in the advantages of the bipolar head.

Declarations

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

This study was approved by the clinical research ethics committee of the Health Sciences University, Prof. Dr. Cemil Taşcıoğlu City Hospital (Date: 30.06.2020 number: 2020/293) and written consent was obtained from all patients participating in the study.

Author's Contribution

M.Y. and M.B.A. designed the protocol, reviewed the literature, analyzed the data, and critically reviewed and wrote the manuscript. A.Y., N.E. and T.O.B. analyzed the data, reviewed the literature, and critically reviewed and wrote the manuscript. B.K and S.S.D. designed the protocol, collected and analyzed the data, and reviewed the literature. Y.İ. and N.İ. collected and analyzed the data. H.G. collected and analyzed the data. All authors read and approved the final manuscript.

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ORIGINAL ARTICLE

Patients with third degree burns in an emergency department

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Abstract

Background: Skin protects the body against external factors, helps maintain physiological body temperature, and has sensory and immune functions. Burns can occur with electricity, radiation, chemicals, hot and cold factors. Since this is a very important public health problem, we aimed to analyze the epidemiological data of third-degree burns with high risk of mortality and morbidity in our emergency department.

Methods: Retrospectively, 73 patients with third-degree burns between January 2011 and December 2012 were included in the study. Demographic data of the patients, location and percentage of burn, cause, and mortality were recorded. Data between genders analyzed statistically.

Results: 79.5% of the patients were male. The mean age was 35±18 years. Flame burns were most common. It was determined that male patients had longer hospital stays. There was no statistically significant difference between age and gender in terms of mortality. It was observed that mortality increased as the percentage of burns increased.

Conclusion: Third-degree burns are the most common cause of burns with flame, as in young adult males. While there is no difference in mortality between age and gender, the death rate increases as the burn area increases. The frequency of burns can be reduced if the society is educated about protective measures against flammable and combustible materials. Thus, the bad results that may occur due to burns can be reduced. Therefore, regional epidemiological studies are needed.

Keywords: Third Degree Burn, Emergency Department, Epidemiology.

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INTRODUCTION

Burns occur when the skin is damaged, which can extend from the epidermis to the bone tissue, caused by the heat generated by flammable and caustic substances. Burns are graded according to the affected layer of the skin. According to this classification, third-degree burns involve all layers of the epidermis and dermis (1-2).Scalding is caused by flame, electricity, radiation and chemical substances.Flame burns cause especially deep and third degree burns.After the burns occur, it continues to be an important health problem due to the additional problems it brings in the healing process.In addition to medical and surgical applications, psychological and visual problems significantly affect the family as well as the patient (2). Burns are the fourth most common cause of trauma affecting humans, with 11 million cases worldwide each year. According to the World Health Organization, more than 300,000 people die from burns. This problem is more common in countries that are below the development chart (3-4). It is estimated that 1% of all people may experience a severe burn once in their lifetime (5). Burn data may contain regional differences. The socio-economic status of the regions may cause changes in data such as the causes and frequency of burns (6). In this study, we aimed to examine the mortality and morbidity of patients who were presented to the emergency department of our hospital with isolated or mosaic type third degree burns. We believe that the results obtained can provide important data in taking precautions to prevent the burn formation mechanism and planning treatment centers.

MATERIALS AND METHODS

Our study was carried out with the decision numbered E-19-2652 of the ethics committee of Ankara Numune Training and Research Hospital. It was carried out in accordance with the Declaration of Helsinki and good clinical practices. There is no conflict of interest between the authors. Our study was planned as a retrospective observational. Patient consent was not obtained because it was in the form of a file review over the hospital automation system and did not contain images that would enable patients to be identified.

Patients with third-degree burns admitted to our emergency department between January 2011 and December 2012 were evaluated retrospectively. The files of 81 patients who presented to the emergency department with burns, including isolated and mosaic type third-degree burns, were analyzed.73 patients were included in the study. Eight patients were excluded due to missing data.A form was prepared for the study. Demographic data, burn site, cause of burn, burn percentage, length of hospital stay and mortality status of the patients included in the study were recorded in this form. The latest status of the patients was followed up via the hospital information system (e-pulse). Data were recorded by 2 emergency medicine specialists. The other 2 emergency medicine specialists checked the data. The patients were divided into 2 groups as male and female. The relationship between age, burn site, percentage, cause, length of hospital stay and in-hospital mortality results was statistically analyzed between the groups. The percentage of burns was calculated according to the rule of 9s. According to the 9's rule, the head and neck are 9%, the trunk is 18%, the back is 18%, each of the arms is 9%, the perineum is 1%, and each of the legs is 18% (7).

This study was approved by the clinical research ethics committee of the Health Sciences University, Ankara Numune Training and Research Hospital (Date: 18.04.2019 number: 2652) and written consent was obtained from all patients participating in the study.

Statistical Analysis

Statistical analysis were made with IBM SPSS for Windows 16.0 Package Program. Frequency distributions of ordinal data were made with Pearson Chi-Square and Fisher's Exact tests.Distribution analysis of continuous data was made with the Shapiro-Wilk test, and the Mann Whitney-U test was used to compare the medians of the data that did not fit the normal distribution between the two groups. As a result of this test, the median, IQR, minimum and maximum values of the data are given.The Independent Samples-t test was used for comparisons of the two-group mean on data with normal distribution, and the results were expressed as mean and standard deviation.The p value was used for statistical significance and a $p < 0.05$ level was considered significant.

RESULTS

79.5% of the patients were male and the mean age was 35±18 years, and 9 (12.3%) patients died in the hospital within 30 days (Table-1).The mean duration of hospitalization was calculated as 27±23.The distribution of the patients according to the burn site and type of burn is shown in Table-1.Flame, electricity and hot water burns

are seen to apply frequently.The mean percentage of total body burns of the patients was 25% and the percentage of third degree burns was 12%.Although the mortality rate in women was higher than in men, but this difference was not statistically significant (12.1% vs 13.3%; p=1,000). Although the age was higher in the mortality group, no statistically significant difference was found (Median: 36 vs 32; p=0.425). Mortality percentages according to burn site and type are given in Table-2. As expected, the percentage of total burns and third-degree burns were found to be significantly higher in the mortality group (Table-3).Among all patients, it was found that the mean age was statistically significantly higher in female patients, and the mean burn percentages and hospitalization times were significantly higher in male patients (Table-4).The distribution in terms of burn location and type by gender is given in Table-5, and the order of frequency in male patients is flame, electrical and hot liquid burns, while in female patients it occurs as hot liquid, flame and solid contact burns (Table-5).

Table 1. Distribution of general data of patients

		Line- N (%)	Mean ± SD	Median (IQR)	Min-max
Gender	Male	58 (79.5)			
	Female	15 (20.5)			
Age			35±18	32 (22-44)	1-85
Hospital stay			27±23	18 (10-42)	0-97
Mortality	Alive	64 (87.7)			
	Exitus	9 (12.3)			
Burn site	Widespread body involvement	5 (6.8)			
	Head-neck+Trunk+extremity	12 (16.4)			
	Head-neck+Trunk+extremity+Perineum	3 (4.1)			
	Head-neck+extremity	3 (4.1)			
	Head-neck+extremity+Perineum	2 (2.7)			
	Trunk+extremity	9 (12.4)			
	Trunk+extremity+Perineum	2 (2.7)			
	extremity	37 (50.7)			
Burn site	Widespread body involvement	5 (6.8)			
	Head-neck	20 (27.4)			
	Trunk front back	26 (35.6)			
	Upper-Lower extremity	67 (93.2)			
	Perineum	7 (9.6)			
Type of burn	Explosion	4 (5.5)			
	Flame burn	24 (32.9)			
	Electrical burn	18 (24.7)			
	Thinner burn	4 (5.5)			
	Solid contact burn	3 (4.1)			
	Hot liquid burn	15 (20.5)			
	Dull burn	3 (4.1)			
	Chemical burn	2 (2.7)			
Percentage of 3rd degree burn			12±16	5 (3-15)	1-65
Burn percentage of total body burn area			25±24	18 (7-40)	1-100

Table 2. Distribution of patients by gender, burn site and type according to mortality.

		Mortality	
		Alive	Exitus
		Line- N (%)	Line- N (%)
Gender	Male	51 (87.9)	7 (12.1)
	Female	13 (86.7)	2 (13.3)
Burn site	Widespread body involvement	2 (40)	3 (60)
	Head-neck+Trunk+Extremity	8 (66.7)	4 (33.3)
	Head-neck+Trunk+Extremity+Perineum	3 (100)	0 (0)
	Head-neck+Extremity	3 (100)	0 (0)
	Head-neck+Extremity+Perineum	2 (100)	0 (0)
	Trunk+Extremity	8 (88.8)	1 (11.2)
	Head-neck+Extremity+Perineum	2 (100)	0 (0)
	Extremity	36 (97.3)	1 (2.7)
Burn site	Widespread body involvement	2 (40)	3 (60)
	Head-neck	16 (80)	4 (20)
	Trunk front-back	21 (80.8)	5 (19.2)
	Upper-Lower extremity	62 (91)	6 (9)
	Perineum	7 (100)	0 (0)
Type of burn	Explosion	2 (50)	2 (50)
	Flame burn	21 (87.5)	3 (12.5)
	Electrical burn	18 (100)	0 (0)
	Thinner burn	1 (25)	3 (75)
	Solid contact burn	3 (100)	0 (0)
	Hot liquid burn	14 (93.3)	1 (6.7)
	Dull burn	3 (100)	0 (0)
	Chemical burn	2 (100)	0 (0)

Table 3. Distribution of patients by age, length of hospital stay and percentage of burns by mortality.

	Mortality				
	Alive		Exitus		p-value
	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	
Age	34±18	32 (22-43)	41±21	36 (26-47)	0.425
Hospital stay	30±23	20 (14-44)	5±4	4 (2-7)	<0.001
3rd degree burn percentage	7±7	5 (3-10)	47±16	50 (40-60)	<0.001
Total Body Burn Area burn percentage	20±18	15 (6-29)	66±22	70 (45-80)	<0.001
Mann Whitney-U test					

Table 4.Distribution of patients by age, length of stay and burn percentage by gender

	Gender				
	Male		Female		P-value
	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	
Age	31±14	30 (21-39)	50±25	49 (28-73)	0.013*
Hospital stay	30±24	21 (12-45)	11±9	12 (2-15)	0.003**
3rd degree burn percentage	13±16	6 (3-15)	9±15	3 (1-8)	0.034**
Total Body Burn Area burn percentage	28±24	20 (8-44)	16±20	8 (4-26)	0.024**
*Independent Samples-t test **Mann Whitney-U test					

Table 5. Distribution of burn site and type of patients by gender

		Gender	
		Male	Female
		Count	Count
Burn site	Widespread body involvement	5 (8.6)	0 (0)
	Head-neck+Trunk+Extremity	10 (17.2)	2 (13.3)
	Head-neck+Trunk+Extremity+Perineum	3 (5.2)	0 (0)
	Head-neck+Extremity	2 (3.4)	1 (6.7)
	Head-neck+Extremity+Perineum	2 (3.4)	0 (0)
	Trunk+Extremity	9 (15.5)	0 (0)
	Trunk+Extremity+Perineum	1 (1.7)	1 (6.7)
	Ekstremity	26 (44.8)	11 (73.3)
Type of burn	Explosion	4 (6.9)	0 (0)
	Flame burn	21 (36.2)	3 (20)
	Electrical burn	17 (29.3)	1 (6.7)
	Thinner burn	4 (6.9)	0 (0)
	Solid contact burn	0 (0)	3 (20)
	Hot liquid burn	7 (12.1)	8 (53.3)
	Dull burn	3 (5.2)	0 (0)
	Chemical burn	2 (3.4)	0 (0)

DISCUSSION

In our study, we found that the patients with third-degree burns who applied to the emergency department due to burns were mostly young adult males and the most common cause was flame burn. When the burn area of the patients was examined, we saw that the extremities burned more. Burns continue to be an important health problem in our country. With the developing treatment methods and the establishment of burn centers, the mortality rate in burns is also decreasing. In the study conducted by Açıkel et al. in the first burn center of Istanbul, it was determined that burns were seen in men with a rate of 81% (8).In our study, 79.5% of the patients were male.In the study of İlhan et al., 78.2% of the patients were male. Halk et al. reported 68%, Demirel et al. 61.7%, and Pal et al. 71.68% burns in men (9-11). It is seen that burns are more common in men than women, but the rates vary according to regions and countries. In our study, it shows

similarity with the literature by drawing a more intense profile in men. Considering the age distribution in these studies, it was seen that the most affected group was in the 20-50 age range (8-11). In our study, we found the mean age to be 35±18 years and it was similar to the literature. When the burn sites were examined, it was seen that there was an effect on the extremities of all patients. The rate of burns limited only to the extremities was 50.7%. In other patients, in addition to extremity burns, torso, head-neck and perineal regions were accompanied. 5 patients had burns in all parts of the body.It was observed that these burns were respectively caused by flame, electricity and hot liquid (32.9-24.7-20.5%).The mechanism of burns was flame burns in 36.2% of men and electrical burns of 29.3%, while hot liquid burns in 53.3% of women.We think that this difference between the sexes is due to the fact that men work with machinery and in places such as industry with flammable-burning and electricity, while women deal with jobs that provide more contact with hot water at home.All results suggest that people do not take protective measures during operations with flammable and combustible materials and that their extremities are tried to be used to reduce the effect of burning.These results were similar to other studies in our study. İlhan et al., in their study, found that the most common type of burn was flame burns, followed by electrical and scalding burns (53.7%, 30.0%, 11.8%, respectively).It was found that men were exposed to flame and electric burns (50.0% and 38.4%, respectively), while women were exposed to flame and scalding (66.6% and 29.1%, respectively) burns (12). In a study conducted in Morocco, it was shown that flame burns were the most common cause of burns (45.6%) and that 93.1% of all patients were affected by thermal burns (13).Considering the percentage of total burns affected by the patients, the average burn area was 25%, while the average area affected by third degree burns was 12%.While the total burn area was 100% in only one of our patients, the third degree burn area was 60%.This patient died on the second day of hospitalization. Calder found the mean total body burn area to be 19% in his study in Afghanistan (14). In the study in which Özçetin et al. shared their 2.5-year experience, the burn area of the patients was found to be 30% or less in 97% of the patients (15).These results are consistent with the data in our study.12.3% of the patients in our study died. Although the mortality rate in women was higher than in men, no statistically significant difference was found.13.3% of women and 12.1% of men died. Although the age of the deceased group was high in the patients who died, it did not create a statistically significant difference. In the study of Shir Khoda et al., the mortality rate was found to be 41.47%, and Verma et al. found 36.5% (16,17).In the study of Ho et al., the mortality rate was found to be 2.3% (18).The reason for the difference between the studies may be due to the high burn rate of the patients in the studies of Shirkhoda and Verma, and the fact that the burn area in most patients was less than 10% in the study of Ho.Considering the results in our study, it was seen that the death rate increased as the burn area increased. The mean area of third-degree burns in deceased patients was 47%, while the total burn area was 66%.This rate was found to be significant in terms of the relationship between survivors.Other studies and our results showed that the death rate increased with the increase in burn area.When Song et al. looked at the duration of hospital stay, they found an average of 28.67 days in patients with a burn area of 30% or more (19).Jayaraman et al. showed that 19.2% of patients hospitalized for burns were hospitalized for longer than 15 days (20).In our study, the average total burn area was 25% and the average hospital stay was 27 days.The mean hospital stay was 30 days in surviving patients, and 5 days in deceased patients. We think that this result is due to the fact that burn treatment causes long-term hospitalizations. As a result; In third-degree burn cases, men are mostly affected and flame and burns are the most common factors. In women, burns are more common with hot liquids.While the death rate increases as the burn area increases, there is no difference between age and gender.Burns continue to be an important health problem in terms of mortality and morbidity, although we encounter different data even in the same geography.However, its incidence can be reduced with effective preventive measures.Programs and plans can be made for raising awareness and education of the society in terms of public health. For this, more regional epidemiological studies are needed.

Declarations

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

This study was approved by the clinical research ethics committee of the Health Sciences University, Ankara Numune Training and Research Hospital (Date: 18.04.2019 number: 2652) and written consent was obtained from all patients participating in the study.

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ORIGINAL ARTICLE

Predictive role of NLR, SII, and PLR in COVID-19 patient mortality and disease severity

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Abstract

Background: In this study, it was aimed to evaluate the factors affecting the prognosis and mortality of patients hospitalized for coronavirus disease 2019 (COVID-19).

Methods: Patients hospitalized with COVID-19 infection between March and November 2020 were examined retrospectively. The Systemic Immune-Inflammation Index (SII), platelet lymphocyte ratio (PLR), and neutrophil-lymphocyte ratio (NLR) values were evaluated for their effect on prognosis.

Results: Of the 1013 patients included in the study, 204 (20.1%) had a severe infection. In the multivariate analysis, it was determined that the prognosis was significantly worse in patients who were >65 years of age, had a Charlson Comorbidity Index (CCI) score of >2, and had a high NLR rate. The C-reactive protein (CRP), PLR, SII values were detected as insignificant variables. Mortality was found to be statistically significant in patients with a CCI score of 2 or more and in patients with high CRP, NLR, PLR, and SII values at the time of admission ($p<0.05$) in the multivariate analysis.

Conclusions: It was found that the most important factor affecting the severity of the disease was advanced age and high comorbidities, and a high NLR value. The most important prognostic factors affecting mortality were high levels of comorbidities, and high NLR, PLR, SII, and CRP values.

Keywords: COVID-19, Mortality, Prognosis, Systemic immune-inflammation index, Neutrophil Lymphocyte Ratio

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INTRODUCTION

The new coronavirus disease 2019 (COVID-19), which is also known as severe acute respiratory syndrome 2 (SARS-CoV-2), has caused unpredictable high morbidity and mortality rates in many countries. The clinical spectrum of COVID-19 ranges from asymptomatic infection to multiorgan failure. In fact, the basic clinical picture is manifested by pneumonia and acute respiratory failure syndrome (ARDS) that develops in lung tissue and thromboembolic events in vital organs, such as the heart and brain (1).

Routine blood test results are generally used to diagnose inflammatory periods of infectious diseases. It is easy to perform inexpensive complete blood tests and provides blood cell types and morphological parameters such as White blood count, lymphocytes, neutrophils, monocytes, platelet count (PLT), and mean platelet volume (2). In addition, combined ratios of these parameters are also used as inflammation indexes and have been used to predict the diagnosis and progress of inflammatory/ infectious diseases (3). Neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and systemic inflammation response index (SII) can be helpful for the diagnosis and severity assessment of COVID-19 patients. The exaggerated and uncontrolled inflammatory response is one of the main reasons for COVID-19 disease severity. Systemic immune-inflammatory index (SII) is another parameter that reflects the immune and inflammatory status of the organism (4). Although there are many retrospective studies in the literature on COVID-19, there is still no clear consensus on prognostic factors affecting the disease (5). To date, there have been publications showing parameters such as leukocytosis, lymphopenia, increased lactate dehydrogenase, C-reactive protein (CRP), and increased interleukin 6 (IL-6) levels are factors that increase the mortality risk of the disease. However, studies on the effect of the Systemic Immune-Inflammation Index (SII) and neutrophil-lymphocyte ratios (NLR) on mortality and prognosis are still controversial (6).

This study aimed to evaluate the factors affecting the prognosis and mortality of patients hospitalized with COVID-19, as well as examine whether the SII is a useful tool in predicting 30-day mortality and identify other factors associated with higher mortality in COVID-19 patients.

MATERIALS AND METHODS

This study was conducted retrospectively with patients hospitalized with COVID-19 between March and November 2020, who were diagnosed with RT-PCR (real-time reverse transcriptase-polymerase chain reaction), or diagnosed with COVID-19 with radiological and clinical features. The epidemiological characteristics, clinical symptoms, and laboratory findings of the patients were taken from the patient files. Hemogram, biochemical tests, inflammation markers, and coagulation tests were conducted for each patient.

The criteria set by the World Health Organization (WHO) were used in the diagnosis of COVID-19 (7). The patients were diagnosed using the standard diagnostic method of studying RT-PCR in respiratory samples, such as nasopharyngeal swabs or sputum, as the test protocols defined by the WHO in the diagnosis of the disease (8). In patients with typical COVID-19 symptoms but negative test results for RT-PCR, a diagnosis of COVID-19 was made in the presence of diffuse ground-glass opacities or multiple viral pneumonic foci on chest computed tomography (CT) radiologically. Severity criteria were defined as set by WHO (9). In non-severe patients, their epidemiological history, fever or other respiratory symptoms, typical CT images of viral pneumonia, and positive RT-PCR results were available. Patients with severe infections had at least one of the following criteria: respiratory distress, a respiratory rate that was ≥30, oxygen saturation (on room air) that was ≤93%, PaO_2/FiO_2 ≤300 mmHg (9).

Systemic Immune-Inflammation Index (SII): Calculated with the formula (neutrophil × platelet count)/ lymphocyte. neutrophil-lymphocyte ratio (NLR): calculated as neutrophil/lymphocyte. The Charlson Comorbidity Index (CCI) was used for the comorbidities (10).

The study was approved by the institutional review board and was conducted in accordance with the principles of the Declaration of Helsinki. (Bakirkoy Dr. Sadi Konuk Eğitim ve Arastırma Hastanesi/ 20-14-12/06-07-2020)

Statistical Analysis

Statistical analyses were conducted using IBM SPSS Statistics for Windows 22.0 (IBM Corp., Armonk, NY, USA). The numerical variables were expressed as the mean ± standard deviation and median (min-max), and

the categorical variables were expressed as numbers and percentages. Parametric test assumptions (normality and homogeneity of variances) were checked before comparing the groups in terms of numerical variables. The Mann-Whitney U test was used to compare the continuous variables. Binary logistic regression analysis was performed among the statistically important factors. The optimal cut-off values of the continuous NLR, PLR, and SII were calculated by applying the receiver operating curve (ROC) analysis. The significance level was accepted as $p<0.05$.

RESULTS

Of the 1013 patients included in the study, 552 (54.5%) were male, 461 (45.5%) were female, and their mean age was 54.31 ± 16.20 years (range: 16–95). While 734 (72.5%) of the patients were ≤65 years of age, 279 patients (27.5%) were >65. While there were 288 patients (28.4%) with a CCI score of 0 and 1, there were 725 (71.6%) patients with a CCI score of 2 or above. The median lymphocyte count of the patients was 1.23 (1000/μL), median neutrophil count was 3.93 (1000/μL), median platelet count was 195 (1000/μL), median CRP level was 44.87 mg/dL. While the median NLR rate was 3.12, the median SII rate was 598.51. The median PLR of the patients was 157.89. The mean hospitalization period of the patients was 9.58 ± 6.88 days.

The disease category of 204 patients (20.1%) was a severe infection. In the univariate analysis, the prognosis of 80 patients (39.2%) who were >65 was significantly worse than those who were ≤65 ($p<0.001$). 170 (83.3%) patients with a CCI of 2 and above had a significantly more severe prognosis than patients with a CCI of 0 to 1. At the same time, the CRP, NLR, SII, and PLR values were significantly higher in the patients with poor prognoses ($p<0.05$). Univariate analyses of the factors affecting the prognosis of the disease are shown in Table 1.

Table 1. Factors affecting the severity of the disease

Variables		Non-severe	Severe	Univariate p-value
		n (%)	n (%)	
Age (Year)	<65	610 (75.4)	124 (60.8)	<0.001
	>65	199 (24.6)	80 (39.2)	
Gender	Women	443 (54.8)	109 (53.4)	0.734
	Men	366 (45.2)	95 (46.6)	
CCI	0-1	254 (31.4)	34 (16.7)	<0.001
	≥2	2.85±0.57	2.34±0.37	
CRP (mg/L)	(Median)	38.0	65.4	<0.001
NLR	(Median)	2.9	4.0	<0.001
PLR	(Median)	152.6	175.4	0.004
SII	(Median)	576.9	744.1	0.009

NLR: neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, SII: systemic immune inflammation index, CCI: Charlson Comorbidity Index
Bold entries are statistically significant values.

In the multivariate analysis, it was determined that the prognosis was significantly worse in the patients who were >65 years of age, and had a CCI score that was >2 and a high NLR rate. The CRP, PLR, SII values were detected as insignificant variables (Table 2).

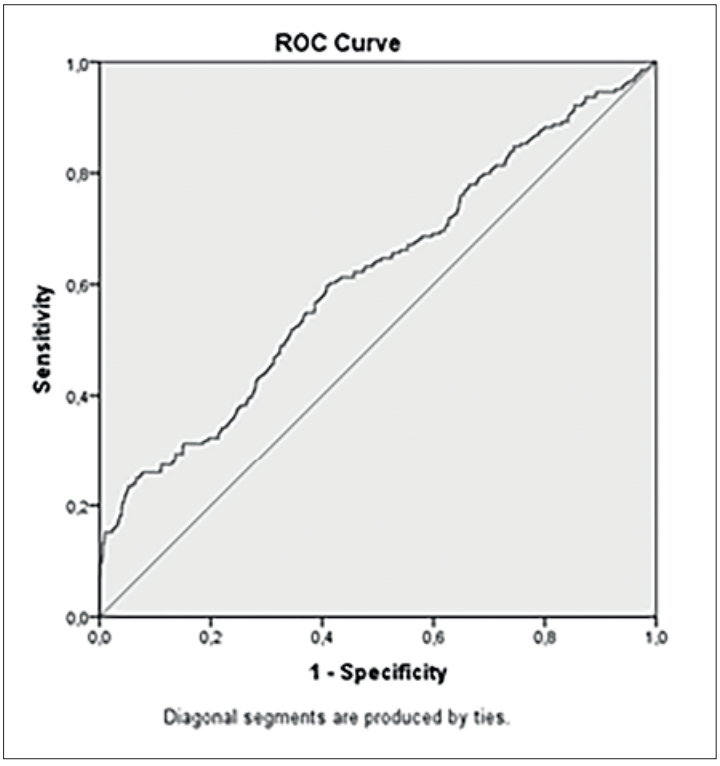
Table 2. Multivariate analysis of factors affecting the severity of the disease

Variables		95% CI		HR	Multivariate p-value
		Lower	Upper		
Age	>65	1.1	2.2	1.5	0.011
CCI	≥2	199 (24.6)	80 (39.2)	0 (3	0 (3
CRP		0.9	1.0	1.0	0.514
NLR		1.0	1.1	1.0	0.001
PLR		1.0	1.0	1.0	0.151
SII		1.0	1.0	1.0	0.585

NLR: neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, SII: systemic immune inflammation index, CCI: Charlson Comorbidity Index Bold entries are statistically significant values.

Due to the absence of a reference cut-off value on NLR mortality, the area under the curve (AUC) of the NLR value was determined as 0.614 in the ROC curve analysis (Figure 1). The optimal NLR cut-off value was 3.38. The highest specificity and sensitivity were 0.585 and 0.603 for the NLR.

Figure 1. The ROC curve analysis of NLR



Mortality was observed in the first 30 days in 52 patients (5.1%). In the univariate analysis, having a CCI score that was >2, and high CRP, NLR, PLR, and SII values were significant in terms of mortality. Mortality was observed in 45 patients (86.5%) with a CCI index that was >2 (p=0.014). The CRP, NLR, PLR, and SII values were higher in the patients with mortality (p<0.001) (Table 3).

Table 3. Factors affecting the mortality of the disease

Variables		No Mortality	With Mortality	Univariate p-value
		n (%)	n (%)	
Age (Year)	<65	694 (72.2)	40 (76.9)	0.459
	>65	267 (27.8)	12 (23.1)	
Gender	Men	524 (54.5)	28 (53.8)	0.924
	Women	437 (45.5)	24 (46.2)	
CCI	0-1	281 (29.2)	7 (13.5)	0.014
	≥2	2.85±0.57	2.34±0.37	
CRP (mg/L)	(Median)	41	126	<0.001
NLR	(Median)	3.0	6.64	<0.001
PLR	(Median)	155.2	226.1	<0.001
SII	(Median)	578.4	1437.6	<0.001

NLR: neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, SII: systemic immune inflammation index, CCI: Charlson Comorbidity Index Bold entries are statistically significant values.

Mortality was found to be statistically significant in patients with a CCI score that was >2 and in patients with high CRP, NLR, PLR, and SII values at the time of admission (p<0.05) in the multivariate analysis affecting mortality (Table 4).

Table 4. Multivariate analysis of the factors affecting the mortality of the disease

Variables		95% CI		HR	Multivariate p-value
		Lower	Upper		
CCI	≥2	1.1	2.2	1.5	0.011
CRP		1.0	1.0	1.0	0.001
NLR		1.0	1.1	1.0	0.032
PLR		1.0	1.0	1.0	0.001
SII		0.9	1	1.0	0.038

NLR: neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, SII: systemic immune inflammation index, CCI: Charlson Comorbidity Index Bold entries are statistically significant values.

There is no reference cut-off value for the NLR, CRP, SII, and PLR on mortality. Therefore, in the ROC curve analysis, the AUC of the CRP, NLR, SII, PLR values were determined as 0.734, 0.761, 0.708, and 0.723. The optimal cut-off values of the CRP, NLR, SII, and PLR were 9.02, 4.15, 909.5, and 181.5. The highest specificity and sensitivity were 0.981 and 0.837, 0.750 and 0.664, 0.692 and 0.683, and 0.673 and 0.626, respectively, for the CRP, NLR, SII, PLR.

DISCUSSION

The NLR, PLR, SII are ratios of hematological cells that regulate inflammatory response during infection and injury. The importance of these ratios has been researched in a wide variety of diseases, including malignancies (11,12). In addition to taking advantage of the relationship between tests such as the PLR, NLR, SII, CRP, and inflammatory conditions, the main benefit of these tests is that they are easily measurable and done more frequently and routinely than other tests. Most importantly, they are cost-effective, and they will not affect the already overburdened healthcare system. In light of this information, during the epidemic that has caused millions of deaths, any cost-effective method that could provide a prediction for the severity of the spectrum will significantly guide clinicians during treatment and follow-up.

The NLR values in the studies conducted by Liu et al. (13) and Fu et al. (14) in China were found to be an independent predictor factor in COVID-19 patients. In the study conducted by Kalabin et al. (15), the NLR and PLR values were significantly increased in COVID-19 patients, although these inflammatory markers were not associated with disease severity. In the current study, the NLR value was significantly increased with the disease severity, while the PLR value was not significant. In the study of Merad et al. (16), it was found that COVID-19 triggered hyper inflammation, and similar findings were found in the current study. While many inflammatory markers, such as CRP, erythrocyte sedimentation rate, lactate dehydrogenase, ferritin, and procalcitonin are frequently measured, the NLR and PLR values, which are particularly cost-effective in COVID-19 patients, can also be easily calculated. In the present study, patients with severe COVID-19 had higher NLR values when compared to those without the severe disease. In a meta-analysis performed by Chan et al. (17), the NLR values were found to be significantly higher in severe COVID-19. Patients with severe COVID-19 presented with increased leukocytosis, neutrophilia, lymphopenia, and thrombocytopenia when compared to those with non-severe disease (18). These patients are more likely to develop ARDS and may require intensive care unit (ICU) level care (19). Different mechanisms of lymphopenia in COVID-19 patients may be that the virus infects T-cells via ACE2 receptors (20). Decreased CD4 + and CD8 + T lymphocyte levels are associated with the severity of the disease, which can lead to an increased NLR (21). In the present study, the NLR value was significant when the factors affecting both the severity of the disease ($p<0.001$) and mortality ($p<0.05$) were considered.

Platelets are immune cells that play an important role in the human body. The meta-analysis investigating the relationship between thrombocytopenia and COVID-19 severity showed that the platelet count tripled the risk of serious illness and death in COVID-19 patients (22). According to another study, increased PLR levels observed in the follow-up of symptomatic and asymptomatic patients were found to be associated with the severity of the disease and the length of hospital stay (4). There have been publications stating that a new indicator can be obtained in the cytokine storm monitoring of patients with high PLR levels (23). In another study conducted in the USA, it was reported that the increase in the PLR value had no effect on the severity of the disease (15). In the current study, statistically, the increase in the PLR value was not significant in the disease severity, but it was significant in mortality.

As a result of our study, we found statistically significant results between the increase in the CRP levels and increased mortality ($p<0.001$). Zeng et al. (24) mentioned that inflammatory markers were important factors of the COVID-19 severity. In their meta-analysis, they found that non-severe group had lower levels for CRP (41.78 mg/l, 95% CI = [31.1-52.4], $p<0.001$) compared with those in the severe group. Hariyanto et al. (25) had written a systematic review and meta-analysis supporting data that elevated CRP levels can be used for predicting severe outcomes in COVID-19. In the data obtained by Ullah et al. (26), the relationship between higher CRP levels and COVID-19 were found to be correlated with sepsis, ICU admission, and increased mortality.

In a retrospective study conducted in Italy, the SII was compared with other commonly used blood cell count-

based inflammation indices, such as the NLR and PLR in COVID-19 patients, and was found to be the most significant survival factor. In the present study, the SII was found to be significant among the factors affecting mortality ($p<0.05$). When the CCI was first invented, it was used to predict the risk of death within one year of hospital stay. The scores are based on a series of comorbidities, which are each given a number from 1 to 6, depending on the severity of the morbidity (27). It is a well-validated, simple, and easy-to-apply index for evaluating the prognosis and survival of patients. During the current pandemic, the severity and mortality of COVID-19 has often been estimated using age, gender, and the presence of comorbidities, such as diabetes, cardiovascular, cerebrovascular, and respiratory diseases. The mortality and risk factors in COVID-19 patients can be evaluated by calculating the CCI score, age, and accompanying comorbidities together. In a study conducted by Imam et al. (28) in the USA, advanced age and multiple comorbidities were specified as independent mortality risk factors in patients with COVID-19.

In the present study, a CCI score that was ≥2 significantly affected both the severity of the disease and mortality ($p<0.05$). Age was found to be a significant factor affecting the severity of the disease, independent of the CCI score ($p<0.001$). As the pandemic continues worldwide, it is essential to understand the clinical characteristics of patients and the risk factors of worse outcomes in COVID-19 to be able to plan comprehensive treatment and appropriately allocate valuable resources (29).

Due to the nature of this study, it is retrospective and single-centered, which creates a major bias. The inflammatory factors, which were found to be significant regarding mortality and morbidity, constituted a bias in this case, because these inflammatory factors also increase in all infectious diseases.

As a result of the current study, it was found that the most important factor affecting the severity of the disease was advanced age and high comorbidities, and a high NLR value. The most important prognostic factors affecting mortality were high levels of comorbidities, and high NLR, PLR, SII, and CRP values. These analyses can be useful in evaluating COVID-19 patients, as they are simple, cost-effective, and rapid laboratory diagnostic tests.

Declarations

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

The study was approved by the institutional review board and was conducted in accordance with the principles of the Declaration of Helsinki. (Bakirkoy Dr. Sadi Konuk Eğitim ve Arastırma Hastanesi/ 20-14-12/06-07-2020)

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ORIGINAL ARTICLE

Evaluation of patients who received erythrocyte transfusion in the emergency department

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Abstract

Backgrounds: Decreased RBC count and decreased Hb concentration in the blood is defined as anemia. Anemia can be caused by acute excessive bleeding, hemolysis or inadequate production. If the patient is symptomatic, an immediate blood transfusion is required.

Methods: A retrospective, single-center study was performed between April 2019 and April 2021 with non-traumatic, non-pregnant patients over 18 years of age, who had erythrocyte transfusion in the emergency department. For the laboratory parameters Hb, Ca and K, the initial levels from the blood analysis performed at admission to the emergency department were recorded as Hb1, potassium K1, and calcium Ca1, and the blood levels after the transfusion as Hb2, K2, and Ca2. Mortality of patients was recorded.

Results: A total of 458 patients were included in the study. 44.3% of patients were male. The mean age was 66.33 ± 17.51/year. Mortality developed in 6.55%. There was a statistically significant difference in laboratory values between non-surviving and surviving patients. The mortality rate increased in patients with Hb1 values below 5.05g/dl and Hb2 values below 7.75g/dl, and patients with Ca1-2 values below 6.85mg/dl. It was determined that this increase in mortality rate was 3 to 6 times on average.

Conclusions: Our findings reveal that the transfusion procedures in our clinic are in accordance with the new transfusion guidelines. It is important to use blood and blood products, the only source of which is human, for the right indication, at the right time, and in the right amounts.

Keywords: Anemia, Emergency, Erythrocyte Transfusion.

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INTRODUCTION

Approximately 80% of the cells in our body are red blood cells (RBC). Hemoglobin (Hb) is the main component of RBC content. Decreased RBC count and decreased Hb concentration in the blood is defined as anemia (1). Anemia can be caused by acute excessive bleeding, hemolysis or inadequate production of erythrocytes. The World Health Organization defines anemia as an Hb level of ≤ 13 g/dl in men and ≤ 12 g/dl in women (2, 3). In cases of acute anemia, traumatic or non-traumatic hemorrhage, an Hb level of < 7 g/dl in critically ill patients, < 9 g/dl in sepsis patients, septic shock, cardiac ischemia, acute or chronic blood loss, and if the patient is symptomatic, an immediate blood transfusion is required (2, 4, 5).

In the United States, 24 million blood or blood products are transfused each year (6). While blood transfusion can be life-saving, it is also associated with life-threatening risks and complications (5, 7, 8). Therefore, blood transfusion is a treatment method that should be used at the right time, for the right indication.

The emergency department of our hospital is a tertiary-care emergency department. Thus, a large number of patients with acute bleeding and/or critical condition present to our department. Treatment of these patients is initiated at our emergency department. One of these treatments is blood transfusion.

In the present study, we aimed to assess the patients who were administered erythrocyte suspension (ES) at our emergency department.

MATERIALS AND METHODS

Study design

This study was a single-center retrospective study. The study was initiated after the approval by the ethics committee of İzmir Katip Çelebi University (Decision date: 24.06.2021, and No: 290).

Patients presenting to our emergency department between April 30, 2019 and April 30, 2021, who had an Hb level of ≤ 9 g/dl and had anemia-related symptoms (shortness of breath, palpitation, dizziness, weakness, chest pain) and signs (tachycardia, hypotension, hypoxia, hypothermia, pallor, signs of ischemia on electrocardiography (ECG)), and received erythrocyte transfusion in the emergency department, were screened using the hospital automation system. Patients over the age of 18 with sufficient data in their files who had undergone erythrocyte transfusion in the emergency department were included in the study.

Patients with trauma and pregnants were excluded from the study.

Study protocol

Patients' age, gender, blood type, repeated transfusions, number of ES units administered at the emergency department, discharge/hospitalization after transfusion at the emergency department, laboratory results, and levels of Hb, calcium (Ca), potassium (K), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red blood cell distribution width (RDW) were recorded from patient files.

For the laboratory parameters Hb, Ca and K, the initial levels from the blood analysis performed at admission to the emergency department were recorded as Hb1, potassium K1, and Ca1, and the blood levels after the transfusion were recorded as Hb2, K2, and Ca2. 30-day mortality was recorded.

Statistical method:

The study data were assessed using IBM SPSS Statistics Version 20. The use of parametric or nonparametric tests was decided by analyzing the normality of the quantitative data using the One-Sample Kolmogorov-Smirnov test. Frequency and percentage distribution were calculated for descriptive statistics, and mean, standard deviation, minimum and maximum values for continuous variables.

Statistical analyses and interpretations of categorical variables were performed using Pearson's Chi-Square and Fisher's Exact tests. Categorical data were expressed as n (number) and percentage (%). The data were analyzed at the 95% confidence level, according to the probability reference value of 0.05.

The effect of laboratory values in determining the final status of the patients was examined using the ROC Analysis, and the cut-off values for the variables with statistical difference were calculated.

RESULTS

A total of 458 of 551 patients who met the study criteria and had sufficient data in their files were included in the study. Male patients accounted for 44.30% of the study participants. The mean age was 66.33 ± 17.51/ year. Demographic characteristics of the study patients and distribution of the study parameters are presented in Table 1.

Table1. Demographic characteristics of patients and distribution of parameters evaluated in the study

Category	Variables	(n)	%
Gender	Male	203	44.30%
	Female	255	55.70%
Age (mean±SD)	66,33 ±17,51	458	
Blood type	0-	14	3.10%
	0+	145	31.60%
	A-	20	4.40%
	A+	156	34.00%
	AB-	4	0.90%
	AB+	27	5.90%
	B-	5	1.10%
	B+	87	19.00%
Repetitive	Yes	152	33.18%
Transfusion	No	306	66.81%
Amount of transfusion (units)	1	60	13.10%
	2	265	57.86%
	3	116	25.33%
	4	17	3.71%
Hospitalization status	Discharged from ED	292	63.80%
	Hospitalization on ward	142	31.00%
	Hospitalization on ICU	24	5.20%
Cause of anemia	Hemorrhagic	128	27.90%
	Nonhemorrhagic	330	72.,10%
Mortality	Yes	30	6.55%
	No	428	93.45%

Mortality developed in 6.55% of our study patients. When the mortality was evaluated, the comparison of non-surviving and surviving patients revealed a statistically significant difference in the number of ES units administered to the patient and the hospitalization of the patient (Table 2).

Table 2. Evaluation of the values obtained in the study in terms of mortality

Mortality						
		Exitus		Live		
Category	Variables	Count	Row n %	Count	Row n %	p
Gender	Male	12	5.90	191	94.10	
	Female	18	7.10	237	92.90	0.622
Age (mean ±SD)		30	70.90±15.15	428	66.01±17.63	0.87
Blood type	0-	0	0.00	14	100.00	
	0+	6	4.10	139	95.90	
	A-	0	0.00	20	100.00	
	A+	15	9.60	141	90.40	
	AB-	0	0.00	4	100.00	
	AB+	2	7.40	25	92.60	
	B-	0	0.00	5	100.00	
	B+	7	8.00	80	92.00	0.415
Repetitive transfusion	Yes	8	5.30	144	94.70	
	No	21	6.90	285	93.10	0.442
Amount of transfusion/ units	1	1	1.70	59	98.30	
	2	13	4.90	252	95.10	
	3	13	11.20	103	88.80	
	4	3	18.80	14	81.30	0.021
Hospitalization status	Discharged from ED	9	3.80	283	96.91	
	Hospitalization on ward	11	7.80	131	92.30	
	Hospitalization in ICU	10	41.70	14	58.30	0
Cause of anemia	Nonhemorrhagic	21	21	309	79	
	Hemorrhagic	9	7,00%	119	93,00%	0.648

ED: Emergency department, ICU: Intensive care unit.

There was a statistically significant difference between Hb1, Hb2, Ca1, and Ca2 values of non-surviving and surviving patients (Table 3). The logistic regression analysis for the effects of these parameters on mortality revealed that the cut-off value for Hb1 and Hb2 was moderately effective, the cut-off value for Ca1 was fairly effective, and the cut-off value for Ca2 was moderately effective (Table 4).

Table 3. Mean laboratory values of patients and relationship with mortality

Laboratory parameters	Exitus (n=30)	Live(n=398)	Total(N=428)	p
	Mean±SD	Mean±SD	Mean ± SD Min-max	
Hb1 g/dl	5.78±1.33 3.30-8.70	6.47±1.07 3.00-8.90	6.43±1.1 3.00-8.90	0.001
Hb2 g/dl	8.76±1.14 6.40-11.50	9.31±1.15 6.80-14.80	9.28±1.15 6.40-14.80	0.014
Ca1 mg/dl	7.78±0.70 6.10-9.60	8.17±0.79 3.20-12.60	8.15±0.79 3.20-12.60	0.002
Ca2 mg/dl	7.49±0.77 6.30-9.70	8.02±0.68 5.90-12. 30	7.99±0.70 5.90-12.30	0.000
K1 mmol/L	4.68±1.05 2.90-7.60	4.38±0.70 2.20-8.40	4.40±0.73 2.20-8.40	0.115
K2 mmol/L	4.35±0.93 2-6.20	4.38±0.54 2.80-5.90	4.38±0.57 2.00-6.20	0.902
MCV fl	82.16±11.60 57.00-105.90	80.8±15.63 50.60-141.90	80.89±15.39 50.60-141.90	0.315
MCH pg	25.28±5.23	24.82±6.48	24.85±6.4 13.40-47.60	0.524
MCHC g/dl	30.55±2.91 23.20-36.90	30.30±2.70 19.40-36.90	30.31±2.71 19.40-36.90	0.532
RDW fl	18.93±3.03	18.56±3.14	18.58±3.14 12.10-32.40	0.540

Hb: Hemoglobin, Ca: Calcium, K: Potassium, MCV: Mean Corpuscular Volume, MCH: Mean Corpuscular Hemoglobin, MCHC: Mean Corpuscular Hemoglobin Concentration, RDW: Red Blood Cell Distribution Width.

Table 4. ROC analysis of laboratory values associated with mortality

Risk factor	AUC (%95)			Cut-Off	P	Sensitivity (%)	Specificity (%)
	AUC (%95)	Lower Bound	Upper Bound				
Ca1 mg/dl	0.669	0.577	0.766	6.85	0.00	13	96
Ca2 mg/dl	0.725	0.625	0.827	6.85	0.00	23	97
Hb1 g/dl	0.681	0.575	0.787	5.05	0.00	33	89
Hb2 g/dl	0.635	0.624	0.826	7.75	0.01	23	95
The test result variable(s): hb1, hb2, potasyum1, potasyum2, kalsiyum1, kalsiyum2, mcv, mch, mchc, rdw has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.							
a. Under the nonparametric assumption							
b. Null hypothesis: true area = 0.5							

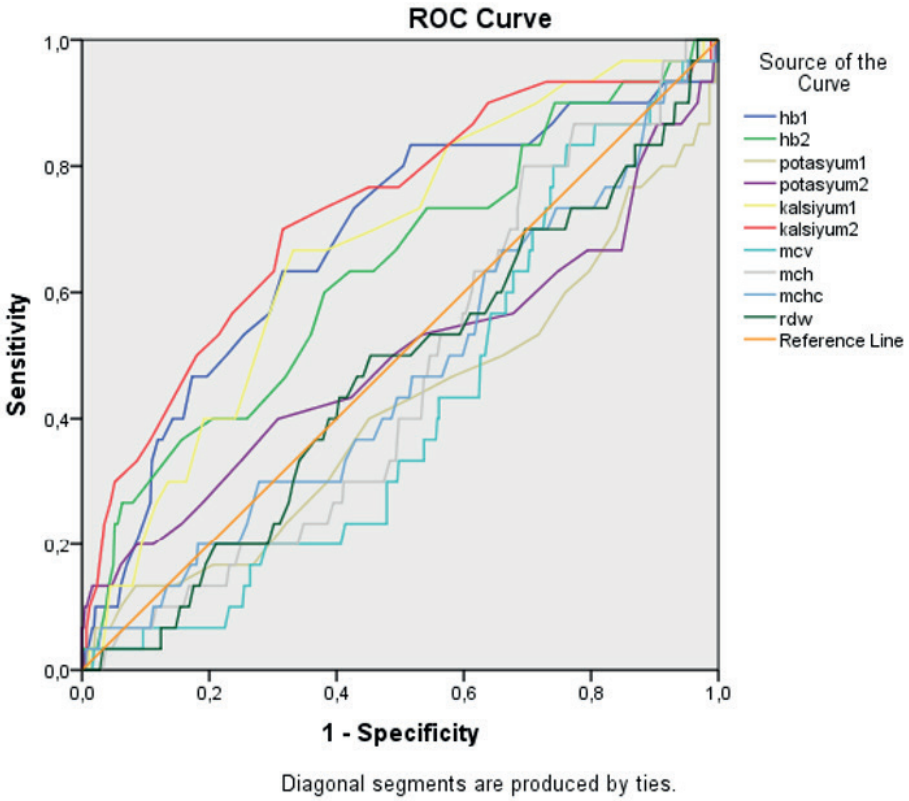
Ca: Calcium, Hb: Hemoglobin.

In Table 5, cut-off values of Hb and Ca, which were associated with mortality before and after transfusion, and mortality rates of the patients were evaluated. It predicted an 18% probability of mortality when the Hb1 cut-off value was below 5.05 g/dl. For Hb1 above this value, the probability of mortality was 5%. It predicted a 32% probability of mortality when the Ca2 cut-off value was below 6.85 mg/dl. For Ca2 above this value, the probability of mortality was found to be 5% (Table 5) (Figure 1).

Table 5. The mortality rates of the patients according to the cutoff values of hemoglobin and calcium, which were determined to be associated with mortality

	Hemoglobin1 g/dl				Hemoglobin2 g/dl				Calsiyum1 mg/dl				Calsiyum2 mg/dl			
Cut-off Value	**5.05**				**7.75**				**6.85**				**6.85**			
	<	%	>	%	<	%	>	%	<	%	>	%	<	%	>	%
Exitus	10	18	20	5	7	24	23	5	4	17	26	6	7	32	23	5
Live	47	82	381	95	22	76	406	95	19	83	409	94	15	68	413	95
Total	57	100	401	100	29	100	429	100	23	100	435	100	22	100	436	100

Figure 1. ROC analysis of laboratory values



DISCUSSION

Blood transfusion has been widely used since the early 20th century to treat anemia and acute blood loss (4, 9). Patient assessment and transfusion decision are of critical importance in emergency departments, which is the first location of admission of these patients.

In our study, female patients accounted for 55.7% of the patient group. Worldwide, women are more susceptible to anemia. Poor nutritional conditions, increased menstrual bleeding, abnormal uterine bleeding, pregnancy and breastfeeding are the factors that increase the susceptibility to anemia in women (10-12). Therefore, anemia is more prevalent in women. The mean age of the patients included in the study was 66 ± 17.51/years. Patients who need urgent ES transfusion are relatively elderly patients. Because young patients can tolerate anemia better, chronic and comorbid diseases are less common in young patients, and etiological factors leading to anemia can be treated more effectively in young patients (13).

Considering the etiological factors that required transfusion in our study, the rate of patients who needed transfusion due to acute bleeding was 27.9%. Anemia, which occurs secondary to the existing diseases in the majority of the patients, becomes symptomatic, and therefore transfusion is needed, which can also be considered an effect of advanced age. The guidelines on the approach to anemia occurring other than acute blood loss recommend that patients without any indication for hospitalization, should be investigated in outpatient clinics, the etiology causing anemia should be determined and the treatment should be continued (2, 5, 14). In our study, 63.8% of the study patients were discharged from the emergency department after transfusion to refer to the outpatient clinic. From this point of view, it can be said that the transfusion procedures carried out in our emergency department comply with the guidelines. Transfusion administration to the patients at the emergency department provided symptomatic treatment of the patients, and thereby the patients were discharged from the emergency department without the need for hospitalization. Thus, both the treatments of the patients were provided and the rate of hospitalization was reduced.

Consensus and guidelines have been established to provide global standardization for blood transfusion. According to these guidelines, the current transfusion approach is restrictive approaches. According to the restrictive transfusion approach, the threshold for transfusion is Hb<6 g/dL for healthy and stable patients who can tolerate low RBC levels. Although different levels have been suggested for specific conditions such as acute coronary syndrome, cardiac surgery, orthopedic surgery, and oncology patients, it is recommended to initiate transfusion after the mean Hb level is ≤7–8 g/dl and the clinical status of the patients is assessed (2, 4-6, 14). In our study, the Hb level of the patients initiated on transfusion was 6.43 ± 1.1 g/dl. Thus, it is observed that the Hb levels during transfusion decision in the present study are consistent with those recommended by the guidelines. It can be said that in our emergency department, the need for transfusion was determined accurately and the patients received adequate and proper transfusions.

The mortality rate of our patients was found to be 6.55%. When the parameters affecting mortality was evaluated, it was found that Hb levels were associated with mortality before and after transfusion. Accordingly, the mortality rate was 18% in patients with an Hb level of <5.05 g/dl before transfusion, while it was reduced to 5% in patients with Hb levels above this value. In their review evaluating studies on Jehovah's Witnesses, Viele et al. reported that the Hb level of non-surviving patients was <5 g/dl (15). In the most recent guidelines, the recommended mean threshold for initiation of transfusion is 7–8 g/dl (2, 5, 14). According to our results, initiation of transfusion before the Hb cut-off value drops down to <5 g/dl may reduce mortality in patients with acute blood loss. For patients with chronic anemia, it should be considered that patients with an Hb cut-off value <5 g/dl are critically ill.

When the post-transfusion Hb levels were evaluated in our study, the mortality rate was 24% in patients with an Hb level of <7.75 g/dl, while the mortality rate decreased to 5% in patients with an Hb level of ≥7.75 g/dl. In the recent guidelines, restrictive transfusion recommendations have emphasized that the patient's blood levels and clinical data should be checked after each unit of transfusion and the transfusion should be maintained accordingly. However, a value to terminate the transfusion has not been determined (2, 5, 16). Considering this aspect, we believe that the cut-off value found in our study is important. The reduced mortality by keeping a target Hb value of

≥7.75 g/dl after transfusion will guide future studies and guidelines. The amount of blood required to reach these critical values, that is, the number of units given to the patient, also plays an important role in the survival of the patient. In our study, it was found that as the amount of blood (unit) given to the patient increases, the mortality also increases. We believe that the volume load due to the blood component administered to the patient and the patient instability due to the condition requiring excessive transfusion contribute to mortality. Therefore, it is necessary to avoid giving too much blood to patients in accordance with restrictive transfusion protocols as recommended in the guidelines. This is supported by our results. The patient's need for transfusion should be determined early and transfusion should be performed gradually.

The level of Ca is another parameter that was found to be associated with mortality. As is known, Ca is involved in cardiomyocytes, coagulation and contraction of skeletal muscle. RBC are preserved in solutions containing citrate. Citrate binds to Ca in the blood to form a dispersible complex, but this complex is weakly ionized. Thus, most of the Ca bound to citrate becomes biologically inactive. Because it binds to citrate, the blood level of Ca decreases in patients receiving transfusion (2, 8). Ca levels should be evaluated in patients during and after transfusion, and replacement should be administered, if necessary (2, 17). In their study, Bıçakçı et al. found that Ca levels of <7.9±1.13 mg/dl were associated with mortality in patients who received ES transfusion, although patients with hypocalcemia received replacement (17). In addition, in our study, the patient's pre-transfusion calcium level was also found to be associated with mortality. It was determined that mortality increased 3 to 6 times in patients with calcium levels below 6.85 mg/dl before and after transfusion. This indicates that it is important to evaluate Ca levels before transfusion and to administer Ca replacement to patients with hypocalcemia.

In conclusion, in acute bleeding and symptomatic anemia, the decision of transfusion is made in the emergency department and it is important to use blood and blood products, the only source of which is human, for the right indication, at the right time, and in the right amounts. It should be kept in mind that female patients are more susceptible to anemia and may need transfusion. In our study, 63.8% of the study patients were discharged from the emergency department after transfusion and the mortality rate was 6.55% in patients who received blood transfusion. We observed that mortality increased in cases where Hb was <5.05 mg/dl before transfusion and Hb <7.75 g/dl after transfusion. We found that mortality increased when the Ca level was <6.85. The results of our study are guiding in decision making and transfusion management in emergency departments and will provide an insight for prospective and multicenter studies to restructure current transfusion practices in the emergency departments.

Declarations

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

This study was approved by the clinical research ethics committee of the İzmir Katip Çelebi University (Date: 26.06.2021 number: 0290) and written consent was obtained from all patients participating in the study.

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ORIGINAL ARTICLE

Something is still wrong: Epinephrine use in venom immunotherapy patients

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Abstract

Backgrounds: Anaphylaxis is hard to recognize and, therefore, a poorly treated systemic allergic reaction. The aim of the treatment in anaphylaxis is to prevent the progression of the clinical picture to life-threatening respiratory and/or cardiovascular symptoms and signs through early diagnosis of anaphylaxis and administration of adrenaline.

Methods: Seventy-eight patients [(Female (F): 22 (28.2%), Male (M): 56 (71.8%)] who received venom immunotherapy were included in this study. A mini questionnaire was applied to these patients about in which situation they should use the adrenaline auto-injector (AAI), what to do after using AAI, and how to use it.

Results: Thirty-four patients (43.6%) were stung by a bee after initiation of immunotherapy while 16 patients (47.1%) developed urticaria/angioedema. Ten patients (29.4%) used AAI following a bee sting, whereas 24 patients (70.6%) didn't use AAI. Fifty-two (66.7%) patients correctly answered the four questions regarding what to do following administering AAI, in what cases and frequency they should have AAI prescribed, storage and transportation conditions of AAI, and how to administer AAI. Among the patients who were stung by a bee during immunotherapy, the rate of answering all questions correctly of the patients who administered AAI during anaphylaxis was determined to be significantly higher (p=0.001).

Conclusions: Although adrenaline treatment is the most vital method of treatment in anaphylaxis, patients still do not have a sufficient level of awareness on the importance and vitalness of adrenaline treatment. It is very important to train patients at risk and patient relatives primarily by physicians at appropriate intervals.

Keywords: Anaphylaxis, Venom Allergy, Adrenaline auto Injector.

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INTRODUCTION

Unfortunately, anaphylaxis is hard to recognize. Thus, a poorly treated systemic allergic reaction is partly related to failure to understand that anaphylaxis is a more extensive syndrome than "anaphylactic shock". The aim of the treatment in anaphylaxis is to prevent the progression of the clinical symptoms to life-threatening respiratory and/or cardiovascular symptoms and signs through early diagnosis and administration of adrenaline. As respiratory or cardiac arrest may develop within minutes of anaphylaxis, rapid evaluation and treatment are vital (1–3). The treatment is most effective in anaphylaxis in this early period, and delayed adrenaline administration is associated with mortality (4–7).

Anaphylaxis to bee stings ranges from 0.3% to 3% (8, 9). Moreover, it was reported to affect 8% of the population in some parts of the world (10, 11). Treatment of venom-related anaphylaxis is similar to the treatment of anaphylaxis due to other causes, which is an intramuscular injection of adrenaline from the anterolateral area of the thighs. Although adrenaline administration is the only effective treatment, studies have reported its limited use to treat anaphylaxis (12, 13). The most important mistakes made in the treatment of anaphylaxis are delaying administration of adrenaline via relying on treatments with drugs such as antihistamines, steroids, and albuterol; not carrying an adrenaline auto-injector (AAI); insufficient training of the patients; not knowing how and when to use the AAI, and the wish to avoid potential side effects of adrenaline (13). Thus, it is important to increase awareness, particularly in patients at risk, and corroborate the educational level of these patients for the rapid and effective administration of adrenaline treatment.

This study aimed to evaluate attitudes and knowledge levels regarding AAI use and approaches to AAI use in case of anaphylaxis to bee stings during venom-specific immunotherapy in patients due to venom-related anaphylaxis and prescribed AAI.

MATERIAL AND METHODS

All patients with a history of venom-related anaphylaxis followed up in our clinic (Necmettin Erbakan University Department of Clinical Immunology and Allergy) were prescribed AAI following recommendations of international guidelines (14–16). At the same time, these patients were referred for venom immunotherapy. Prior to each venom immunotherapy shot, the patients were asked about whether a local and/or systemic reaction occurred; if yes, what interventions were made; whether they have had bee sting; and if yes, whether they used adrenaline. Following a bee sting, a dose adjustment was made under international guidelines. Furthermore, when the patient's required adrenaline, where and how the anaphylaxis occurs, by whom adrenaline is administered, adrenaline side effects, difficulties in administration, and the mistakes made were investigated. Knowledge levels of the patients regarding the use of AAIs were evaluated, and, if needed, training on the use of adrenaline auto-injectors was repeated. Seventy-eight patients [(Female (F): 22 (28.2%), Male (M): 56 (71.8%)] who were followed-up in the Necmettin Erbakan University Department of Adult Allergy Clinic between 2014 and 2019, who participated and received venom immunotherapy, were included in the study. The patients who participated in the study were asked to complete a mini-survey. Whether they had anaphylaxis after prescription of AAI; if yes, where it was; what was used for treatment; the number of AAIs used; by whom AAI shot was administered; whether a side effect occurred following the shot and; if not used, why they did not use the AAI were investigated. Furthermore, independent of the history of anaphylaxis, following the AAI training, the patients were asked about how they were feeling, from where and how the AAI should be administered, how frequently they should have it prescribed, and what they should do after administration.

Venom (*Apis mellifera* and *Vespula vulgaris*) specific IgE antibody levels and baseline tryptase levels were measured using the CAP fluoroenzyme method (ImmunoCAP Tryptase, Unicap 100; Phadia, Uppsala, Sweden).

The whole blood count was measured by Sheath reagent with Abbott Cell Dyn 3700 series (Chicago, USA). Quantitative determination of serum immunoglobulin IgE was made using particle-enhanced immunonephelometry by the Siemens BN II/BN ProSpec system (Erlangen, Germany).

This study was approved by the clinical research ethics committee of the Necmettin Erbakan University (Date: 21.02.2020, number: 2020/2323), and written consent was obtained from all patients participating in the study.

Statistical analysis was performed using the IBM SPSS Statistics Version 22 (IBM Corporation, Armonk, NY, USA) software package. Normally distributed parameters were presented as mean ±standard deviation, and data not normally distributed were expressed as median (minimum-maximum). Descriptive data were presented as frequencies and percentages and compared using a Chi-square or Fisher exact test. Comparisons of continuous variables between baseline characteristics were performed by independent Student-t or Mann-Whitney rank-sum tests, where appropriate.

RESULTS

Seventy-eight patients [(Female (F): 22 (28.2%), Male (M): 56 (71.8%)] with the mean age of 40.13 ±12.20 (F: 34.91 ±8.56, M: 47.81 ±12.75) years were included in the study. Sixty-eight patients (87.2%) had a history of anaphylaxis to bee sting before diagnosis of venom allergy and prescription of AAI. Venom immunotherapy was initiated in ten patients due to significant local reactions.

Thirty patients (38.5%) were on *Apis mellifera* (honey bee) immunotherapy, 38 patients (48.7%) were on *Vespula* spp. (yellow jacket) immunotherapy, and ten patients (12.8%) were on venom-specific immunotherapy with both species. The characteristics of the patients are summarized in Table 1. Following the venom allergy diagnosis, 70 patients (89.7%) were prescribed two AAIs and eight patients (10.3%) one AAI.

Table 1. Demographic and laboratory properties of patients

Parameters	Results
Current age, years (mean ±standard deviation)	40.13 ±12.20
Gender, Female, n (%) Male, n (%)	22 (28.2) 56 (71.8)
Personal education level, • Primary school, n (%) • High school, n (%) • University, n (%)	 36 (46.2) 16 (20.5) 26 (33.3)
Type of immunotherapy, n (%) • Apis mellifera • Vespula spp. • Apis mellifera + Vespula spp.	 30 (38.5) 38 (48.7) 10 (12.8)
Concomitant diseases n (%) • Asthma • Allergic rhinitis • Atopic dermatitis	 4 (5.1) 6 (7.7) 8 (10.3)
Eosinophil count, mm3	124.89 ±69.14
Total IgE (IU/L), median (min-max)	122.15 (18.80–275)
Serum tryptase (ng/mL), median (min-max)	3.37 (1–49.2)

Ig: immunoglobulin

In addition to the AAI training provided by an allergy specialist, twenty-four patients (30.8%) watched training videos on the internet. Following the AAI training, 64 patients (82.1%) felt safe and qualified on this issue, whereas four patients (5.1%) reported anxiety and ten patients (12.8%) fear. AAI training was repeated for 12.8% of the patients at each visit.

Thirty-four patients (43.6%) were stung by a bee after immunotherapy initiation. No complaints were reported among 14 patients (41.2%) following a bee sting. However, 16 patients (47.1%) developed itching, urticaria, and angioedema, and 4 (11.7%) dizziness, blackout, and (pre-) syncope. Ten patients (29.4%) used AAI following a bee sting, whereas 24 patients (70.6%) did not use AAI.

However, six patients (17.7%) used an antihistamine drug as a self-medicine or antihistamine together with steroid treatment (2 out of 34 patients) instead of AAI.

All ten patients using AAI had used one single auto-injector, and none of the patients required a second administration. Of these patients, six patients (60%) reported no side effects related to the injector. In contrast, two patients (20%) reported pain, ache, and bleeding at the injection site, and two patients (20%) reported headaches following the administration.

Twenty-four patients did not use AAI following a bee sting. Four patients did not use AAI because they were not carrying it along with them, whereas six patients (25%) did not find it necessary because they were admitted to an emergency department. The Mini-survey is summarized in Table 2.

Table 2. Questions and answers of the mini-survey

Questions of Mini-survey	Answers
Have you had anaphylaxis before the adrenaline auto injector was prescribed? n (%)	Yes: 68 (87.2) No: 10 (12.8)
How many injectors were prescribed? n (%)	One: 8 (10.3) Two: 70 (89.7)
Have you been informed about the use of the AAI by anyone other than your doctor? n (%)	None: 44 (56.4) Pharmacist: 2 (2.6) Allergy Nurse: 6 (7.7) Internet/YouTube: 24 (30.8) Another patient: 2 (2.6)
Did you feel sufficient to use an adrenaline injector after injector training? n (%)	I felt, safe and sufficient: 64 (82.1) anxiety: 4 (5.1) fear: 10 (12.8)
Was adrenaline auto injector training done at every visit? n (%)	Yes: 10 (12.8) No: 68 (87.2)
Have you been stung by any bees during immunotherapy? n (%)	Yes: 34 (43.6) No: 44 (56.4)
Where did the bee sting take place? n (%)	Home: 8 (23.5) Work place: 2 (5.9) Garden: 16 (47.1) Other: 8 (23.5)
What kind of complaint did you have after the bee sting while immunotherapy continued? n (%)	No complaints: 14 (41.2) Pruritus, urticaria, angioedema: 16 (47.1) Dizziness, tinnitus, syncope: 4 (11.7)
Did you use the adrenaline auto-injector after the bee sting? n (%)	Yes: 10 (29.4) No: 24 (70.6)
Did you take a drug before applying an adrenaline auto-injector? n (%)	Yes: 6 (17.7) No: 28 (82.3)
Which drugs did you take, after the bee sting? n (%)	Antihistamines: 4 Steroids: 0 Anti-histamines + Steroids: 2 Salbutamol: 0
Who applied the adrenaline auto-injector? n (%)	Myself: 4 (40) My partner: 2 (20) My friend: 2 (20) Emergency staff: 2 (20)
Where did you apply the adrenaline auto-injector? n (%)	Work: 2 (20) Home: 4 (40) Social area: 4 (40)
What side effects did you see if you used it? n (%)	No adverse effect: 6 (60) Palpitation: 0 Pain/bleeding at the injection site: 2 (20) Nausea and vomiting: 0 Headache: 2 (20)
If you used it, how many have you used? n (%)	One: 10 (100) Two: 0
If you have not used it, what is your reason for not using it? n (%)	AAI was not with me: 4 (16.7) Since I went to the emergency room, I did not need to apply an AAI: 6 (25) I do not know exactly how to use AAI I took antihistamine/steroid drugs instead of applying AAI. My complaints were not serious. I did not need to use AAI: 14 (58.3)

AAI: Adrenaline Auto-Injector

Fifty-two (66.7%) patients correctly answered four questions regarding what to do following administering AAI, what cases and frequency they should have AAI prescribed, storage and transportation conditions of AAI, and how to administer AAI. No significant differences were determined between those who correctly answered. It was not related to age, gender, personal atopy, and training provision on AAI at each visit (Table 3) (Table 4).

Table 3. Comparison of patients who answered all questions about AAI use correctly with patients who did not

	Patients who got full points (n: 52)	Patients who did not get full points (n: 26)	p
Gender, Female, n (%)	14 (26.9)	8 (30.8)	0.792
Age	39.0 ±13.14	42.38 ±9.61	0.248
Education status (high school and upper), n (%)	22 (42.3)	14 (53.8)	0.335
Patients who have had anaphylaxis before prescribing AAI, n (%)	46 (88.5)	22 (84.6)	0.724
Personal Atopy, n (%)	12 (23.1)	6 (23.1)	0.999
AAI training given at each visit	8 (15.4)	2 (7.7)	0.482
Patients stung by a bee during immunotherapy	18 (52.9)	16 (47.1)	0.031

AAI: Adrenaline Auto-Injector

Among the patients stung by a bee during immunotherapy, no difference between patients who gave and did not give full scores to the questions was determined regarding age, gender, and personal atopy. In contrast, the rate of answering correctly to all questions of the patients who were administered AAI during anaphylaxis was significantly higher ($p = 0.001$). These results are summarized in Table 5.

Table 4. Binomial regression analysis demonstrating the relationship between baseline characteristics and getting full points from mini-survey

Variables	Univariate		Multivariate	
	OR (95% CI)	P	OR (95% CI)	P
Age, year	1.024 (0.984–1.065)	0.245	1.010 (0.968–1.54)	0.635
Education status (high school and upper)	0.629 (0.244–1.621)	0.337	0.961 (0.317–2.916)	0.944
Stung by a bee during IT	3.022 (1.140–8.012)	0.026	3.022 (1.140–8.012)	0.026

IT: Immunotherapy

Table 5. Features of patients stung by a bee during venom-specific immunotherapy

	Patients who received full points (n: 18)	Patients who did not receive full points (n: 16)	P
Gender, Female, n (%)	4 (22.2)	6 (37.5)	0.329
Age	36.41 ±11.75	37.60 ±11.11	0.777
Education status (high school and upper), n (%)	6 (33.3)	6 (37.5)	0.800
Patients who have had anaphylaxis before prescribing AAI, n (%)	16 (53.3)	14 (46.7)	0.900
Personal Atopy, n (%)	4 (22.2)	6 (37.5)	0.329
AAI training given at each visit	2 (11.1)	2 (12.5)	0.900
Patients who administered AAI after stung by a bee	10 (55.6)	0	0.001

AAI: Adrenaline Auto-Injector

DISCUSSION

Hymenoptera venom allergy is the most common cause of anaphylaxis in adults and the second most common after food in children. Moreover, it is an important cause of anaphylaxis-related mortality worldwide (17, 18). Adrenaline, however, is the indispensable first-line treatment and is life-saving (14). In our study, of the patients who received venom immunotherapy, 34 patients (43.6%) were stung by a bee after initiation of immunotherapy. Despite 20 patients (25.6%) who developed bee sting-related anaphylaxis, only 10 (12.8%) used AAI. These ratios revealed that approximately one-fourth of the patients prescribed with AAI had anaphylaxis within five years.

In our study, the rate of AAI use among the patients who were prescribed AAI was 12.8%. This rate is very low compared to the administration rate of AAI (29.9%) reported by Fleisher et al. (19). In another study from Turkey, the rate of AAI use was 6.84% (20). In the European Anaphylaxis Registry, the rate of AAI use (12%) in 2011 increased by up to 25% in 2014. Although there has been some increase in awareness and diagnosis of anaphylaxis and rates of AAI use, these rates are still below expected. Therefore, giving regular training to all clinicians, regardless of their specialty, that adrenaline is indispensable in treating anaphylaxis will increase awareness of this issue. In addition, the inclusion of patients and their relatives in these training may increase AAI usage rates.

Approximately 1–20% of cases of anaphylaxis have a biphasic pattern, i.e., after presenting symptoms disappear completely, and anaphylaxis symptoms recur in the absence of additional exposure in 1–20% of the patients (15, 21–23). Furthermore, some anaphylactic reactions may persist from hours to days, and in extreme conditions, weeks (3). Therefore, it is recommended to prescribe at least two AAIs for these patients (24). Song et al. reported that 82% of the patients who were prescribed two AAIs did not carry two AAIs with them (25). In our study, 89.7% of the patients were prescribed two AAIs.

Following training on AAI, anxiety and perturbation may develop because of both reinforced awareness on anaphylaxis and self-administration of AAI. Esenboga et al., in a study on a pediatric patient group (20), reported that of the family of the patients, 42.6% reported anxiety, and 15.4% felt fear following training on AAI. In our study, 5.1% reported anxiety, and 12.1% reported fear following AAI.

There may be mistakes made in AAI use, as it should be used only when necessary, and its administration includes some steps. Only 30–44% of the patients can appropriately administer AAI after prescription of the drug and attaining training (26). This makes training on AAI use essential. Although the use of the internet and smartphones has become popular, in our study, the rate of those watching training videos on AAI use on the internet was only 30.8%. In addition, training on AAI use by physicians at

each visit for only 10.8% of the patients is also a critical deficiency. Rate of those who correctly answered all questions regarding what to do following administering AAI, in what cases and frequency they should have AAI prescribed, storage and transportation conditions of AAI, and how to administer AAI was relatively low (66.7%). In another study on a pediatric patient group, these rates were ≥85% (20). The difference may result from our deficiency in training on AAI, and thus it is important for physicians and necessary to be corrected.

Bee sting-related anaphylaxis can occur at any place. Therefore, it is imperative that patients carry AAI with themselves continuously. Nevertheless, 30–70% of the patients do not carry AAI with them (26). Patients (16.6%) did not administer adrenaline following a bee sting because they did not have AAI along with them. In addition, in 6 (60%) out of 10 patients, AAI was administered by another person beyond themselves. Therefore, we believe that it is vital to train relatives (husband/wife, children, colleagues, etc.) of the patients at risk of anaphylaxis due to panic and hypotension, needle phobia, and risk of failure to administer AAI. In the International consensus on (ICON) anaphylaxis report, it was highlighted to train not only the patients at risk and their caregivers but also all clinicians, including the emergency department and primary physicians, and to spread this training to the whole society to increase awareness on anaphylaxis (16).

In all age groups, adrenaline administration may lead to side effects, including anxiety, palpitation, headache, and tremor, regardless of the route of administration. Nevertheless, there is no absolute contraindication for the use of adrenaline to treat anaphylaxis (4, 7). In our study, two patients (20%) had a headache, and two patients (20%) had palpitation, whereas 60% of the patients who used adrenaline did not report any side effects.

Adrenaline must be administered immediately after anaphylaxis is diagnosed. In anaphylaxis, delayed adrenaline administration is the leading cause of mortality (1, 27, 28). H1 antihistamines relieve itching, angioedema, and urticaria but are ineffective for stridor, shortness of breath, gastrointestinal symptoms, and hypotension (5). Albuterol, however, may be accompanied by adrenaline for patients with severe bronchospasm but does not resolve airway edema and treat hypotension or shock. Despite this, six (17.7%) out of 34 patients lost time on AAI administration following a bee sting by receiving treatment with antihistamines and steroids. Retrospective design and relatively small study population are the most important limitations in our study.

In conclusion, although adrenaline treatment is the most vital treatment method in anaphylaxis, patients do not have sufficient awareness of the importance and vitalness of adrenaline treatment. It is imperative to train patients at risk and patient's relatives primarily by the physicians at appropriate intervals. The results of this study revealed the weaknesses of the practices in our clinic. Particularly the necessity of stepping up from patient enlightenment to "raising patients' awareness." Even though training on drug or device use is ideally provided, unfortunately, the studies on AAI use will not be very different unless consciousness and awareness of AAI administration are provided.

Declarations

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This study was approved by the clinical research ethics committee of the Necmettin Erbakan University (Date: 21.02.2020, number: 2020/2323), and written consent was obtained from all patients participating in the study.

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