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Original Articles

Original Article

MEDICINE PALLIATIVE CARE

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The relationship between hemoglobin to red cell distribution width (RDW) ratio (HRR) and prognosis in patients with acute coronary syndrome

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ABSTRACT

Aims: The use of hematological parameters in the prognostic assessment of acute coronary syndrome (ACS) has become common in recent years. Thus, our study aimed to evaluate the relationship between hemoglobin to red cell distribution width (RDW) ratio (HRR) and prognosis of these patients.

Methods: A retrospective evaluation was conducted on patients who presented to the emergency department between 01.09.2023 and 01.04.2024 and received a diagnosis of ACS. HRR was determined by dividing the hemoglobin concentration by the red cell distribution width (RDW). The patients were categorized into two groups based on their HRR values: high HRR patients and low HRR patients, using a specified HRR cut-off value. Statistical comparisons were conducted on all parameters between the two patient groups. The variables potentially linked to mortality were analyzed using receiver operating characteristic (ROC) analysis.

Results: The in-hospital mortality rate, vasopressor needs, and MV support requirements were significantly higher in the low HRR (≤0.828) group than in the high HRR (>0.828) group ($p<0.05$ for all). The ROC analysis revealed that the HRR cut-off value for predicting mortality was 0.828. The sensitivity was determined to be 78.8% and the specificity was 92.5% (AUC: 0.885, $p<0.001$).

Conclusion: In patients with ACS, HRR measured at admission is a marker with a high prognostic value.

Keywords: Hemoglobin/red cell distribution width, acute coronary syndrome, prognosis, mortality

INTRODUCTION

Coronary artery disease (CAD), one of the most common causes of morbidity and mortality, endangers human health.[1] Acute coronary syndrome (ACS) is the prevailing type of CAD characterized by acute myocardial ischemia (AMI).[2] ACS encompasses a range of pathologies affecting the coronary arteries, including unstable angina (USAP), non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI).[3] Major adverse cardiovascular events (MACE) are common in these patients, despite technological advancements like percutaneous coronary intervention (PCI). Hence, it is crucial to uncover suitable biomarkers that may be utilized for risk classification and enhance the prognosis of these patients.[4] Hematological markers have been increasingly essential in the prognostic assessment of ACS due to their comprehensive advantages, in recent years.[5]

Atherosclerosis is an inflammatory disease that significantly contributes to the development of cardiovascular disease (CVD). It is widely recognized that the prognosis of ACS is influenced by inflammatory markers.[6] The red cell distribution width (RDW) is a hematological parameter that indicates the size heterogeneity of red blood cells. Moreover, there is substantiated data indicating that RDW, which serves as an indicator of systemic inflammation, can accurately forecast an unfavorable prognosis in ACS.[7] Hemoglobin is another hematological parameter that serves as both a diagnostic and prognostic indicator of inflammatory diseases.[3] Leonardi S et al.[8] demonstrated that low hemoglobin levels are common in invasively treated ACS patients and increase 1-year mortality.In recent years, the hemoglobin/RDW ratio (HRR), calculated by dividing hemoglobin by RDW, has been shown to be a significant prognostic indicator in inflammatory disorders such stroke and sepsis.[9,10] However, few studies have

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been reported in the literature that investigate the association between HRR and patient outcomes in CAD.[1,2,11] Therefore, in our study, the link between HRR and prognosis in patients with ACS was examined.

METHODS

Study design and patient population

The study was carried out with the permission of the Faculty of Medicine, Necmettin Erbakan University Clinical Researches Ethics Committee (Date: 07.06.2024, Decision No: 5024-19823). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

A retrospective evaluation was conducted on patients who applied to the emergency department (ED) of a training and research hospital between 01.09.2023 and 01.04.2024. These patients were diagnosed with ACS based on their complaints, medical history, electrocardiography (ECG), and laboratory examinations. Additionally, they underwent coronary angiography (CAG). Patients over 18 years of age, male or female, whose all clinical and laboratory information could be accessed from the hospital registry system and whose diagnosis of ACS was confirmed according to current guidelines, were included in the study.[12]

The severity of the lesion in patients with USAP/NSTEMI was determined by calculating the thrombolysis in myocardial infarction (TIMI) and history, ECG, age, risk factors, and troponin (HEART) scores at the time of admission to the ED. Additionally, the SYNTAX risk scores were calculated for all patients after CAG.[13-15] Upon admission to the ED, the following information was collected from patients: age, gender, medical history, routine blood tests, type of ACS (including STEMI, NSTEMI, USAP), the need for vasopressor support and/or mechanical ventilation (MV) in the intensive care unit (ICU), length of stay in the ICU (LOS-ICU), length of hospital stay (LOHS), and outcomes (discharge or death). This data was obtained through the hospital registry system.

The evaluation of mortality was determined by the occurrence of death during hospitalization. The study excluded patients who were under 18 years old, receiving acute thrombolytic therapy, pregnant, had a history of acute/chronic hematological disease, cancer, active infection, immunosuppressed, or had inaccessible information in the electronic record system. The calculation of HRR involves dividing the hemoglobin concentration (g/dl) obtained from hemogram analysis by the RDW-CV (coefficient of variation) (%). The patients were categorized into two groups based on their HRR values: high HRR and low HRR, using a specified HRR cut-off value. Statistical comparisons were made between all parameters in these two patient groups. The variables potentially linked to mortality underwent receiver operating characteristic (ROC) analysis. In addition, the correlation between hemoglobin, RDW-CV, and HRR levels with TIMI, HEART, and SYNTAX risk scores was also assessed.

Hematological and Biochemical Analysis

During admission to the ED, blood samples were obtained to test RDW, hemoglobin, and Troponin I level. The hematological markers were assessed using the Mindray auto hematology analyzer BC-6800 device (Shenzhen, China). The biochemical parameters were measured using the Mindray chemistry analyzer BS-2000M device, (Shenzhen, China).

Statistical Analysis

Statical analysis in the study was performed using SPSS 27.0 (IBM Inc, Chicago, IL, USA) program. Kolmogrov-Smirnov test, histogram analysis, skewness/kurtosis data and Q-Q plots were used to evaluate the assumptions of normal distribution. Qualitative parameters were expressed as frequency and percentage (%). Descriptive statistics of scale data were expressed as IQR (median minimum - maximum) or mean±standart deviation according to distribution pattern. Relationships between the two groups are evalutated with independent t test or Mann-Whitney U test. Relationships between nominal parameters were detailed with either Chi-Square analysis or Fisher's exact tests. ROC analysis was performed to reveal the predictive values. In the entire study, the type-I error rate was taken as 5% (α=0.05) and $p<0.05$ was accepted as the significant limit.

RESULTS

Table 1 demonstrates the characteristics of the patients based on their HRR groupings. Out of the 245 patients, 42 had a low HRR group (≤0.828), whereas 203 had a high HRR group (>0.828). When comparing the high and low HRR groups based on gender, STEMI, NSTEMI, USAP, SYNTAX score, LOHS, and LOS-ICU, no significant difference was found ($p>0.05$ for all). In the low HRR group, several factors were found to have significantly higher values compared to other group. These factors include age, RDW, troponin I levels, TIMI score, HEART score, the need for vasopressor and MV support, and the in-hospital mortality rate ($p<0.05$ for all). In addition, the low HRR group exhibited significantly lower hemoglobin levels ($p<0.001$).

The ROC analysis of parameters in mortality prediction is presented in Table 2. Of all the parameters, the SYNTAX score did not show a statistically significant difference ($p>0.05$). Hemoglobin and HRR had exceptional predictive value among the blood parameters, (AUC:0.903, 0.885, respectively). Among the risk scores, the TIMI score had the highest AUC value, while the HEART score had the lowest AUC value (AUC: 0.775, 0.688, respectively).

The correlation between parameters is presented in Table 3. RDW had a significant positive correlation with both TIMI and HEART risk scores. A significant negative correlation was seen between hemoglobin levels and Troponin I, TIMI, and HEART risk scores. A significant negative correlation was identified between HRR and Troponin I, TIMI, and HEART risk score ($p<0.05$ for all).

Table 1. Characteristics of patients according to HRR groups

Variables	Low group (HRR ≤ 0.828) (n=42, %17.1)	High group (HRR >0.828) (n=203, %82.9)	p
Age, years	65.0±10.0	61.0±11.0	0.014
Gender			
Male, n(%)	28 (66.7%)	147 (72.4%)	0.453
Female, n(%)	14 (33.3%)	56 (27.6%)	
Laboratory parameters			
RDW-CV, (%)	16.6 (13.2-18.4)	13.4 (9.5-17)	<0.001
Hemoglobin (g/dl)	11.5 (8.5-13.6)	14.7 (11.3-17.7)	<0.001
Troponin I	1284.0 (4.0-21200)	178.0 (2.0-25000)	0.002
Diagnosis			
STEMI	10 (23.8%)	46 (22.7%)	0.223
NSTEMI	26 (61.9%)	103 (50.7%)	
USAP	6 (14.3%)	54 (26.6%)	
Scores			
TIMI	5 (2-7)	4 (2-7)	<0.001
HEART	8 (0-10)	7 (0-10)	0.035
SYNTAX	16 (3-39)	15 (1-50.5)	0.310
MV support, n (%)			
No	25 (59.5%)	193 (95.1%)	<0.001
Yes	17 (40.5%)	10 (4.9%)	
Vasopressor support			
No	19 (45.2%)	195 (96.1%)	<0.001
Yes	23 (54.8%)	8 (3.9%)	
LOHS, day	3 (0-5)	3 (2-8)	0.255
LOS-ICU, day	1 (1-5)	1 (1-3)	0.176
In-hospital mortality			
No	16 (38.1%)	196 (96.6%)	<0.001
Yes	26 (61.9%)	7 (3.4%)	

HRR: Hemoglobin to red blood cell distribution width ratio, RDW: Red blood cell distribution width, STEMI: ST-segment elevation myocardial infarction, USAP: Unstable angina pectoris, TIMI: Thrombolysis in myocardial infarction, HEART: History, electrocardiogram, age, risk factors, and troponin, MV: Mechanical ventilation, LOHS: Length of hospital stay, LOS-ICU: length of stay in the ICU.

Table 2. ROC analysis of parameters in mortality prediction

	AUC	95% CI		Cut-off	Sensitivity (%)	Specificity (%)	p
		Lower limit		Upper limit			
RDW	0.797	0.691	0.902	14.85	72.7%	85.8%	<0.001
Hemoglobin*	0.903	0.828	0.979	12.4	81.8%	93.4%	<0.001
Troponin I	0.787	0.717	0.856	842.0	84.8%	73.6%	<0.001
HRR*	0.885	0.798	0.973	0.828	78.8%	92.5%	<0.001
TIMI	0.775	0.688	0.862	≥4.5	81.8%	59.4%	<0.001
HEART	0.688	0.650	0.817	≥8.5	69.7%	74.5%	0.004
SYNTAX	0.601	0.488	0.714	≥17.7	60.6%	60.4%	0.080

ROC: Receiver operating characteristic, AUC: Area under the curve, CI: Confidence interval.
*Lower values are associated with positive (exitus) results.
HRR: Hemoglobin to red blood cell distribution width ratio, RDW: Red blood cell distribution width, TIMI: Thrombolysis in myocardial infarction, HEART: History, electrocardiogram, age, risk factors, and Troponin.

Table 3. Correlation relationship between parameters

		Troponin I	TIMI	HEART	SYNTAX	LOHS	LOS-ICU
RDW	rho (ρ)	0.111	0.167	0.153	0.098	0.023	0.016
	p	0.083	0.009	0.017	0.125	0.719	0.797
HBG	rho (ρ)	-0.165	-0.263	-0.145	-0.06	-0.049	-0.061
	p	0.01	<0.001	0.023	0.348	0.441	0.345
HRR	rho (ρ)	-0.135	-0.215	-0.154	-0.075	-0.029	-0.048
	p	0.035	0.001	0.016	0.240	0.652	0.456

HRR: Hemoglobin to red blood cell distribution width ratio, RDW: Red blood cell distribution width,HBG: Hemoglobin, TIMI: Thrombolysis in myocardial infarction, HEART: History, Electrocardiogram, age, risk factors, and troponin, LOHS: Length of hospital stay, LOS-ICU: Length of stay in the ICU.

DISCUSSION

Currently, it is recognized that systemic inflammation plays a significant role in the development and progression of CVD, regardless of traditional risk factors.[3] Multiple studies have demonstrated the significant predictive value of hematological parameters in patients with CAD. RDW is a hematological marker that is associated with inflammatory diseases and is an indicator of anisocytosis.[2] While the exact process remains uncertain, it is believed that RDW levels rise due to uncontrolled inflammation in patients with ACS.[1] Currently, there is evidence showing a significant relationship between elevated RDW values and the prognosis of CVD.[7,16] In a study conducted by Khaki et al.,[17] they found that patients with high RDW had a greater 6-month death rate compared to patients with low RDW, as shown in their analysis of 649 patients with ACS. According to Wei et al,[18] in a study involving 2078 patients with chest pain, the RDW cut-off value was determined to be 13.25%. This value was found to have a sensitivity of 78.10%, specificity of 87.44%, and an AUC of 0.88 in predicting myocardial damage. Additionally, RDW was found to be associated with hs-cTnT (r=0.607). Our study found a significant correlation between RDW and TIMI and HEART risk scores. Additionally, RDW predicted mortality with 72.7% sensitivity, 85.8% specificity, and an AUC value of 0.797. Consequently, RDW may serve as a prognostic marker in patients with ACS.

Hemoglobin levels, which indicate the capacity of the body to carry oxygen, serve as a significant marker of inflammation in patients with CAD.[3] Anemia, a frequently occurring condition caused by chronic inflammation, has been demonstrated to be linked with increased cardiac load, left ventricular hypertrophy, and CVD.[19] Acute anemia can disturb the natural balance of myocardial oxygen requirement, potentially leading to the development of AMI.[20] The study conducted by Ndrepepa et al.[21] examined 3838 patients with ACS and found that a reduction in hemoglobin levels during hospitalization was linked to an increased risk of mortality within one year, even in cases where there was no major bleeding. In their study, Kılıç et al.[2] examined 1.146 patients with ACS and found that the hemoglobin level was significantly lower in mortality group. Our study found a significant correlation between hemoglobin levels and Troponin I, TIMI, and HEART risk scores. Hemoglobin also demonstrated remarkable predictive ability for mortality in these patients (AUC: 0.903, sensitivity: 81.8%, specificity: 93.4%). While numerous studies have demonstrated the significance of RDW and hemoglobin levels in AMI, the prognostic value of HRR in this specific patient group remains uncertain.[2] By combining the data from hemoglobin and RDW into a single variable, HRR can be utilized as a more potent prognostic marker. Furthermore, considering that hemoglobin and RDW can be influenced by several factors such as nutrition, infection, etc., and so on, it is believed that HRR can mitigate these negative effects.[11] Several studies have established a significant relationship between HRR and the likelihood of survival among individuals diagnosed with cancer.[22,23] A study involving 1816 patients with heart failure demonstrated that HRR exhibited a non-linear relationship with 3-month hospital readmission.[24] Kılıç et al.[1] shown that HRR is a predictive value for MACE in the long-term follow-up after AMI. Xiu et al.[2] demonstrated that among patients with CAD who had low HRR levels (HRR<10.25), the long-term mortality rate following PCI was 1.470 times higher. In the study conducted by Huo et al.[4] with 4651 patients who underwent PCI, it was observed that the HRR was significantly lower in the group of patients

who died compared to those who survived. The findings of our study were in line with the aforementioned studies. Patients with low HRR were found to have a significantly higher need for vasopressor, MV support, and in-hospital death rate. ROC analysis revealed that the predictive power of HRR for mortality was found to be significantly high. Furthermore, since HRR has a significant correlation with Troponin I, TIMI, and HEART risk scores, HRR can also be employed as a valuable marker in the risk classification for these patients. However, no significant correlation was observed between HRR and the LOHS or LOS-ICU. This may be attributed to the characteristics of the patient population under study.

Limitations

We have a few limitations. First, due to the study's single-center and retrospective nature, it is not possible to rule out potential factors that may have influenced our findings. Secondly, only blood parameters at the time of admission were investigated, dynamic measurements of these parameters were not feasible. Third, due to the evaluation of short-term mortality and the limited sample size, the findings of our study cannot be extrapolated to a broader population. In order to validate our study findings, it is necessary to conduct larger-scale, multicenter studies including a significant number of participants.

CONCLUSION

Our study indicates that the levels of HRR evaluated upon admission are an employable marker that determines the prognosis of individuals with ACS. HRR can assist doctors in the risk classification of patients by virtue of its significant correlation with troponin I, TIMI, and HEART risk scores.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Faculty of Medicine, Necmettin Erbakan University Clinical Researches Ethics Committee(Date: 07.06.2024, Decision No: 5024/19823).

Informed Consent

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

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

REFERENCES

1. Xiu WJ, Zheng YY, Wu TT, et al. Hemoglobin-to-red-cell distribution width ratio is a novel predictor of long-term patient outcomes after percutaneous coronary intervention: a retrospective cohort study. *Front Cardiovasc Med*. 2022;16(9):726025.
2. Kılıç O, Mustu M, Suygun H, Con E, Karakurt A, Fatma S. Hemoglobin/red cell distribution width ratio is associated with poor prognosis in patients with acute coronary syndrome in long-term follow-up. *Int J Cardiovasc Sci*. 2024;37(1):20230099.
3. Aktas G, Tel BA, Duman TT. Inflammatory indices derived from hemogram as prognostic markers of cardiovascular outcome. *Int J Cardiovasc Sci*. 2024;37(1):20240012.
4. Huo LK, Chen KY, Tse G, Liu T. Association of inflammatory markers based on routine blood with prognosis in patients underwent percutaneous coronary intervention. *Medicine*. 2024;103(19):38118.
5. Li D, Ruan Z, Wu B. Association of red blood cell distribution width-albumin ratio for acute myocardial infarction patients with mortality: a retrospective cohort study. *Clin Appl Thromb Hemost*. 2022;28(1):10760296221121286.
6. Jian L, Zhang Z, Zhou Q, Duan X, Ge L. Red cell distribution width/albumin ratio: a predictor of in-hospital all-cause mortality in patients with acute myocardial infarction in the ICU. *Int J Gen Med*. 2023;27(16):745-756.
7. Huang S, Zhou Q, Guo N, et al. Association between red blood cell distribution width and in-hospital mortality in acute myocardial infarction. *Medicine*. 2021;100(15):25404.
8. Leonardi S, Gragnano F, Carrara G, et al. Prognostic implications of declining hemoglobin content in patients hospitalized with acute coronary syndromes. *J Am Coll Cardiol*. 2021;77(4):375-388.
9. Qin Z, Liao N, Lu X, Duan X, Zhou Q, Ge L. Relationship between the hemoglobin-to-red cell distribution width ratio and all-cause mortality in ischemic stroke patients with atrial fibrillation: an analysis from the MIMIC-IV database. *Neuropsychiatry Dis Treat*. 2022;18(18):341-354.
10. Wang J, Chen Z, Yang H, Li H, Chen R, Yu J. Relationship between the hemoglobin-to-red cell distribution width ratio and all-cause mortality in septic patients with atrial fibrillation: based on propensity score matching method. *J Cardiovasc Dev Dis*. 2022;9(11):400.
11. Qu J, Zhou T, Xue M, et al. Correlation analysis of hemoglobin-to-red blood cell distribution width ratio and frailty in elderly patients with coronary heart disease. *Front Cardiovasc Med*. 2021;27(8):728800.
12. Byrne RA, Rossello X, Coughlan JJ, et al. 2023 ESC Guidelines for the management of acute coronary syndromes. *Eur Heart J*. 2023;44(38):3720-3826.
13. Ababneh MJ, Smadi MM, Al-Kasasbeh A, et al. Validity of TIMI risk score and heart score for risk assessment of patients with unstable angina/ non-st elevation myocardial infarction presented to an emergency department in Jordan. *Open Access Emerg Med*. 2023;18(15):465-471.

14. Salimi A, Zolghadrasli A, Jahangiri S, et al. The potential of HEART score to detect the severity of coronary artery disease according to SYNTAX score. *Sci Rep*. 2023;13(1):7228.
15. Rostami A, Tajlil A, Separham A, et al. Association between neutrophil-to-lymphocyte ratio and the systemic inflammatory immunologic index and the angiographic SYNTAX score and the TIMI flow grade in acute STEMI: a cohort study. *J Tehran Heart Cent*. 2021;16(4):147-155.
16. Li N, Zhou H, Tang Q. Red blood cell distribution width: a novel predictive indicator for cardiovascular and cerebrovascular diseases. *Dis Markers*. 2017;17(20):7089493.
17. Khaki S, Mortazavi SH, Bozorgi A, Sadeghian S, Khoshnevis M, Mahmoodian M. Relationship between red blood cell distribution width and mortality of patients with acute myocardial infarction referring to TEHRAN heart center. *Crit Pathw Cardiol*. 2015;14 (33):112-115.
18. Wei J, Yang RX, Ye Q, et al. Higher risk of myocardial injury in chest pain patients with elevated red blood cell distribution width. *Clin Chim Acta*. 2018;481(1):121-125.
19. Ishigami J, Grams ME, Naik RP, et al. Hemoglobin, albuminuria, and kidney function in cardiovascular risk: the ARIC (atherosclerosis risk in communities) study. *J Am Heart Assoc*. 2018;7(2):007209.
20. Uyarel H, Ergelen M, Cicek G, et al. Red cell distribution width as a novel prognostic marker in patients undergoing primary angioplasty for acute myocardial infarction. *Coron Artery Dis*. 2011;22(3):138-144.
21. Ndrepepa G, Neumann FJ, Menichelli M, et al. Prognostic value of hemoglobin drop in patients with acute coronary syndromes. *Eur J Clin Invest*. 2021;51(12):13670.
22. Bozkaya Y, Kurt B, Gürler F. A prognostic parameter in advanced non-small cell lung cancer: The ratio of hemoglobin-to-red cell distribution width. *Int J Clin Oncol*. 2019;24(7):798-806.
23. Yılmaz A, Mirili C, Tekin SB, Bilici M. The ratio of hemoglobin to red cell distribution width predicts survival in patients with gastric cancer treated by neoadjuvant FLOT: a retrospective study. *Ir J Med Sci*. 2020;189(1):91-102.
24. Song J, Yu T, Yan Q, Zhang Q, Wang L. Association of hemoglobin to red blood cell distribution width-standard deviation (RDW-SD) ratio and 3-month readmission in elderly chinese patients with heart failure:a retrospective cohort study. *Int J Gen Med*. 2023;24(16):303-315.

Original Article

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Exploring attitudes towards infertility: insights from a primary healthcare setting

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ABSTRACT

Aims: This study aimed to assess attitudes and knowledge regarding infertility among adults attending a primary healthcare facility in Turkey, along with identifying influencing factors.

Methods: A descriptive cross-sectional survey was conducted among individuals aged 18-49 who admitted to a Hamidiye tranining and research hospital Family Medicine Outpatient Clinic. Participants completed the attitudes towards infertility scale (ATIS) and the Infertility Knowledge Test (IKT). Demographic data including age, gender, marital status, educational level, and reproductive history were collected.

Results: A total of 237 individuals participated in the study. The median ATIS score of the participants in the study was 50, and the median IKT score was 19. ATIS scores were lower among male (p:0,023), those who were married, had children, had experienced pregnancy, had lower education level compared to other groups (p<0.001 for all). Participants who expressed willingness to consider adoption if unable to have children had significantly higher ATIS scores (p=0.010). Higher knowledge scores correlated positively with more positive attitudes (p=0.006, R=0.178).

Conclusion: The study highlights a correlation between knowledge about infertility and attitudes toward the condition. These findings underscore the importance of educational programs aimed at increasing awareness about infertility and promoting a more positive societal attitude towards it.

Keywords: Infertility, attitude, knowledge, primary healthcare

INTRODUCTION

Infertility is defined as the inability to conceive after 12 months of regular, unprotected sexual intercourse.[1] Globally, it affects an estimated 13-15% of couples,[2] with similar prevalence observed in Turkiye, ranging from 10-20%.[3,4]

The desire to have children is a fundamental instinct and is a crucial aspect of identity and family for most couples.[5] In addition to social and financial consequences, infertility often leads to psychological issues such as depression and sexual dysfunction, making it a significant health concern.[5-8] Studies indicate that the psychological impacts and pressures associated with infertility are particularly pronounced in women.[2,6,9] In some cultural contexts, infertility, referred to as sterility, is perceived as a deficiency or defect, perpetuated by societal influences and misinformation.[10,11]

Various factors including genetics, age, smoking, caffeine intake, sexually transmitted diseases, and stress contribute to infertility.[12,13] Awareness of these factors is essential for taking preventive measures. Understanding the causes of infertility and seeking early medical intervention are crucial for managing the condition effectively. Research has shown that attitudes between partners can change significantly following an infertility diagnosis; and nearly half of infertile couples, irrespective of gender, often conceal their diagnosis due to societal stigma.[6]

This study aims to explore the relationship between individuals' knowledge about infertility and their attitudes towards the condition, along with identifying influencing factors.

METHODS

The study was carried out with the permission of the University of Health Sciences Hamidiye Faculty of Medicine

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Clinical Researches Ethics Committee (Date: 30.09.2022, Decision No: 22/08). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This study is a descriptive cross-sectional survey conducted with individuals aged 18-49 who were admitted to the Family Medicine Outpatient Clinic of a training and research hospital for any reason between October 1, 2022, and December 1, 2022.

The study's inclusion criteria specified individuals between 18 and 49 years of age who volunteered to participate and completed all surveys and forms in their entirety. Informed consent was obtained from all participants. Demographic data including age, educational level, financial status, and number of children were recorded. The attitudes of couples towards infertility and their levels of infertility knowledge were assessed using the Turkish versions of the Attitudes Towards Infertility Scale (ATIS) and the Infertility Knowledge Test (IKT). The study enrolled voluntary participants, excluding those who did not fully complete the survey forms or did not meet the age criteria specified.

Instruments

The Attitudes Towards Infertility Scale (ATIS) was developed by Siyez and colleagues in 2018 to assess individuals' attitudes towards infertility. In the scale development study, exploratory factor analysis and confirmatory factor analysis methods were used, and the scale's Cronbach's alpha value was calculated as 0.85. ATIS comprises 12 items, with responses given on a five-point scale: (1) strongly disagree, (2) disagree, (3) neutral, (4) agree, (5) strongly agree. Items 1, 2, 5, 6, 8, 9, 11, and 12 are reverse-scored. The total possible score ranges from 12 to 60, with higher scores reflecting a more positive attitude towards infertility.[14]

The Infertility Knowledge Test (IKT) was developed to assess individuals' level of knowledge regarding infertility. The test includes response options of "True," "False," and "Don't Know". It consists of 33 items, with 19 items scored normally and 14 items reverse-scored. The reverse-scored items are 2, 3, 10, 17, 18, 19, 20, 21, 22, 23, 24, 25, 27, and 32. Participants receive 1 point for each correct answer. The highest possible score is 33, and the lowest is 0, with higher scores indicating a greater level of knowledge about infertility. The validity and reliability study of the IKT found the average item difficulty index to be 0.49 and the reliability coefficient to be 0.77. The KR-20 formula was used to determine the reliability coefficient, considering the true-false scoring and varying item difficulty levels.[15]

Statistical Analysis

Statistical analyses were conducted using SPSS statistics 25 (IBM Corporation, NY, US). The normality of the distribution of quantitative data was assessed using the Kolmogorov-Smirnov and Shapiro-Wilks tests. Descriptive statistical methods, including percentages and mean± standard deviation (±SD) or median (interquartile range IQR), were used to summarize the basic characteristics of the data based on the normality assessment. For comparisons of quantitative data, the Mann-Whitney U test was used for comparisons between two groups, and the Kruskal-Wallis test was used for comparisons among more than two groups. Bonferroni correction was applied for pairwise comparisons to provide adjusted analysis results. Spearman's correlation test was employed for correlation analysis of quantitative variables that did not follow a normal distribution. Statistical significance was set at $p<0.05$.

RESULTS

A total of 237 individuals participated in the study, comprising 164 women (69.2%) and 73 men (30.8%). The average age of the participants was 32.68±8.66 years. Among them, 90 (37.9%) were married, and 70 (29.5%) had children, with the median number of children being 2 (range: 1-2). It was noted that 57 (35%) of the female participants had experienced pregnancy. Additionally, 40 participants (16.9%) reported a family history of infertility (Table 1).

Table 1. Demographic characteristics of the participants in the study

	Participants (n=237)
Age (year)	32.68±8.66[a]
Gender	
Female	163 (68,8%)
Male	74 (31.2%)
Marital status	
Married	90 (38%)
Single+ Widowed	147 (62%)
Parental Status	
Participants with children	70 (29.5%)
Median number of children	2 (1-2)[b]
Women who experienced pregnancy	57 (35%)
Family history of infertility	40 (16.9%)
Educational level	
High school and lower	55 (23.2%)
College and higher	182 (76.8%)
Income Status	
Income less than expenses	43 (18.1%)
Income equal to expenses	103 (43.5%)
Income more than expenses	91 (38.4%)
Receiving treatment support for infertility	
No	226 (95.4%)
Yes	11 (4.6%)
If you couldn't have children, would you consider adoption?	
No	44 (18.6%)
Yes	102 (43%)
Undecided	91 (38.4%)

a: Mean±SD (Standard deviation). b: Median (interquartile interval)

When examining the educational levels of the participants, it was found that 55 (23.2%) had a high school education or lower, while 182 (76.8%) had a college or higher (college and university) education. Among the participants, 43 (18.1%) reported that their income was less than their expenses, 103 (43.5%) stated that their income was equal to their expenses, and 91 (38.4%) indicated that their income was more than

their expenses. A total of 226 participants (95.4%) reported that they did not receive treatment support to have children, while 11 (4.6%) stated that they did receive treatment support (Table 1). In response to the question, "If you couldn't have children, would you consider adoption?" 44 participants (18.6%) answered "no," 102 (43%) answered "yes," and 91 (38.4%) were undecided.

The median ATIS score of the participants in the study was 50 (45-53), and the median IKT score was 19 (14-23). When ATIS scores were evaluated by gender, it was found that female participants had significantly higher ATIS scores (p=0.023). ATIS scores were lower among those who were married, had children, and had experienced pregnancy compared to other groups (p<0.001 for all); however, there was no statistically significant difference between groups with and without a family history of infertility (p>0.05). Participants with a college education or higher were found to have higher ATIS scores (p<0.001). There was no significant statistical difference found between participants' income levels, treatment status for having children, and their attitudes towards infertility (p>0.05, p>0.05) (Table 2).

Table 2. Comparison of ATIS scores across demographic characteristics of participants

	ATIS	p
Gender		
Female	51 (45-54)[a]	0.023[b,*]
Male	49 (45-51)[a]	
Marital status		
Married	47.50 (43-52)[a]	<0.001[b,*]
Single+ widowed	51 (47-54)[a]	
Parental status		
Yes	46.50 (40-51)[a]	<0,001[b,*]
No	51 (47-54)[a]	
Pregnancy experience		
Yes	48 (40-52.50)[a]	<0.001[b,*]
No	51 (47.75-54)[a]	
Family history of infertility		
Yes	45 (40-53)[a]	0.910[b]
No	51 (44.75-53)[a]	
Education level		
High school or lower	46 (40-51)[a]	<0.001[b,*]
College or higher	51 (47-53.25)[a]	
Income level		
Income less than expenses	51 (44-54)[a]	0.547[c]
Income equal to expenses	50 (44-53)[a]	
Income more than expenses	51 (46-53)[a]	
Receiving treatment support for infertility		
Yes	50 (45-53)[a]	0.750[b]
No	52 (44-55)[a]	
If you couldn't have children, would you consider adoption?		
No	49(43-55)[a]	p=0.010[c,*]
Yes	51 (47-54)[a,k]	pk=0.002[b,*]
Undecided	49 (44-52)[a,k]	

ATIS : Attitudes towards infertility scale ,a: Median (interquartile interval). b: Mann-Whitney U Test, c: Kruskal-Wallis Test. k, l: Letters indicating the statistical difference based on the Mann-Whitney U test. * Statistically significant (p<0.05).

In the study, participants who answered "Yes" to the question "Would you consider adoption if you couldn't have children?" had a median ATIS score of 51 (47-54), those who were undecided had a score of 49 (44-52), and those who answered "No" had a score of 49 (43-55). There was a significant difference in ATIS scores among the groups (p=0.010). Specifically, participants who answered "Yes" had higher ATIS scores compared to those who were undecided (p=0.002).

In the study, there was no significant statistical difference found in IKT scores across gender, marital status, presence of infertility in the family, and receiving treatment for having children. However, participants with a college education or higher and participants without children had significantly higher IKT scores (p<0.001, p=0.002). Furthermore, a positive correlation was found between participants' ATIS scores and IKT scores (p=0.006 R:0.178).

DISCUSSION

Our study assessed attitudes and knowledge levels regarding infertility among the reproductive-age population, revealing that as individuals' knowledge about infertility increased, their attitudes towards infertility improved. Although studies concerning attitudes towards fertility have been conducted in different populations such as midwifery and university students,[16,17] this study holds significance as it is the first in the literature to evaluate the Turkish version of the ATIS among individuals accessing primary healthcare services.

During the World infertility awareness month in 2006, a survey involving approximately 17,500 individuals highlighted the global lack of knowledge about infertility.[18] In a cross-sectional study by Ali et al.[19] involving 447 participants, low levels of knowledge about infertility were reported.

A study conducted with Moroccan youth found that both women and men had low levels of knowledge regarding infertility.[20] Another study utilizing the IKT demonstrated that medical students exhibited a good level of knowledge about infertility.[21] Similarly, Dönmez et al.[17] found comparable results among nursing students.

The high knowledge levels observed in these studies may be attributed to participants receiving education in the healthcare field. In our study, participants achieved a median IKT score of 19, which was above average. We attribute this to the fact that 76.8% of our participants were college educated or had higher education levels. Research indicates that as individuals' knowledge and awareness about infertility increase, their attitudes improve.[2]

Those who have more information about infertility are better able to understand it as a treatable medical condition and may develop a more supportive attitude towards infertility. Conversely, individuals with inadequate or incorrect

knowledge about infertility may exhibit more negative or fear-driven attitudes.[22] In our study, we also found a positive correlation between individuals' attitudes towards infertility and their knowledge levels about infertility, and we observed significantly higher ATIS scores among the college and higher educated group. These findings align with existing literature on the subject. In a study conducted in 2023 involving fertile and infertile women, it was observed that infertile women demonstrated a significantly higher level of knowledge compared to fertile counterparts. Additionally, it was found that as knowledge levels increased, there was a corresponding improvement in attitudes towards infertility.[23] In countries like Turkiye, where motherhood holds significant societal gender roles, women who are unable to fulfill this role often face stigma and negative discourse.[24] Numerous studies have reported that many women diagnosed with infertility experience social stigma.[25,26] Even when infertility is not attributed to the woman, the societal emphasis on motherhood can significantly impact women's sense of self-integrity, leading to greater identity crises compared to men.[27]

In our study, we found that women had more favorable attitudes towards infertility compared to men, as assessed by scale scores. We attribute this to women being more affected by the social consequences of infertility and approaching the issue with empathy. Additionally, attitudes towards infertility were more positive among singles, childless individuals, and women who had not experienced pregnancy compared to other groups. A study conducted in Bangladesh found that women's attitudes towards infertility were more positive, and it was also observed that as knowledge levels increased, their attitudes towards infertility improved.[28] Acar et al.[29] (2022) similarly demonstrated in their study using ATIS that singles exhibit more positive attitudes towards infertility compared to married individuals.

Limitations

Our study has several limitations. Firstly, the evaluation was limited to individuals attending a single outpatient clinic, resulting in a relatively small sample size. This may restrict the generalizability of our findings. Additionally, the predominance of participants with a college and higher education could potentially limit the representativeness of our results to the broader population. Conducting studies with larger and more diverse samples across multiple centers would enhance the inclusivity and generalizability of findings that can be applied to the wider community.

CONCLUSION

As a result, this study demonstrates that attitudes towards infertility are associated with individuals' level of knowledge about infertility, and these attitudes have significant social and psychological consequences. These findings underscore the importance of educational programs aimed at increasing awareness about infertility and promoting a more positive societal attitude towards it.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the University of Health Sciences Hamidiye Faculty of Medicine Clinical Researches Ethics Committee (Date: 30.09.2022, Decision No: 22/08).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

REFERENCES

1. World Health Organisation. Sexual and reproductive health: infertility definitions and terminology. Geneva, Switzerland: WHO; 2019 Apr 12. Accessed May 20, 2024. https://www.who.int/reproductivehealth/topics/infertility/definitions/en/
2. Abolfotouh MA, Alabdrabalnabi AA, Albacker RB, AlJughaiman UA, Hassan SN. Knowledge, attitude, and practices of infertility among Saudi couples. *Int J Gen Med*. 2013;10(6):563-573.
3. Emekli H, Şakiroğlu M. İnfertilite tanısı alan kadınların stigma deneyimleri ve baş etme yolları: bir derleme. *Dünya İnsan Bilimleri Derg*. 2022;2(1):139-150.
4. Yanıkkerem E, Kavlak O, Sevil U. İnfertil çiftlerin yaşadıkları sorunlar ve hemşirelik yaklaşımı. *Nurs Philos*. 2008;11(4):112-121.
5. Yazdani F, Kazemi A, Samani HR. Studying the relationship between the attitude to ınfertility and coping strategies in couples undergoing assisted reproductive treatments. *J Reprod Infertil*. 2016;17(1):56-60.
6. Ergin RN, Polat A, Kars B, Öztekin D, Sofuoğlu K, Çalışkan E. Social stigma and familial attitudes related to infertility. *TJOD*. 2018;15(1):46-49.
7. Yücesoy H, Yıldırım F, Şahin E. İnfertilitenin kültürel, ekonomik, psikososyal ve cinsel yönüne güncel bir bakış: temel hemşirelik yaklaşımları. *Androl Bul*. 2021;23(1):256-263.
8. Kamel RM. Management of the infertile couple: an evidence-based protocol. *Reprod Biol Endocrinol*. 2010;8(1):21.
9. Cserepes RE, Kollár J, Sápy T, Wischmann T, Bugán A. Effects of gender roles, child wish motives, subjective well-being, and marital adjustment on infertility-related stress: a preliminary study with a Hungarian sample of involuntary childless men and women. *Arch Gynecol Obstet*. 2013;288(4):925-932.
10. Bayraktar E. Toplumsal cinsiyet, kültür ve şiddetin infertilite ile ilişkisi. *J Health Sci*. 2018;27(1):234-238.

11. Uyar EB, Özkan M, Gül T. Level of belief in sexual myths women with infertility treatment. *J Clin Psy*. 2017;20(3):209-217.
12. Chavarro JE, Rich JW, Rosner BA, Willett WC. Diet and lifestyle in the prevention of ovulatory disorder infertility. *Obstet Gynecol*. 2007;110(5):1050-1058.
13. Baird DT, Collins J, Egozcue J, et al. Fertility and ageing. *Hum Reprod Update*. 2005;11(3):261-276.
14. Siyez DM, Esen E, Baran B, Seymenler S, Kağnıcı DY, Siyez E. İnfertiliteye yönelik tutum ölçeğinin geliştirilmesi: geçerlik ve güvenirlik çalışması. *Çukurova Med*. 2018;43(1):173-180.
15. Seymenler S. Üniversite öğrencilerinin infertilite ile ilgili bilgi düzeyi ve tutumlarının incelenmesi. Doctoral thesis. İzmir, Dokuz Eylül Üniv., Eğitim Bilimleri Enstitüsü; 2017.
16. Güner Emül T, Çokan Dönmez Ç, Vefikuluçay Yılmaz D. The determining knowledge and attitude of midwife and nurses towards infertility: descriptive research. *Turkiye Klinikleri J Nurs Sci*. 2021;13(4):815-821.
17. Dönmez Ç, Güner Emül T. The knowledge and attitudes of nursing students infertility and determination of factors affecting these variables. *Ordu Üniv. Hemşirelik Çalışmaları Derg*. 2021;4 (3):375-381.
18. Bunting L, Boivin J. Knowledge about infertility risk factors, fertility myths and illusory benefits of healthy habits in young people. *Hum Reprod*. 2008;23(8):1858-1864.
19. Ali S, Sophie R, Imam AM, et al. Knowledge, perceptions and myths regarding infertility among selected adult population in Pakistan: a cross-sectional study. *BMC Public Health*. 2011;11(1): 760.
20. El Adlani S, Benksim A, Kaddour YAB, Soummani A, Cherkaoui M. Infertility: knowledge and attitudes of Moroccan young people-gender approach. *Middle East Fertil Soc J*. 2021;26(1):14.
21. Thomson AA, Brown M, Zhang S, et al. Evaluating acquisition of knowledge about infertility using a whiteboard video. *J Obstet Gynaecol Can*. 2016;38(7):646-650.
22. Rouchou B. Consequences of infertility in developing countries. *Perspect Public Health*. 2013;133(3):174-179.
23. Sharma A, Kamboj N, Saraswathy KN, Puri M, Babu N, Mahajan C. Knowledge, attitude, and practice of infertility: A comparative study in infertile and fertile Indian women. *J Biosoc Sci*. 2023;55 (5):947-959.
24. Keskin, G, Babacan Gümüş A. Infertility: an examination hopelessness perspective. *Int J Nurs Stud*. 2014;5(1):9-16.
25. Donkor ES, Sandall J. The impact of perceived stigma and mediating social factors on infertility-related stress among women seeking infertility treatment in Southern Ghana. *Soc Sci Med*. 2007;65(8):1683-1694.
26. Missmer SA, Seifer DB, Jain T. Cultural factors contributing to health care disparities among patients with infertility in Midwestern United States. *Fertil Steril*. 2011;95(6):1943-1949.
27. Ying LY, Wu LH, Loke AY. Gender differences in experiences with and adjustments to infertility: A literature review. *Int J Nurs Stud*. 2015;52(10):1640-1652.
28. Iktidar MA, Chowdhury S, Roy S, et al. Knowledge, attitude and perception among medical students and healthcare professionals regarding male infertility: a cross-sectional survey from Bangladesh. *BMJ Open*. 2022;12(11):062251.
29. Acar Z, Güngör Satilmiş İ. Cultural perspective on infertility in Turkish society: the İstanbul sample. *İzmir Democracy Univ Health Sci J*. 2022;5(3):635-650.

Original Article

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Assessment of depression and anxiety and their relationship with functional status in patients with stroke

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Aims: This study aimed to investigate the anxiety and depression levels and the relationship between functional status and depression, anxiety, pain, and quality of life in stroke patients.

Methods: 65 stroke patients and 65 healthy controls were involved in the study. After recording the sociodemographic characteristics of all patients, anxiety, and depression levels were evaluated with the hospital anxiety depression (HAD) scale, and the quality of life with the Nottingham Health Profile (NHP) questionnaire. In stroke patients, functional status was evaluated with the functional ambulation categories (FAC), disease stages with the Brannstrom Staging system, and pain intensity with the visual analogue scale (VAS).

Results: Anxiety levels were high in 33 patients (50.77%) in the stroke group and 16 patients (24.60%) in the control group. Depression levels were high in 35 patients (53.85%) in the stroke group and 25 patients (38,46%) in the control group. In the stroke group, the HAD anxiety, HAD depression, and HAD total scores of patients were statistically significantly higher compared to the control group (p:0.036, p:0.013, p: 0.010,respectively). When the quality of life of the patients was examined, the NHP energy level was statistically significantly lower in the stroke group (p:0.008). Examination of the stroke patients by their functional ambulation levels revealed statistically lower HAD anxiety, HAD depression, and HAD total scores with higher functional status (p:0.003, p: <0,001, p: <0,001, respectively). NHP pain, sleep, physical mobility, energy, distress subdomains, and NHP total scores were statistically significantly different with the functional status of patients. Negative correlations were found between FAC scores with pain, HAD anxiety, HAD depression, HAD total, and NHP total scores.

Conclusion: Anxiety and depression levels are higher in stroke patients. And also there is an inverse relationship between functional status and the severity of pain, anxiety, depression, and quality of life.

Keywords: Anxiety, depression, functional status, quality of life, stroke

INTRODUCTION

Strokes occur due to either a cerebral infarction or a cerebral hemorrhage and constitute the major cause of permanent disability. Stroke is a leading cause of mortality after heart disease and cancer. Stroke patients face not only physical disability but also psychosocial problems that will unfavorably act on physical rehabilitation and recovery processes.[1] Depression and anxiety are among the most common psychiatric disorders following a stroke. Patients with post-stroke anxiety disorder often suffer from comorbid depression. Depression can occur in 20-60% of stroke patients.[2] Although post-stroke depression is common, not all patients receive adequate diagnosis and treatment. Failure to differentiate depressive findings from cognitive impairment due to ischemic brain damage in post-stroke patients complicates diagnosis.[3] The rates of depression in the first three years following a stroke vary between 14% and 30%. The risk of developing depression is highest during the first year after a stroke. However, depression can occur at any time in a stroke patient.[4] The mechanism of developing post-stroke depression is not fully known, but various biological factors such as disruption of the hypothalamic and adrenal axis or changes in cortisol and interleukin 6 levels are suggested to play a major role. Magnetic resonance images of patients with post-stroke depression reveal white matter lesions and lacunar infarcts as the primary pathological culprits. The likelihood of suicide or a new ischemic event is high in patients suffering from post-stroke depression, contributing further to increased stroke-related mortality.[5] Moreover, early diagnosis and treatment of post-stroke depression is important for an effective rehabilitation process.

Anxiety can be defined as a state of unsubstantiated worry and fear accompanied by somatic symptoms. Generalized anxiety disorder is defined as a condition characterized by excessive worrying and anxiousness, which are difficult to control. These should occur in more than one day during at least six months. The condition causes severe distress and impairs daily activities of living.[6] Post-stroke anxiety is common and occurs in one out of three stroke patients. Patients develop anxiety due to the fear of having another stroke and because of worries

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about restoration of function and fall-related accidents.[7,8] However, anxiety acts on the physical rehabilitation process and quality of life untowardly. Therefore, adequate diagnosis and treatment are important.

Pain is common after a stroke, unfavorably affecting the quality of life and the functional status in daily life. However, pain is often not inquired actively and is overlooked. Post-stroke pain leads to a delayed recovery process, impairs the quality of life, and causes psychosocial problems in stroke patients. Pain affects the rehabilitation process adversely. Post-stroke pain can present as central pain, complex regional pain syndrome, shoulder pain, spasticity-related pain, or a headache. The pathophysiology of these subtypes awaits to be established and post-stroke pain is usually resistant to treatment.[9]

Depression, anxiety, and pain following a stroke are common medical conditions, and adequate diagnosis and treatment favorably affect recovery, rehabilitation, and the restoration of daily function. Thus, to avoid overlooking the appropriate diagnosis, it may be prudent to screen these clinical conditions with relevant screening scales before patients present with distress and symptoms. This study aimed to investigate the relationship between functional status and depression, anxiety, pain, and quality of life in stroke patients.

METHODS

This study was approved by the Clinical Researches Ethics Committee of the Hitit University Faculty of Medicine (Date: 28.09.2023, Decision No: 118) and written informed consent was obtained from each participant and written informed consent was obtained from each participant. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study with a controlled and prospective design included 65 stroke patients, who were admitted to the neurology outpatient clinic with a diagnosis of a stroke during the period between September 2023 and May 2024. For the control group with a similar age and gender distribution to that of the patient group, the study included 65 healthy subjects, who were admitted to the neurology outpatient clinic during the same period for routine check-ups and diagnosed with no neurological disease.

Patients older than 18 years of age, who passed the acute phase of a stroke diagnosed as with the World Health Organization criteria by an experienced neurologist, were included in the study. Patients and the healthy control subjects having a condition that might involve the central nervous system, having a severe cardiovascular disease such as heart failure, arrhythmia, or myocardial infarction that would affect the functional status, having a psychiatric disorder, Alzheimer's disease, dementia, or a condition that would cause cognitive dysfunction, having severe visual or hearing impairment that would interfere with proper communication with the patient, having a malignant disease, having joint contractures or amputation that would impair the functional status, or pregnant or breastfeeding women were excluded. After recording the socio-demographic characteristics and physical examination findings of all patients, patients' anxiety and depression levels were assessed with the hospital anxiety depression (HAD) scale questionnaire. The HAD scale questionnaire consists of 14 items and is filled out by patients. The scale includes two subscales, which assess depression and anxiety. The cut-off scores for the Turkish version of the HAD scale were found to be 10 for the anxiety subscale and 7 for the depression subscale. The validity and reliability of the Turkish version of the HAD scale were studied previously.[10]

In stroke patients, functional status was evaluated with the functional ambulation categories (FAC), disease stages with the Brunnstrom staging system, the quality of life with the nottingham Health Profile (NHP) questionnaire, and the pain intensity with the visual analogue scale (VAS).

The Brunnstrom Staging system is one of the tests to evaluate the restoration of the motor control ability of the body following a stroke. Synergistic movement patterns occurring during the recovery process are evaluated for the assessment. The upper extremity, the hand, and the lower extremity findings are scored on a scale from 1 to 6. Higher scores indicate closer to normal functioning.[11]

FAC is a classification system consisting of 6 categories from 0 to 5, aiming to grade the ambulation ability of patients by evaluating the dependence on personal support during the ambulation process. FAC category 0 refers to nonfunctional ambulation, indicating that the ambulatory and non-dependent patient, who can walk freely on any surface, including stairs.[12]

The health-related quality of life was assessed by using the Turkish version of the NHP questionnaire. NHP consists of the subdomains of physical mobility (pm), pain (p), sleep (sl), emotional reaction (em), social isolation (so), energy (en), and distress (d). Each subdomain is scored from 0 to 100. Higher scores indicate more severe health problems.[13]

The pain severity was assessed with VAS, patients marked the average pain severity they felt in the last week along a 10-centimeter scale. A zero score indicated "no pain", while a score of 10 indicated pain severity of "as bad as it could be".[14] According to the previous study, the power analysis performed with the G* Power program (Power=0.80; α=0.05; d (effect size)=0.70) based on the anxiety and depression scores obtained from the study, the sample size was calculated as 110 patients.[15]

Statistical Analysis

The statistics of the study were performed using IBM SPSS statistics 23.0 program. Descriptive statistics were expressed as mean±standard deviation if the numerical variables fit the normal distribution, median and minimum-maximum value if they do not fit the normal distribution, and number and percentage for categorical variables. Comparisons between groups were made by t-test or Mann-Whitney U test for numerical variables and chi-square test for categorical variables according to normal distribution. Pearson correlation test was used for correlation analysis between FAS score and VAS, NHP, anxiety, depression, and total HAD scores. $p<0.05$ was considered statistically significant.

RESULTS

65 healthy subjects and 65 stroke patients were included in the study. The distribution of age, marital status, smoking, alcohol use, or having a computer, internet, or smartphone at home was not different between the groups. However, the working status and the education level of the patients were statistically significantly different between the groups, the rate of primary school graduates and non-workers was higher in the patient group (Table 1).

Table 1. Demographic characteristics of patient and control groups

	Patient (n=65)	Control (n=65)	p
Age	60 (53-68)	61 (55-70)	0.302
Sex (female)	31 (47.7%)	32 (49.2%)	0.849
Educational Status			
0-8 year 9-12 year >12 year	40 (61.5%) 13 (20%) 12 (18.5%)	34 (52.3%) 6 (9.2%) 25 (38.5%)	0.038
Marital Status			
Married Single	53 (81.5%) 12 (18.5%)	55 (84.6%) 10 (15.4%)	0.801
Working Status			
Worker Nonworker	8 (12.3%) 57 (87.7%)	23 (35.4%) 42 (64.6%)	0.004
Smoke status			
Smoker Nonsmoker Ex-smoker	15 (23.1%) 35 (61.5%) 10 (15.4%)	21 (32.3%) 37 (56.9%) 7 (10.8%)	0.408
Alcohol user	5 (7.7%)	6 (9.2%)	0.751
Presence of comorbid diseases	52 (80%)	20 (30.7%)	<0.001
Computer presence at home	23 (35.4%)	22 (33.8%)	0.842
Smartphone presence	42 (64.6%)	47 (72.3%)	0.409
Internet presence	36 (55.4%)	35 (53.8%)	0.600

%: Column percent, p values in bold indicate statistically significant.

Anxiety levels were high in 33 patients (50.77%) in the stroke group and 16 patients (24.60%) in the control group. Depression levels were high in 35 patients (53.85%) in the stroke group and 25 patients (38.46%) in the control group. In the stroke group, the HAD anxiety, HAD depression, and HAD total scores of patients were statistically significantly higher compared to the control group (p:0.036, p:0.013, p: 0.010, respectively). When the quality of life of the patients was examined, the NHP energy level was statistically significantly lower in the stroke group (p:0.008), but other subdomain scores of NHP were similar between the groups (Table 2). Examination of the stroke patients by their functional ambulation levels revealed statistically lower HAD anxiety, HAD depression, and HAD total scores with higher functional status (p:0.003, p: <0.001, p: <0.001, respectively). NHP pain, sleep, physical mobility, energy, distress subdomains, and NHP total scores were statistically significantly different with the functional status of patients (Table 3). As seen in (Table 4), negative correlations were found between FAC scores with pain, HAD anxiety, HAD depression, HAD total, and NHP total scores. No correlations found with VAS and HAD anxiety, HAD depression and HAD total scores (p:0.150, p:0.174, p:0.175, respectively).

Table 2. Comparisions of the groups

	Patient(n=65)	Control(n=65)	p
HAD anxiety	9 (5-12)	7 (4-10)	0.036
HAD depression	10 (6-13)	7 (5-11)	0.013
HAD total	18.16 ± 8.06	14.63 ± 5.78	0.010
NHP pain	20.18 (5.83-56.68)	35.27 (5.83-65.38)	0.507
NHP emotional reaction	31.50 (9.31-79.25)	17.55 (0-62.3)	0.388
NHP sleep	38.47 (0-77.63)	12.57 (0-43.36)	0.221
NHP social isolation	22.01 (0-44.54)	23.58 (0-41.37)	0.419
NHP physical mobility	36.5 (10.79-36.5)	31.63 (0-59.83)	0.288
NHP energy	63.2 (24-100)	24 (0-100)	0.008
NHP distress	30.50 (9.11-76.55)	21.57 (0-68.3)	0.358
NHP total	222 (106-409)	189 (52.87-292.47)	0.195

Numerical data are given as mean±standard deviation or median (interquartile range) values. p values in bold indicate statistically significant. HAD: Hospital anxiety depression scale NHP: Nottingham health profile (NHP) questionnaire

Table 3. Comparision between functional disability levels with depression and quality of life scores

	FAS 3 (n=21)	FAS 4 (n=20)	FAS 5(n=24)	p
Brunnstrom				
Upper extremity	4 (1.75-5)	5 (4-5)	6 (5-7)	
Hand	3.5 (1.75-5)	5 (4-5)	6 (5-6)	<0.001
Upper extremity	3 (3-4)	5 (4.5-5)	6 (5-6)	
VAS	5.5 (4-7.25)	4 (3-5)	3.5 (2-5)	0.099
HAD anxiety	12.5 (5.6-15)	8 (4-10)	8 (3.25-11)	0.003
HAD depression	13 (10-15)	8 (5.5-12)	7.5 (4-10.75)	<0.001
HAD total	24.66 ± 5.95	15.55±6.57	14.5 ± 7.51	<0.001
NHP pain	54.15 (24.54-87.09)	17.05 (7.39-43.41)	7.39 (0-24.71)	0.002
NHP emotional reaction	82.63 (27.12-100)	17.54 (10.47-53.36)	14.01 (0-38.85)	0.003
NHP sleep	77.63 (38.47-77.63)	12.57 (0-77.96)	16.77 (0- 36.06)	0.001
NHP social isolation	40.1 (0- 88.02)	22.01 (0- 31.01)	16.39 (0- 22.4)	0.096
NHP physical mobility	72.52 (44.72-88.46)	32.56 (5.28-54.55)	11.2 (0- 28.93)	<0.001
NHP energy	100 (100- 100)	63.2 (12- 100)	38 (0- 90.75)	0.001
NHP distress	30.50 (9.11-76.55)	21.57 (5.1-68.4)	11.28 (0-45.2)	0.003
NHP total	449.32 (249.75- 483.93)	218.57 (106.07- 319.94)	113.43 (36.95- 225.61)	<0.001

Numerical data are given as mean±standard deviation or median (interquartile range) values. *p* values in bold indicate statistically significant. VAS: Visual analog scale, HAD: Hospital anxiety depression scale NHP: Nottingham health profile (NHP) questionnaire

Table 4. Correlation between functional status and clinical features of stroke patients

		VAS	HAD Anksiyete	HAD Depresyon	HAD Total	NHP
FAS	Pearson Correlation	-.305*	-.407**	-.564**	-.522**	-.598**
	Sig. (2-tailed)	.024	.002	.000	.000	.000

r: Pearson correlation *. Correlation is significant at the 0.05 level (2-tailed). **. Correlation is significant at the 0.01 level (2-tailed). VAS: Visual anolog scale, HAD: Hospital anxiety depression scale NHP: Nottingham health profile (NHP) questionnaire

DISCUSSION

Stroke is a debilitating condition that not only impairs physical health but also acts profoundly on mental well-being. Beyond the immediate physical consequences, individuals who have experienced a stroke, often grapple with emotional challenges, including anxiety and depression. This study aimed to investigate the complex relationship between depression, anxiety, pain, and functional status in stroke patients. We found that anxiety and depression levels were higher in stroke patients and that functional capacity was inversely related to pain, anxiety, depression, and quality of life.

The most common mental health symptoms in post-stroke patients are anxiety and depression. Post-stroke depression is one of the most important factors that may affect mental health.[16] Anxiety or depression is a serious but treatable condition; therefore, it is important to screen the entire population at risk. In our study, we evaluated anxiety and depression levels with HADS in stroke patients. A study conducted on 1443 patients in London previously reported that HADS gave accurate and reliable results about the severity of anxiety and depression.[17] A study conducted on stroke patients in Australia reported the median HAD anxiety and depression scores as 6 and 5, respectively.[18] That study included patients with a stroke and TIA but excluded patients, who were in their first three months following a stroke. In our study, HAD anxiety and depression scores were 9 and 10, respectively. The poorer functional status of the patients in our study may explain these higher scores compared to the abovementioned results in the literature. The frequencies of anxiety and depression in stroke patients have been evaluated in various studies in the literature. In our study, anxiety and depression levels were high in half of the stroke patients (50.77% and 53,85%). A review study reported that the frequency of anxiety in stroke patients ranged from 4.8 to 63.6%.[19] Another review study reported that the frequency of depression in stroke patients was in the range of 11-41%.[20] Although the reported rates vary across the studies in the literature, all studies show an increased frequency of anxiety in stroke patients.

An in-depth analysis of the impact of anxiety and depression on the functional status of the patient sheds light on the interconnectedness of these variables. Emotional distress may appear as reduced motivation, impeding rehabilitation efforts and delaying the overall recovery process. On the other hand, improvements in functional status have the potential to act on mental health favorably, highlighting the symbiotic relationship between physical and emotional well-being. A Chinese study found an inverse relationship between physical function and depression severity.[21] Astuti et al.[22] showed decreased depression severity with increased functional ability of the patient. Similar to these studies, we found an inverse relationship between the functional status of the patients and their anxiety and depression severity. Stroke patients with low levels of functional ability have an increased likelihood of developing anxiety and depression, impeding the treatment success and leading to permanent disability. This suggests that a thorough examination for anxiety and depression will increase the success of treatment in a stroke patient, who has a low level of functional ability.

Stroke survivors often experience pain,[23] either directly related to the stroke or as a consequence of altered movement patterns. Research indicates a bidirectional relationship between depression, anxiety, and pain.[24] A relationship between pain and the development of depression and anxiety is likely and the emotional distress associated with these conditions may exacerbate the perception of pain. We attempted to demonstrate this relationship in our study. Despite the availability of several scales to assess pain, there is no specific method for pain assessment in stroke patients. Therefore, we evaluated pain severity with VAS in our study. However, we did not find a relationship between pain and anxiety or depression levels. A study conducted in Sweden reported an association between pain and depression severity, but patients were evaluated in the 16th month after a stroke.[25] Another study conducted in Denmark reported a relationship between pain and depression, but that study included chronic stroke patients with an average duration of the condition of 794 days.[26] In our study, we evaluated patients not later than in the 12th month after a stroke. Similar to our findings, Şahin et al.[27] reported that, in stroke patients, there was no relationship between pain and functional outcomes or between pain and depression and mental scores. Furthermore, a review study conducted to examine the relationship between pain and depression in stroke patients reported inconclusive findings and the authors concluded that this subject matter needed to be examined more comprehensively.[28] This study adds to the growing body of literature by providing robust evidence of the intricate relationship between functional status and emotional well-being in stroke patients. The novel contribution of this study lies in its simultaneous examination of anxiety, depression, pain, and quality of life in a single cohort of stroke patients. This holistic approach highlights the multifaceted challenges faced by stroke survivors, emphasizing the need for integrated care strategies that address both physical and psychological aspects of recovery. The findings underscore the importance of considering emotional health as a critical component of stroke rehabilitation, particularly in patients with lower functional status.

Limitations

Because of the cross-sectional design of our study, we were able to evaluate the anxiety and depression severity only at the time of examination of the patients. We used a self-assessment scale to assess the anxiety and depression levels of the patients in our study.

CONCLUSION

Depression and anxiety commonly develop in stroke patients. In this study, there is an inverse relationship between functional status and the severity of pain, anxiety, depression, and quality of life. Therefore, stroke patients with functional limitations need to be examined thoroughly for early management of anxiety and depression. The recognition and

management of both the emotional and physical aspects of stroke recovery will help healthcare professionals contribute to a holistic and effective rehabilitation process for their patients. While this study has made significant strides in understanding the relationship between functional status and emotional well-being in stroke patients, further research is needed to explore these dynamics over longer follow-up periods and across different patient populations. Future studies could focus on longitudinal analyses to track changes in anxiety, depression, and functional status over time, providing deeper insights into the long-term effects of integrated rehabilitation strategies.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Clinical Researches Ethics Committee of the Hitit University Faculty of Medicine(Date: 28.09.2023, Decision No: 118) and written informed consent was obtained from each participant.

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

REFERENCES

1. Rafsten L, Danielsson A, Sunnerhagen KS. Anxiety after stroke: a systematic review and meta-analysis. *J Rehabil Med*. 2018;28(50):769-778.
2. Altınbaş K, Oral ET, Soysal A, Arpacı B. Poststroke depression. *J Clin Psy*. 2006;9(3):148-153.
3. Chemerinski E, Robinson R. The neuropsychiatry of stroke. *Psychosomatics*. 2000;41(1):5-14.
4. Flick CL. Stroke rehabilitation. 4. Stroke outcome and psychosocial consequences. *Arch Phys Med Rehabil*. 1999;80(5): 21-26.
5. Jamil A, Csendes D, Gutlapalli SD, et al. Poststroke depression, an underrated clinical dilemma. *Cureus*. 2022;26;14(12):32948.
6. Darrel A, Kuhl AE. The DSM-5: classification and criteria changes. *World Psychiatry*. 2013;12(2):92-98.
7. Gilworth G, Phil M, Cert A, Sansam KA, Kent RM. Personal experiences of returning to work following stroke: an exploratory study. *Work*. 2009;34(1):95-103.
8. Watanabe Y. Fear of falling among stroke survivors after discharge from inpatient rehabilitation. *Int J Rehabil Res*. 2005;28(2):149-152.
9. Yang S, Chang MC. Poststroke pain. *Semin Neurol*. 2021;41(1):67-74.
10. Aydemir Ö, Güvenir T, Küley L. Validity and reliability of Turkish version of hospital anxiety and depression scale. *Türk Psikiyatr. Derg*. 1997;8(4):280-287.
11. Brunnstrom S. Motor testing procedures in hemiplegia: based on sequential recovery stages. *Phys Ther*. 1966;46(4):357-375.
12. Dobkin BH, Plummer D, Amato P, et al. International randomized clinical trial, stroke inpatient rehabilitation with reinforcement of walking speed (SIRROWS), improves outcomes. *Neurorehabil Neural Repair*. 2010;24(3):235-242.
13. Küçükdeveci AA, McKenna S, Kutlay S, Gürsel Y, Whalley D, Arasıl T. The development and psychometric assessment of the Turkish version of the nottingham health profile. *Int J Rehabil Res*. 2000;23(1):31-38.
14. Frank AJ, Moll JM, Hort JF. A comparison of three ways of measuring pain. *Rheumatol Rehabil*. 1982;21(4):211-217.
15. Chun HYY, Whiteley WN, Dennis MS, Mead GE, Carson AJ. Anxiety after stroke: the importance of subtyping. *Stroke*. 2018;49(3):556-564.
16. Kong K, Yang S. Health-related quality of life among chronic stroke survivors attending a rehabilitation clinic. *Singapore Med J*. 2006;47(3):213-218.
17. Ayis SA, Ayerbe L, Ashworth M, Wolfe CD. Evaluation of the hospital anxiety and depression scale (HADS) in screening stroke patients for symptoms: item response theory (IRT) analysis. *J Affect Disord*. 2018;228(1):33-40.
18. Thayabaranathan T, Andrew NE, Stolwyk R, Lannin NA, Cadilhac DA. Comparing the EQ-5D-3L anxiety or depression domain to the hospital anxiety and depression scale to identify anxiety or depression after stroke. *Top Stroke Rehabil*. 2022;29(2):146-155.
19. Knapp P, Dunn RA, Sahib N, et al. Frequency of anxiety after stroke: an updated systematic review and meta-analysis of observational studies. *Int J Stroke*. 2020;15(3):244-255.
20. Guo J, Wang J, Sun W, Liu X. The advances of post-stroke depression: 2021 update. *J Neurol*. 2022;269(3):1236-1249.
21. Chau JP, Lo SH, Zhao J, et al. Factors associated with post-stroke depression in Chinese stroke survivors. *J Stroke Cerebrovasc Dis*. 2021;30(11):106076.
22. Astuti P, Kusnanto K, Novitasari F. Depression and functional disability in stroke patients. *J Public Health Res*. 2020;9(2):1835.
23. Naess H, Lunde L, Brogger J. The effects of fatigue, pain, and depression on quality of life in ischemic stroke patients: the bergen stroke study. *Vasc Health Risk Manag*. 2012;8(1):407-413.
24. Harrison RA, Field TS. Post stroke pain: identification, assessment, and therapy. *Cerebrovasc Dis*. 2015;39(3-4):190-201.
25. Jönsson AC, Lindgren I, Hallström B, Norrving B, Lindgren A. Prevalence and intensity of pain after stroke: a population based study focusing on patients' perspectives. *J Neurol Neurosurg Psychiatry*. 2006;77(5): 590-595.
26. Klit H, Finnerup NB, Overvad K, Andersen G, Jensen TS. Pain following stroke: a population-based follow-up study. *PloS One*. 2011;6(11):27607.
27. Şahin Onat Ş, Ünsal Delialioğlu S, Kulaklı F, Özel S. The effects of central post-stroke pain on quality of life and depression in patients with stroke. *J Phys Ther Sci*. 2016;28(1):96-101.
28. Payton H, Soundy A. The experience of post-stroke pain and the impact on quality of life: an integrative review. *Behav Sci*. 2020;10(8):128.

Original Article

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Neutrophil-to-lymphocyte ratio as a predictor of progression in patients with early-stage cervical cancer

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ABSTRACT

Aims: The neutrophil-to-lymphocyte ratio (NLR) has shown promise as a prognostic marker in various cancers, but its role in early-stage cervical cancer is not well defined. This study evaluates the association between pre-treatment NLR and progression risk in patients with early-stage cervical cancer.

Methods: This retrospective study included 220 patients with stage I and II cervical cancer treated from 2010 to 2024. Patients with prior treatment, infection at diagnosis, or hematological diseases were excluded. Pre-treatment NLR was calculated from blood counts taken within a week before treatment. Primary outcome was progression-free survival (PFS). Cox regression analyses identified prognostic factors.

Results: The median follow-up was 46 months (range, 1-120). Disease progression occurred in 17.3% of patients, and 15% died. The 5-year overall survival and PFS rates were 84.8% (95% CI: 79.3-90.3) and 77.7% (95% CI: 71.4-84), respectively. Univariate analysis identified non-squamous cell carcinoma (non-SCC) histology, tumor size >4 cm, and elevated NLR as significant factors affecting PFS. Multivariate analysis confirmed non-SCC histology (HR: 3.2, p=0.002), tumor size >4 cm (HR: 2.3, p=0.007), and elevated NLR (HR: 1.1, p=0.041) as independent PFS risk factors. Higher NLR correlated with larger tumor size.

Conclusion: Elevated pre-treatment NLR independently predicts disease progression in early-stage cervical cancer. Incorporating NLR into risk stratification could enhance prognostic assessments and guide personalized treatments. Larger prospective studies are needed for validation.

Keywords: Neutrophil-to-lymphocyte ratio, cervical cancer, progression-free survival.

INTRODUCTION

Cervical cancer remains a significant contributor to morbidity and mortality among women globally, especially in developing nations where access to screening and treatment is often limited.[1,2] Despite advancements in diagnostic modalities and therapeutic interventions, a subset of patients diagnosed with early-stage cervical cancer experience disease progression or recurrence.[3-5] Thus, there is an urgent need to identify reliable prognostic markers that can assist in risk stratification and inform personalized therapeutic strategies.

In recent years, the host inflammatory response has garnered substantial attention in the oncology landscape as a potential determinant of cancer progression and treatment outcome.[6,7] The neutrophil-to-lymphocyte ratio (NLR), a simple and easily accessible marker reflecting the balance between pro-inflammatory neutrophils and anti-tumoral lymphocytes, has emerged as a promising prognostic indicator in various malignancies.[8,9] Elevated NLR has been associated with adverse clinical outcomes, including advanced disease stage, metastasis, and reduced survival, across a spectrum of cancer types.[10] While the prognostic significance of NLR has been extensively explored in several solid tumors, its role in early-stage cervical cancer remains relatively underexplored and inconclusive. This retrospective study aims to assess the association between pre-treatment NLR and progression risk in patients diagnosed with early-stage cervical cancer. By elucidating the prognostic value of NLR within this specific cohort, we endeavor to augment the current body of evidence and offer insights into refining risk stratification algorithms and optimizing therapeutic decision-making for the management of early-stage cervical cancer.

METHODS

The study was carried out with the permission of Hacettepe University Faculty of Medicine Clinical Researches Ethics Committee (Date: 19.03.2024, Decision No: 2024/06-15). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

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Informed consent was waived due to the retrospective nature of the study and the use of anonymized data.

The study included a total of 220 patients diagnosed with stage I and stage II cervical cancer according to the 2018 International Federation of Gynecology and Obstetrics (FIGO) classification, who were followed up in our tertiary center between 2010 and 2024. Patients who had received prior treatment for cervical cancer, had an infection at the time of diagnosis, were using corticosteroids, or had concurrent hematological disorders were excluded from the study. Age at diagnosis, Eastern Cooperative Oncology Group- performance status (ECOG-PS), comorbid diseases, histological subtype, FIGO stage, presence of parametrial invasion, the greatest dimension of tumor, pre-treatment blood neutrophil and lymphocyte counts, progression and death data were obtained retrospectively from the hospital electronic database. Patients were treated with surgery, radiotherapy, or concurrent chemoradiotherapy, depending on their stage and disease burden. No one underwent fertility-sparing surgery. The pre-treatment NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count obtained from routine complete blood count tests conducted within one week prior to the initiation of cancer-directed therapy. The primary outcome of interest was progression-free survival (PFS), defined as the duration from initial diagnosis to progression, death from any cause, or the last follow-up visit. Disease progression was determined based on radiological imaging and/or clinical findings. The time from diagnosis to death or last follow-up visit was determined as overall survival (OS). OS defined the time from diagnosis to death from any cause or last follow-up visit. In analyzing the impact on survival outcomes, NLR was assessed as a continuous variable in its pure form. The term 'elevated NLR' refers to high NLR values without specifying any particular cutoff.

Statistical Analysis

All data of the study were analyzed with IBM® SPSS® Statistics 27 and GraphPad Prism 9 software. Descriptive statistics were presented as frequency (percent) or median (min-max). The Mann-Whitney U test was used to compare nonparametric continuous variables between two independent groups. Survival estimates were calculated with the Kaplan-Meier method. Univariate and multivariate analyses of PFS were conducted using the Cox regression method. A 5% type-I error level set to determine statistical significance.

RESULTS

Patient Characteristics

The study included 220 patients with a median age at diagnosis of 56 years (range, 33-84). The ECOG-PS scores were 0 in 143 patients (65%), 1 in 73 patients (33.2%), and 2 in 4 patients (1.8%). The most common comorbidity was hypertension, affecting 32.7% of the patients. Other comorbidities included diabetes mellitus (18.2%), hypothyroidism (2.3%), asthma (2.3%), and various other diseases (7.3%). Histologically, 87.3% of cervical cancer cases were Squamous cell carcinoma (SCC), 6.8% were adenocarcinoma, and 5.9% were other histological subtypes. Regarding 2018 FIGO staging, 38 patients (17.3%) were classified as stage IB, 25 patients (11.4%) as stage IIA, and 157 patients (71.4%) as stage IIB. Parametrial invasion was observed in 157 patients (71.4%), and the largest tumor diameter exceeded 4 cm in 114 patients (51.8%), (Table 1).

Table 1. Patient characteristics (total 220 patients)

Characteristics	Groups	Frequency (%)
Age at diagnosis	<65 years ≥65 years	165 (75) 55 (25)
ECOG-PS	0 1 2	143 (65) 73 (33.2) 4 (1.8)
Comorbid diseases	Hypertension Diabetes mellitus Hypothyroidism Asthma Others	72 (32.7) 40 (18.2) 5 (2.3) 5 (2.3) 16 (7.3)
Histological subtype	Squamous cell carcinoma Adenocarcinoma Others	192 (87.3) 15 (6.8) 13 (5.9)
2018 FIGO stage	IB IIA IIB	38 (17.3) 25 (11.4) 157 (71.4)
Parametrial invasion	Absent Present	63 (28.6) 157 (71.4)
The greatest dimension of tumor	≤4 cm >4 cm	106 (48.2) 114 (51.8)

ECOG-PS: Eastern cooperative oncology group-performance status, FIGO: International federation of gynecology and obstetrics.

Factors Associated with NLR

The median NLR level was 2.73 (range, 0.97-39.4). Possible relationships between patient characteristics and median NLR levels were investigated. No significant relationships were found between median NLR levels and age at diagnosis (≥65 vs. <65 years, p=0.865), ECOG-PS (≥1 vs. 0, p=0.738), presence of comorbid diseases (p=0.084), non-SCC histology (p=0.618), or presence of parametrial invasion (p=0.863). However, the median NLR level was significantly higher in patients with the greatest tumor dimension >4 cm compared to those with the greatest tumor dimension ≤4 cm (3.04 (2.19-4.10) vs. 2.34 (1.74-3.51), p=0.002] (Table 2, Figure 1).

Table 2. Comparison of patient characteristics according to median NLR level

Characteristics	Groups	NLR, median (IQR)	p
Age at diagnosis	<65 years ≥65 years	2.67 (1.98-3.78) 2.93 (1.74-4.15)	0.865
ECOG-PS	0 ≥1	2.64 (1.89-3.88) 2.93 (1.99-3.65)	0.738
Comorbid disease(s)	Absent Present	2.83 (0.08-4.03) 2.67 (1.74-3.43)	0.084
Histological subtype	SCC Others	2.79 (1.94-3.87) 2.54 (1.86-3.50)	0.618
Parametrial invasion	Absent Present	2.57 (1.86-4.00) 2.87 (1.93-3.81)	0.863
The greatest dimension of tumor	≤4 cm >4 cm	2.34 (1.74-3.51) 3.04 (2.19-4.10)	0.002

ECOG-PS: Eastern cooperative oncology group-performance status, IQR: Interquartile range, NLR: Neutrophil-to-lymphocyte ratio, SCC: Squamous cell carcinoma.

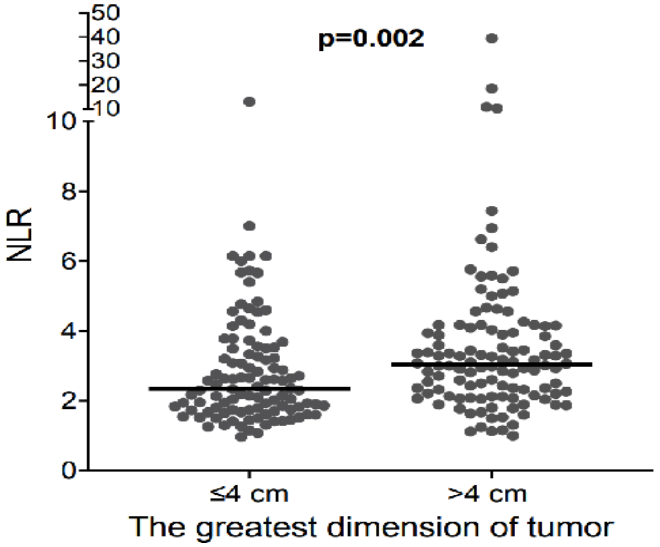

Figure 1. Comparison of pre-treatment median neutrophil-to-lymphocyte ratio (NLR) levels between cases with the greatest dimension of tumor ≤4 cm and those with the dimension >4 cm.

Survival Analysis

During a median follow-up period of 46 months (range, 1-120), 38 patients (17.3%) experienced disease progression, and 33 patients (15%) died. The 5-year PFS and OS rates were 77.7% (95% CI: 71.4-84) and 84.8% (95% CI: 79.3-90.3), respectively. The median PFS and OS times were not reached. In univariate Cox regression analyses, non-SCC histology (HR: 2.7, p=0.003), the greatest tumor dimension >4 cm (HR: 2.3, p=0.006), and NLR level (HR: 1.1, p<0.001) were found to significantly affect PFS. The independent effects of parameters estimated to have a clinical impact on survival were examined by multivariate Cox regression analysis. Examination of the correlation matrix confirmed no significant multicollinearity between the parameters. The final model included age at diagnosis (≥65 vs. <65 years), ECOG-PS (≥1 vs. 0), presence of comorbid diseases, non-SCC histology, presence of parametrial invasion, the greatest tumor dimension (>4 vs. ≤4 cm), and NLR level. Non-SCC histology (HR: 3.2, 95% CI: 1.5-6.8, p=0.002), the greatest tumor dimension >4 cm (HR: 2.3, 95% CI: 1.3-4.2, p=0.007), and NLR level (HR: 1.1, 95% CI: 1.0-1.1, p=0.041) were identified as independent poor prognostic factors for PFS (Figure 2, Table 3).

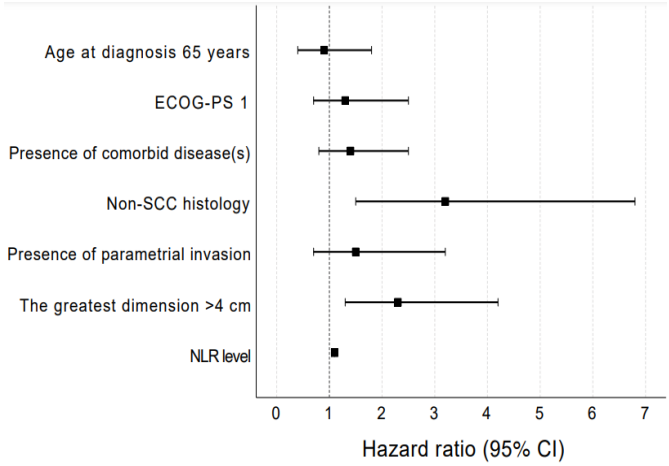

Figure 2. Forest plot depicting risk factors for progression-free survival based on multivariate Cox regression analysis.

Table 3. Risk factors for progression-free survival - Cox regression analysis.

Risk factors	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p	HR (95% CI)	p
Age at diagnosis ≥65 years	1.3 (0.7-2.3)	0.463	0.9 (0.4-1.8)	0.697
ECOG-PS ≥1	1.3 (0.8-2.3)	0.296	1.3 (0.7-2.5)	0.477
Presence of comorbid disease(s)	1.2 (0.7-2.1)	0.436	1.4 (0.8-2.5)	0.269
Non-SCC histology	2.7 (1.4-5.2)	0.003	3.2 (1.5-6.8)	0.002
Presence of parametrial invasion	1.3 (0.7-2.7)	0.402	1.5 (0.7-3.2)	0.245
The greatest dimension >4 cm	2.3 (1.3-4.1)	0.006	2.3 (1.3-4.2)	0.007
NLR level	1.1 (1.0-1.1)	<0.001	1.1 (1.0-1.1)	0.041

Confidence interval, ECOG-PS: Eastern cooperative oncology group-performance status, HR: Hazard ratio, NLR: Neutrophil-to-lymphocyte ratio, SCC: Squamous cell carcinoma.

We categorized the NLR values into four quartiles: 0-1.93, 1.94-2.73, 2.74-3.83, and ≥3.84, with 55 patients in each group. Analyzing the relationship between these NLR categories and PFS, we observed a 2-year PFS rate of 92.6% (95% CI: 84.6-100.6) in the first group, 87.9% (95% CI: 78.7-97.1) in the second group, 82.4% (95% CI: 72-92.8) in the third group, and 68.9% (95% CI: 56.2-81.6) in the fourth group (p=0.005), (Figure 3). NLR of ≥3.84 was associated with a 2-fold increased risk of progression during follow-up (HR: 2.1, 95% CI: 1.2-3.7, p=0.010).

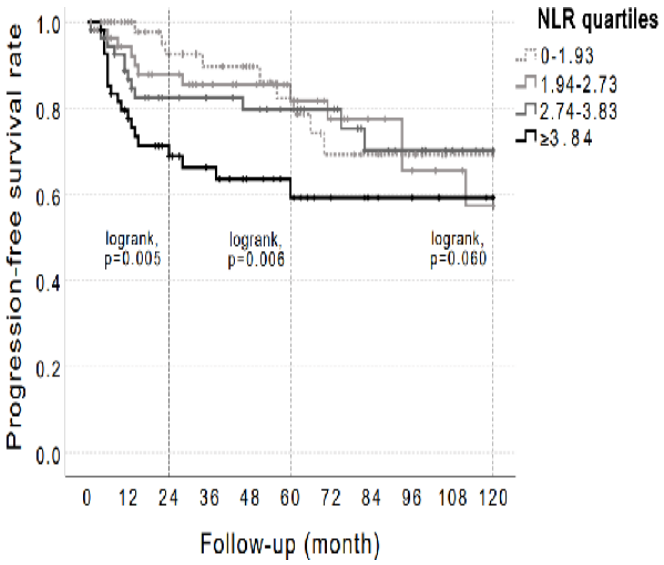

Figure 3. Kaplan-Meier curves for progression-free survival according to neutrophil-to-lymphocyte ratio (NLR) quartiles.

DISCUSSION

This study revealed a significant association between elevated pre-treatment NLR and an increased risk of disease progression, underscoring the prognostic relevance of this easily accessible hematological parameter in the context of cervical cancer. Neutrophils are integral components of the tumor microenvironment and contribute to progression through various mechanisms, including secretion of proliferative factors and suppression of T-lymphocyte activity.[11] The underlying mechanisms driving this association

are multifaceted and likely involve the interplay between the host immune response and tumor microenvironment dynamics.[12,13] Neutrophils can directly interact with tumor cells to enhance their invasive and metastatic potential. Neutrophil-derived proteases, such as matrix metalloproteinases, facilitate extracellular matrix degradation, promoting tumor cell invasion and dissemination to distant sites.[14] Moreover, neutrophils can form heterotypic interactions with tumor cells, leading to the formation of neutrophil-tumor cell aggregates that facilitate tumor cell extravasation and metastatic seeding. Conversely, lymphocytopenia may signify impaired cellular immunity and compromised tumor surveillance, thereby fostering tumor escape mechanisms and disease dissemination.[15]

In a meta-analysis of 14 studies including 6041 cervical cancer patients, higher NLR was associated with worse OS (HR 1.9, 95%CI: 1.4-2.4) and PFS (HR 1.7, 95%CI: 1.3-2.2) compared with lower NLR.[16] In another study including 99 cervical cancer patients receiving definitive chemoradiotherapy, NLR values before, during, and after treatment were found to be related to PFS and OS.[17] Most recently, Du et al.,[18] demonstrated the association of high NLR level with shorter PFS in their study including 203 patients with early-stage cervical cancer. Consistent with prior investigations, our study demonstrates that elevated NLR serves as an independent prognostic factor for disease progression in early-stage cervical cancer.

In the study conducted by Prabowo IPY, et al.,[19] the median NLR level was found to be higher in stage III-IV cervical cancer patients than in stage I-II cases, and a strong positive correlation was revealed between the disease stage and the NLR level (r=0.638). We also observed association between elevated NLR and larger tumor size, underscores the potential role of NLR as a surrogate marker for aggressive tumor behavior. While the precise biological underpinnings linking NLR to tumor aggressiveness warrant further elucidation, our findings support that NLR reflects the disease progression.

From a clinical perspective, the incorporation of pretreatment NLR into risk stratification algorithms holds promise for refining prognostic assessment and guiding personalized therapeutic decision-making in early-stage cervical cancer. Identifying patients at higher risk of disease progression based on NLR status may facilitate tailored treatment approaches, such as intensified surveillance protocols, adjuvant therapies, or enrollment in clinical trials evaluating novel therapeutic agents. Moreover, serial monitoring of NLR dynamics throughout the disease course may offer valuable insights into treatment response and disease trajectory, enabling timely modifications to therapeutic strategies by evolving risk profiles.

Limitations

Nevertheless, several limitations inherent to retrospective studies warrant consideration when interpreting the findings of this investigation. Despite efforts to adjust for potential confounders through multivariate analysis, residual biases and unmeasured variables may have influenced the observed associations. Additionally, the single-center nature of the study and the relatively modest sample size limits the generalizability of the findings and underscore the need for validation in larger, multicenter cohorts. Prospective studies are warranted to elucidate the dynamic interplay between NLR, tumor biology, and clinical outcomes in early-stage cervical cancer.

CONCLUSION

In conclusion, our study provides compelling evidence supporting the prognostic significance of pretreatment NLR in early-stage cervical cancer. Future prospective studies are warranted to validate these findings, elucidate underlying biological mechanisms, and explore the clinical utility of NLR-guided therapeutic algorithms in optimizing patient outcomes in managing early-stage cervical cancer.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of HacettepeUniversity Faculty of Medicine Clinical Researches Ethics Committee (Date: 19.03.2024, Decision No: 2024/06-15)

Informed Consent

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

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209-249.
2. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. *CA Cancer J Clin*. 2024;74(1):12-49.
3. Hsieh HY, Lu CH, Wang L. Long-term treatment outcomes/toxicities of definite chemoradiotherapy (intensity-modulated radiation therapy) for early-stage "bulky" cervical cancer and survival impact of histological subtype. *J Formos Med Assoc*. 2023;122(3):221-229.
4. Dasari S, Wudayagiri R, Valluru L. Cervical cancer: biomarkers for diagnosis and treatment. *Clin Chim Acta*. 2015;445(12):7-11.
5. Yadav G, Srinivasan G, Jain A. Cervical cancer: novel treatment strategies offer renewed optimism. *Pathol Res Pract*. 2024;254(15):155136.
6. Denk D, Greten FR. Inflammation: the incubator of the tumor microenvironment. *Trends Cancer*. 2022;8(11):901-914.

7. Davidson B, Goldberg I, Kopolovic J. Inflammatory response in cervical intraepithelial neoplasia and squamous cell carcinoma of the uterine cervix. *Pathol Res Pract*. 1997;193(7):491-495.
8. Templeton AJ, McNamara MG, Seruga B, et al. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. *J Natl Cancer Inst.* 2014;106(6):124.
9. Zahorec R. Neutrophil-to-lymphocyte ratio, past, present and future perspectives. *Bratisl Lek Listy.* 2021;122(7):474-488.
10. Cupp MA, Cariolou M, Tzoulaki I, et al. Neutrophil to lymphocyte ratio and cancer prognosis: an umbrella review of systematic reviews and meta-analyses of observational studies. *BMC Med.* 2020;18(1):360.
11. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. *Cell.* 2010;140(6):883-899.
12. Bonavita E, Galdiero MR, Jaillon S, Mantovani A. Phagocytes as corrupted policemen in cancer-related inflammation. *Adv Cancer Res.* 2015;128(1):141-171.
13. Xiong S, Dong L, Cheng L. Neutrophils in cancer carcinogenesis and metastasis. *J Hematol Oncol.* 2021;14(1):173.
14. Ardi VC, Kupriyanova TA, Deryugina EI, Quigley JP. Human neutrophils uniquely release TIMP-free MMP-9 to provide a potent catalytic stimulator of angiogenesis. *Proc Natl Acad Sci USA*. 2007;104(51):20262-20267.
15. Ethier JL, Desautels DN, Templeton AJ, et al. Is the neutrophil-to-lymphocyte ratio prognostic of survival outcomes in gynecologic cancers? A systematic review and meta-analysis. *Gynecol Oncol.* 2017;145(3):584-594.
16. Zou P, Yang E, Li Z. Neutrophil-to-lymphocyte ratio is an independent predictor for survival outcomes in cervical cancer: a systematic review and meta-analysis. *Sci Rep.* 2020;10(1):21917.
17. Trinh H, Dzul SP, Hyder J, et al. Prognostic value of changes in neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and lymphocyte-to-monocyte ratio (LMR) for patients with cervical cancer undergoing definitive chemoradiotherapy (dCRT). *Clin Chim Acta.* 2020;510(1):711-716.
18. Du JQ, Zhang F, Wang CQ, et al. Effects of peripheral blood neutrophil/lymphocyte ratio levels and their changes on the prognosis of patients with early cervical cancer. *Front Oncol.* 2023;13(1):1139809.
19. Prabawa IPY, Bhargah A, Liwang F, et al. Pretreatment neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) as a predictive value of hematological markers in cervical cancer. *Asian Pac J Cancer Prev.* 2019;20(3):863-868.

Original Article

MEDICINE PALLIATIVE CARE

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Comparison of St. John's wort oil and thiocilline ointment on wound healing in a diabetic rat model

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ABSTRACT

Aims: In diabetic patients, wound healing is impaired and wounds are often infected with multifactorial agents. This study aimed to compare the effectiveness of St. John's wort and ointment containing bacitracin-neomycin (thiocilline) to improve wound healing in a diabetic infected wound model.

Methods: Rats in which diabetes was induced by administering 60 mg/kg streptozotocin (STZ) were considered diabetic if their blood sugar levels were above 300 mg/dl 72 hours later. Group 1: Control (Non diabetic) group, Group 2: Diabetes group. During wound care, both groups were disinfected with povidone iodine (PI) and the right lumbar region of each rat was dressed with thiocilline and the left lumbar region was dressed with St. John's wort oil. Considering the wound healing period, the study was terminated after an average of 20 days. In histopathological examination, ulceration, necrosis, epithelialization, congestion, edema, polymorphous nucleated leukocyte (PNL), monocyte, fibroblast, and neovascularization were evaluated.

Results: In histopathological evaluation, there was a statistically significant decrease in ulceration and necrosis in the group treated with St. John's wort oil compared to the group given thiocilline (p=0.04). In terms of epithelialization, there was a statistically significant increase in the group dressed with St. John's wort oil compared to the group given thiocilline (p=0.03). There was a statistically significant decrease in congestion and edema in the group treated with St. John's wort oil compared to the group given thiocilline (p=0.03). There was a statistically significant increase in fibroblast and neovascularization in the group treated with St. John's wort oil compared to the group given thiocilline (p=0.02).

Conclusion: Histopathologic ally, epithelialization, fibroblast, and neovascularization, which have important functions in the wound healing process, increased in diabetic rats administered St. John's wort. Although it is used in traditional medicine due to its antidepressant effectiveness, we believe that St. John's wort can be used in wounds that develop in diabetic patients, as it has the potential to increase the wound healing process.

Keywords: Diabetes, rat, wound model, St. John's wort oil, thiocilline, wound healing

INTRODUCTION

Problems in wound healing in diabetes can be summarized as a decrease in cellular infiltration, angiogenesis, granulation tissue, collagen amount and organization, and an increase in infectious complications.[1] Although the causes of wound healing problems that may occur in diabetes have not been fully explained, hyperglycemia is basically held responsible for this situation. It has been shown that high blood glucose inhibits cell proliferation and collagen production. In addition, situations such as decreased growth factors and fibroblast proliferation, increased apoptosis in wound tissue cells, decreased chemotaxis and phagocytosis and infection formation can be listed among the negative effects of hyperglycemia on wound healing.[2-4]

Wound healing is characterized by epithelial, endothelial, inflammatory cells, platelets and fibroblasts coming together and performing their normal functions in a certain order and order.[5-7] Wound healing continues as a rapid and regular process in healthy people. Clinically, wound healing is delayed in infections, diabetes, systemic steroid and radiation applications, and the use of chemotherapeutic agents. It is thought that this may be the result of inadequate release or delay in the release of growth factors that come into play at various stages of wound healing.[8]

The basic principles in topical wound care and treatment are to remove obstacles and provide an environment conducive

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to repair so that the skin can perform its repair function. This environment is possible by keeping the wound clean and protecting the wound surface by keeping it moist and insulated.[9] Daily topical antibiotic-based ointment or white petroleum jelly is widely used in clinical practice, especially for postoperative wound care. Topical antibiotic ointments are medications that are considered safe and effective for local wound treatment. In addition, these drugs support wound healing and provide a moist environment by minimizing the adhesion of bandages. Bacitracin, fusaric acid, gentamicin, mupirocin, neomycin sulfate, and polymyxin B sulfate are topical antibiotics commonly used in the United States and Europe.[10] Thiociline is an antibacterial ointment containing bacitracin+neomycin sulfate.[11]

In Turkiye, locally known as Binbirdelik grass, Kan grass, Kılıç grass, Mayasır grass, Yara grass, Kuzukır and in English St. Hypericum perforatum L., known as John's wort, is a plant belonging to the Hypericaceae family and growing in Europe, Asia, North Africa and the United States. It is used in traditional medicine due to its antidepressant effect.[12] It is widely used in the field of phytotherapy in various European countries. There are about 70 species in Turkiye. It is an herbaceous or bushy plant with bright yellow flowers. H. perforatum contains many compounds with biological activity such as chlorogenic acid, many flavonoids, naphthodianthrones and phloroglucinols.[13] Although St. John's wort is used in traditional medicine for its antidepressant activity, it has been reported that it has antiviral and antibacterial activities.[14,15] Diabetic wounds are often multi-bacterial and exhibit impaired healing. This study aims to compare the efficacy of St. John's Wort oil and an ointment containing bacitracin+neomycin (Thiocilline) in enhancing wound healing in a diabetic infected wound model.

METHODS

The study was carried out with the permission of Mustafa Kemal University Ethics Committee (Date: 0X.0X.2015, Decision No: 07/5). The study was conducted in accordance with the ethical principles of the "Guide for the Care and Use of Laboratory Animals.".

This study utilized male Wistar Albino rats, aged 12-16 weeks. The rats were acclimatized to the experimental environment one week prior to the study. They were housed under standard conditions, with free access to tap water, a 12-hour light/dark cycle, approximately 55% humidity, and a temperature range of 20-22°C. The rats were fed standard rat chow.

Sample Size Determination

The sample size for each group was determined based on statistical considerations to ensure the results would be interpretable and significant, accounting for potential animal loss during the experiments. Literature from previous studies was also reviewed to inform group sizes.

Experimental Groups

A total of 20 Wistar Albino rats were randomly divided into two groups, each consisting of 10 animals:

Group 1: Control (Non-diabetic rats)

Group 2: Diabetic rats (Thiocilline and St. John's Wort oil treatment)

Induction of Diabetes

Diabetes was induced in the experimental rats using a single intraperitoneal injection of streptozotocin (STZ) at a dose of 60 mg/kg, freshly dissolved in 0.9% NaCl. Seven days post-STZ administration, rats with a fasting blood glucose level of 300 mg/dl or higher, as measured by a glucometer (Gloated), were considered diabetic. Non-diabetic rats served as the control group.

Surgical Procedures

All rats were anesthetized with a single intraperitoneal dose of 90 mg/kg Ketamine (0.1 ml) and 10 mg/kg Xylazine (0.2 ml). After achieving anesthesia, the dorsal skin of the rats was shaved. Two open wounds, approximately 2x3 cm in size, were created on each rat's back at a distance of 1.5 cm from the midline on both lumbar regions, with four full-thickness skin loss wounds spaced 0.5 cm apart (Figure 1).

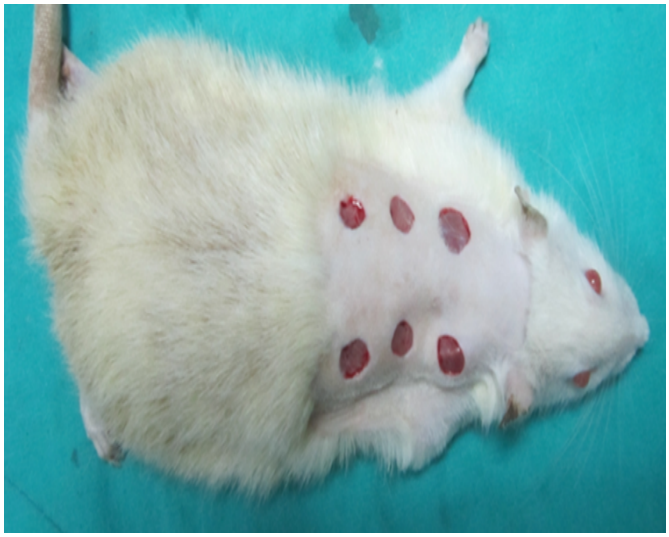

Figure 1. Diabetic wound model

Wound dressing procedures were performed daily at the same time each day. After the wounds were created, rats were housed individually in separate cages. For wound care, both diabetic and non-diabetic rats were disinfected with povidone-iodine before dressing. In the dressing process, the right lumbar region of each rat was treated with Thiocilline, and the left lumbar region was treated with St. John's Wort oil. Considering the wound healing period, the study was terminated after approximately 20 days.

Anesthesia and Tissue Collection

On the 20th day of the study, anesthesia was induced in the rats by administering a single intraperitoneal dose of 90 mg/kg Ketamine (0.1 ml) and 10 mg/kg Xylazine (0.2 ml). After achieving anesthesia, wound tissues, including a 0.5 cm margin of surrounding healthy tissue, were excised and fixed in 10% formalin for 72 hours for pathological examination.

Histopathological Evaluation

Histopathological analysis was conducted by scoring ulceration, necrosis, epithelialization, congestion, edema, polymorphonuclear leukocytes (PNL), monocytes, fibroblasts, and neovascularization across three high-power fields (40X magnification) on the wound bed. Each sample was anonymized and assigned a number before being sent for pathological evaluation to ensure blinded assessment. The tissue sections were examined using a light microscope (Olympus CX31RTSF, Olympus Optical, Japan), and images of specific sections were captured digitally (Olympus E 330, Olympus Optical, Japan) to assess changes in the nerves and other histological features.

Statistical Analysis

In examining the obtained data, it was evaluated using SPSS (The statistical package for social sciences) 15.0 statistical package program. Kruskal-Wallis was used to determine whether there was homogeneity and statistical difference between all groups. Student t test was used to determine which group caused the difference. In all groups, p values below 0.05 were considered statistically significant within the 95% confidence interval.

RESULTS

Comparison of weight and blood glucose levels in the groups was shown in Table 1. The substantial reduction in weight observed in the DM group (342.7±57.4) compared to the control group (440.8±40.8) could be indicative of diabetes-related weight loss (p<0.01). The significantly higher blood glucose levels in the DM group (398.2±89.5) compared to the control group X(84.6±13.8) are consistent with the pathophysiology of diabetes mellitus (p<0.001).

Table 1. Comparison of weight and blood glucose levels in the groups

	Control group	DM group	p
Weight (kg)	440.8±40.8	342.7±57.4	<0.01
Blood glucose (mg/dl)	84.6±13.8	398.2±89.5	<0.001

DM: Diabetes mellitus

Histopathological Findings

Comparison of histopathological parameters in the groups was shown in Table 2. In histopathological evaluation, there was a statistically significant decrease in ulceration and necrosis in the group treated with St. John's Wort oil compared to the group given thiocilline (p = 0.04). In terms of epithelialization, there was a statistically significant increase in the group dressed with St. John's Wort oil compared to the group given thiocilline (p=0.03). There was a statistically significant decrease in congestion and edema in the group treated with St. John's Wort oil compared to the group given thiocilline (p=0.03). There was a statistically significant increase in fibroblast and neovascularization in the group treated with St. John's Wort oil compared to the group given thiocilline (p=0.02). Although PNL and monocyte numbers decreased in the St. John's wort group compared to the thiocilline group, there was no statistical significance (p>0.05) (Table 2, Figure 2 and 3).

Table 2. Comparison of histopathological parameters in the groups

	Control Thiocilline	Control St.John's wort oil	DM Thiocilline	DM St. John's wort oil	p
Ulceration	0.16±0.4	0.12±0.3	0.15±0.35	0.10±0.25	0.04
Necrosis	0.14±0.2	0.10±0.15	0.13±0.18	0.08±0.12	0.04
Epithelialization	0.25±0.3	0.30±0.35	0.27±0.33	0.35±0.40	0.03
Congestion	0.20±0.25	0.15±0.20	0.18±0.22	0.10±0.15	0.03
Edema	0.22±0.3	0.18±0.25	0.20±0.27	0.15±0.20	0.03
PNL	0.18±0.2	0.16±0.18	0.17±0.19	0.15±0.17	0.06
Monocyte	0.12±0.15	0.10±0.12	0.11±0.13	0.09±0.11	0.05
Fibroblast	0.30±0.4	0.34±0.42	0.31±0.41	0.37±0.45	0.02
Neovascularization	0.25±0.3	0.30±0.35	0.27±0.33	0.35±0.40	0.02

DM: Diabetes mellitus

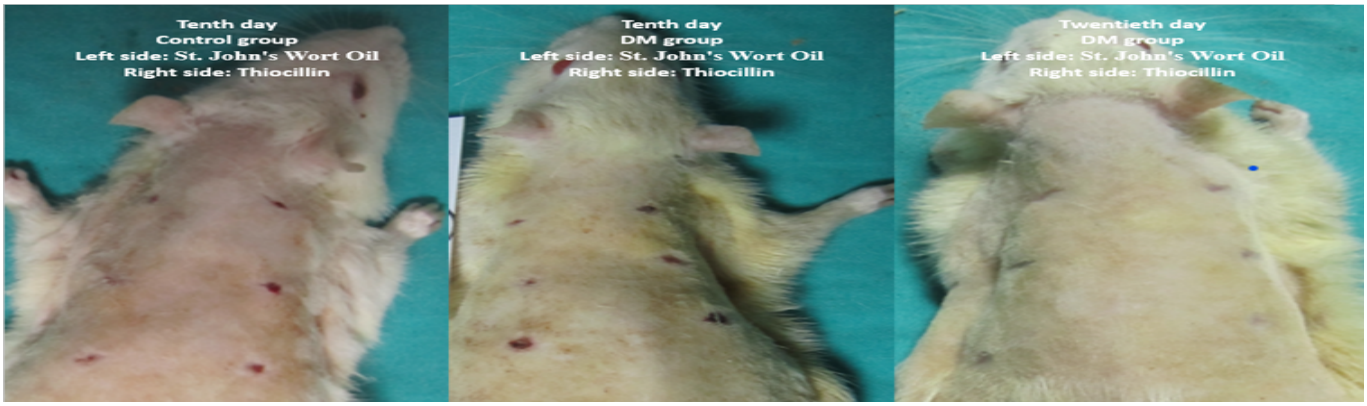

Figure 2. Morphological appearance of wound healing on the 10th and 20th days of treatment.

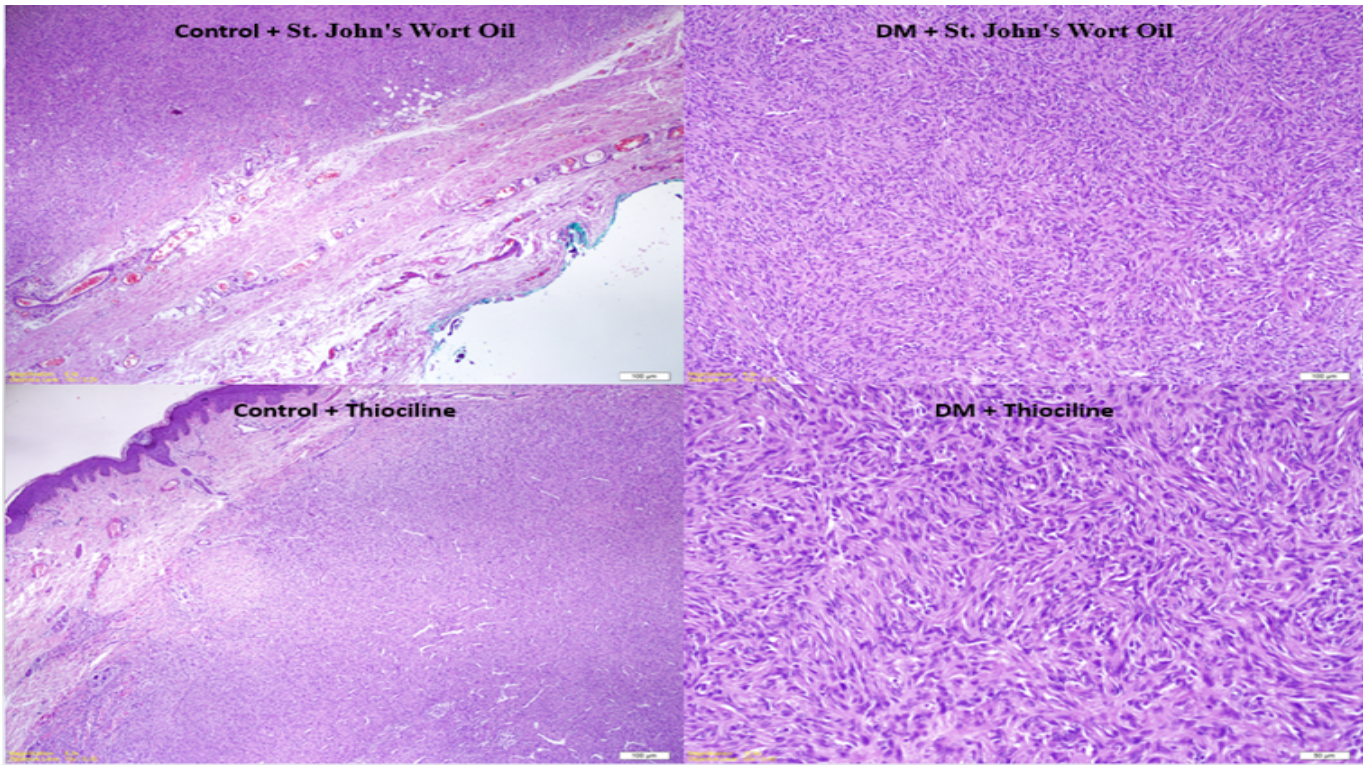

Figure 3. Histopathological appearance of wound healing in control and treatment groups.

DISCUSSION

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from inadequate insulin production or impaired insulin action. This condition often leads to impaired wound healing, frequently complicated by infections with various bacterial agents. This study aimed to compare the effectiveness of St. John's Wort oil (Hypericum perforatum) and thiocilline ointment (containing bacitracin and neomycin) in enhancing wound healing in a diabetic rat model.[16,17]

St. John's Wort oil has a longstanding history in herbal medicine for its beneficial effects on wound healing. The bioactive substances it contains, such as hypericin, hyperforin and flavonoids, offer many benefits, including anti-microbial, anti-inflammatory, and antioxidant properties.[13,18] Studies in the literature have shown its effectiveness in promoting epithelialization, reducing inflammation and accelerating the wound healing process.[19,20] Our findings are consistent with studies in the literature and show significant improvements in wound healing in diabetic rats treated with St. John's Wort oil. Compared to the thiocillin group, there was a significant reduction in ulceration and necrosis in the St. John's Wort oil group. Additionally, the significant increases in epithelialization and neovascularization observed in the St. John's Wort oil group indicate increased tissue regeneration and blood vessel formation, which are vital for effective wound healing.

Thiocillin, a compound containing neomycin and bacitracin, is widely used in routine practice due to its strong antibacterial properties.[10] Its anti-bacterial activity has a less significant effect compared to St. John's Wort oil on fundamental aspects of wound healing such as epithelialization, fibroblast proliferation and neovascularization. Our research revealed a significant reduction in edema and congestion in the group treated with St. John's Wort oil, demonstrating its potent anti-inflammatory effects.[21]

The wound healing effectiveness of St. John's Wort oil and its versatile effects can be attributed to physiological processes. Its anti-inflammatory effects help reduce edema and congestion often seen in diabetic wounds. Additionally, the antimicrobial properties of St. John's Wort oil can prevent infections and create an optimal environment for healing. St. John's Wort oil also supports fibroblast activity and neovascularization, which are necessary for tissue repair and regeneration.[22] Our study shows that St. John's Wort oil may be a valuable alternative or supplement to routine treatments such as thiocilline in the treatment of diabetic wounds. The significant effects of St. John's Wort oil on wound healing processes suggest that it may improve outcomes for diabetic patients. However, further clinical studies are needed to confirm these results and investigate potential side effects and best use practices of St. John's Wort oil in diabetic wound care.

Studies in the literature have shown the wound healing properties of St. John's Wort oil. [20,21,23-25] Özdemir et al.[23] reported that St. John's wort, thyme, and sage essential oils significantly increased wound healing in a rat model. These studies emphasize that St. John's Wort oil can be used as an effective agent in improving wound healing processes. Similarly, Arsic et al.[21] observed that creams containing St. John's Wort oil extract exhibited significant anti-inflammatory effects and accelerated wound healing in a sodium lauryl

sulfate-induced dermatitis model. Other studies have also highlighted the synergistic effects of combining herbal extracts.[23,24,26] Özdemir et al.[23] showed that the combination of St. John's Wort oil and Neem oil had a remarkable supportive impact on wound healing in pressure ulcer patients in intensive care units. Coban et al.[24] showed that composite films made from okra mucilage and methylcellulose, functionalized with Hypericum perforatum oil and gentamicin, exhibit enhanced wound dressing properties. Akturk et al.[26] showed that Hypericum perforatum oil (HPO) and vitamin A palmitate (VAP) incorporated into gelatin nanofibrous scaffolds, cross-linked with tannic acid (TA), effectively enhance wound healing. This aligns with our findings that St. John's Wort oil enhances epithelialization, fibroblast activity, and neovascularization, contributing to improved wound healing outcome. Hypericin and hyperforin, the main components of St. John's wort, are known to promote collagen synthesis, inhibit pro-inflammatory cytokines, and reduce oxidative stress. These effects are particularly beneficial for diabetic wounds, where chronic inflammation and oxidative stress inhibit the healing process. Additionally, St. John's Wort oil supports neovascularization, which is necessary to provide nutrients and oxygen to healing tissue, thus aiding tissue repair and regeneration. The increase in fibroblast proliferation observed in our study is very important for the development of granulation tissue and the accumulation of extracellular matrix components necessary for wound closure.[27,28]

Limitations

This study has some limitations. The use of a single diabetic rat model in the study may not fully reflect the complex processes of wound healing in human diabetic patients. The short duration may be insufficient to observe the long-term effects of St. John's Wort oil and thiocilline on wound healing. However, the strength of our study is that it contributes to the limited body of research on wound healing, filling a critical gap in the literature and encouraging further research in this area. Another limitation of this study was the insufficient number of cases.

CONCLUSION

In conclusion, St. John's Wort oil shows substantial potential for enhancing wound healing in a diabetic rat model, outperforming thiocilline in several crucial histopathological aspects. These results are consistent with existing research on the wound healing benefits of St. John's Wort oil and highlight the need for further studies to confirm its efficacy and safety in clinical settings. Incorporating St. John's Wort oil into wound care protocols could offer an effective, natural alternative for improving wound healing in diabetic patients.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Mustafa Kemal University Ethics Committee (Date: 29.05.2014, Decision No: 07/5).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

REFERENCES

1. Mieczkowski M, Mrozikiewicz-Rakowska B, Kowara M, Kleibert M, Czupryniak L. The Problem of Wound Healing in Diabetes-From Molecular Pathways to the Design of an Animal Model. *Int J Mol Sci.* 2022;23(14):7930.
2. Okur ME, Bulbul EO, Mutlu G, et al. An updated review for the diabetic wound healing systems. *Curr Drug Targets.* 2022;23(4): 393-419. doi:10.2174/1389450122666210914104428
3. Comino Sanz IM, Lopez Franco MD, Castro B, Hidalgo PL. The role of antioxidants on wound healing: a review of the current evidence. *J Clin Med.* 2021;10(16):3558. doi:10.3390/jcm10163558
4. Madiseh M, Tehrani A, Bahmani M, Kopaei M. The research and development on the antioxidants in prevention of diabetic complications. *Asian Pac J Trop Med.* 2016;9(9):825-831. doi:10.1016/j.apjtm.2016.07.001
5. Han SK. Basics of wound healing. Innovations and Advances in Wound Healing: Springer. 2023;1(2):1-42.
6. Rodrigues M, Kosaric N, Bonham CA, Gurtner GC. Wound healing: a cellular perspective. *Physiol Rev.* 2019;99(1):665-706. doi:10.1152/physrev.00067.2017
7. Pakyari M, Farrokhi A, Maharlooei MK, Ghahary A. Critical role of transforming growth factor beta in different phases of wound healing. *Adv Wound Care.* 2013;2(5):215-224. doi:10.1089/wound.2012.0406
8. Anderson K, Hamm RL. Factors that impair wound healing. *J Am Coll Clin Wound Spec.* 2012;4(4):84-91. doi:10.1016/j.jccw.2014.03.001
9. Putri IL, Alyssa A, Aisyah IF, Permatasari A, Pramanasari R, Wungu CDK. The efficacy of topical oxygen therapy for wound healing: A meta-analysis of randomized controlled trials and observational studies. *Int Wound J.* 2024;21(7):14960.
10. Ozhathil DK, Wolf SE. Prevention and treatment of burn wound infections: the role of topical antimicrobials. *Expert Rev Anti Infect Ther.* 2022;20(6):881-96.
11. Firat C, Samdanci E, Erbatur S, et al. Beta-glucan treatment prevents progressive burn ischaemia in the zone of stasis and improves burn healing: an experimental study in rats. *Burns.* 2013;39(1):105-112. doi:10.1016/j.burns.2012.02.031
12. Sargin SA, Akçiçek E, Selvi S. An ethnobotanical study of medicinal plants used by the local people of Alaşehir (Manisa) in Turkey. *J Ethnopharmacol.* 2013;150(3):860-874.
13. Yılmazoğlu E, Hasdemir M, Hasdemir B. Recent studies on antioxidant, antimicrobial, and ethnobotanical uses of hypericum perforatum L.(Hypericaceae). *J Sci Food Agric.* 2022;9(1):373-394.

14. Nobakht SZ, Akaberi M, Mohammadpour AH, Tafazoli Moghadam A, Emami SA. Hypericum perforatum: traditional uses, clinical trials, and drug interactions. *Iran J Basic Med Sci.* 2022;25(9):1045-1058. doi:10.22038/IJBMS.2022.65112.14338
15. El Biali M, Wolfl Duchek M, Jackwerth M, et al. St. John's wort extract with a high hyperforin content does not induce P-glycoprotein activity at the human blood-brain barrier. *Clin Transl Sci.* 2024;17(5):13804. doi:10.1111/cts.13804
16. Yilmaz M, Dokuyucu R. Assessment of sensitivity to the anesthesia in a diabetic rat model. *Eur Rev Med Pharmacol Sci.* 2023;27(19):9029-9033. doi:10.26355/eurrev_202310_33927
17. Dokuyucu R, Gozukara KH, Ozcan O, et al. The effect of Bongardia Chrysogonum on prostate tissue in a rat model of STZ-induced diabetes. *Springerplus.* 2016;5(1):1322. doi:10.1186/s40064-016-2973-z
18. Gul V, Cetinkaya H, Dinler BS, Sefaoglu F. Comparative analysis of biochemical content, antimicrobial and antioxidant activities of hypericum perforatum l. Species is grown in Turkiye. *Pak J Bot.* 2023;55(1):1277-1285.
19. Farasati Far B, Gouranmohit G, Naimi Jamal MR, et al. The potential role of Hypericum perforatum in wound healing: a literature review on the phytochemicals, pharmacological approaches, and mechanistic perspectives. *Phytother Res.* 2024;38(7):3271-3295. doi:10.1002/ptr.8204
20. Yalcinkaya E, Basaran MM, Tunckasik ME, Yazici GN, Elmas C, Kocaturk S. Efficiency of hypericum perforatum, povidone iodine, tincture benzoin and tretinoin on wound healing. *Food Chem Toxicol.* 2022;166(1):113209. doi:10.1016/j.fct.2022.113209
21. Arsic I, Zugic A, Tadic V, et al. Estimation of dermatological application of creams with St. John's Wort oil extracts. *Molecules.* 2011;17(1):275-294. doi:10.3390/molecules17010275
22. Aksu AN, Bilgic T, Kayhan CK, Saglam ZMI, Caf N. Partial healing effects of St. John's Wort oil on the rat excisional wound model. *Marmara Med J.* 2022;35(1):281-287.
23. Ozdemir S, Bostanabad SY, Parmaksiz A, Canatan HC. Combination of St. John's Wort oil and neem oil in pharmaceuticals: an effective treatment option for pressure ulcers ini ntensive care units. *Medicina.* 2023;59(3):467.
24. Coban SN, Polatoglu I, Eroglu E. Methyl cellulose/okra mucilage composite films, functionalized with Hypericum perforatum oil and gentamicin, as a potential wound dressing. *Int J Biol Macromol.* 2024;254(1):127757. doi:10.1016/j.ijbiomac.2023.127757
25. Markoska E, Gramatnikovski N, Pechijareva-Sadikarijo I, Krstevska-Blazhevska S, Matevski V. Home care and the effects of Hypericum tetrapterum oil extract in the treatment of chronic wounds during the COVID-19 pandemic. *Pril.* 2022;43(3):79-89. doi:10.2478/prilozi-2022-0040.
26. Akturk A, Kasikci FN, Dikmetas DN, Karbancioglu Guler F, Erol Taygun M. Hypericum perforatum oil and vitamin A palmitate-loaded gelatin nanofibers cross-linked by tannic acid as wound dressings. *ACS Omega.* 2023;8(26):24023-24031. doi:10.1021/acsomega.3c02967
27. Kaplan V, Hasanoglu Erbasar GN, Cigerim L, Altay Turgut H, Cerit A. Effect of St. John's Wort oil and olive oil on the postoperative complications after third molar surgery: randomized, double-blind clinical trial. *Clin Oral Investig.* 2021;25(4):2429-2438. doi:10.1007/s00784-020-03639-0
28. Novelli M, Masiello P, Beffy P, Menegazzi M. Protective role of St. John's wort and Its components hyperforin and hypericin against diabetes through Inhibition of inflammatory signaling: evidence from In vitro and In vivo studies. *Int J Mol Sci.* 2020;30(21):8108. doi:10.3390/ijms21218108

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Impaired left ventricular function in lean women with PCOS: insights from speckle tracking echocardiography

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ABSTRACT

Aims: We aimed to conduct a study examining left ventricular function (LVEF) in lean women PCOS patients with speckle tracking echocardiography.

Methods: The study included 60 patients diagnosed with PCOS and 30 healthy controls matched for age and body mass index. Morning fasting blood samples were collected to measure levels of glucose, insulin, high-sensitivity C-reactive protein (hs-CRP), and lipids. Left ventricular function (LVF) was evaluated using two-dimensional speckle tracking echocardiography (2D-STE) and real-time three-dimensional echocardiography (3D-Echo). Global strain was assessed from three standard apical views using 2D-STE.

Results: The hs-CRP levels in lean women with PCOS were significantly higher compared to the control group (2.34±1.07 vs. 1.13±0.54; p=0.01). The peak longitudinal strain values in the 2-chamber, 4-chamber, and long-axis views were lower in lean women with PCOS compared to the control group (15.9±1.2 vs. 19.4±1.2; p=0.01, 17.0±1.1 vs. 19.2±1.4; p=0.01, 16.3±1.3 vs. 19.2±1.5; respectively, p=0.01). According to the multiple regression model, global strain was independently associated with hs-CRP (β=0.31, p=0.04), the ratio of early diastolic mitral inflow velocity (E) to early diastolic annular velocity (E/E' ratio) (β=0.33, p=0.01), and ejection fraction (EF) (β=0.35, p=0.01).

Conclusion: Our findings reveal that lean women with PCOS exhibit significantly higher levels of high-sensitivity C-reactive protein (hs-CRP) compared to healthy controls. Furthermore, the peak longitudinal strain values across multiple cardiac views were notably lower in the PCOS group, suggesting impaired left ventricular function. These results highlight the importance of monitoring cardiovascular health in lean women with PCOS, as they are at an increased risk of developing left ventricular dysfunction despite their lean body mass index.

Keywords: PCOS, high-sensitivity C-reactive protein, echocardiography

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a heterogeneous chronic disease that is common in women of age and causes endocrine and metabolic disorders.[1] PCOS affects 6-10% of women of childbearing age. The prevalence of PCOS in premenopausal women ranges from approximately 6% when older, more restrictive criteria are applied to approximately 20% when more inclusive definitions are applied. It is characterized by menstrual dysfunction, chronic anovulation, polycystic ovaries and hyperandrogenism. It appears that the prevalence of polycystic ovary syndrome varies according to diagnostic criteria. Criteria used to diagnose PCOS; NIH (National Institutes of Health) and Rotterdam criteria.[2] Individuals with PCOS often exhibit high luteinizing hormone (LH), high prolactin, and high androgen concentrations. Additionally, sex hormone binding globulin (SHBG) levels also decrease.[3,4]

The incidence of diseases that cause mortality and morbidity has increased in patients with PCOS. Although the mechanism is not clearly revealed, they are Diabetes Mellitus (DM), Hypertension (HT), Dyslipidemia, and Diastolic Dysfunction.[5,6] Moreover, LVF impairment has been reported to be often associated with obesity and insulin resistance.[7] It is known that increased CVD risk is not only seen in obese women with PCOS. There are studies showing increased CVD risk in lean women with PCOS due to the effect of chronic inflammation.[8,9] In the assessment of LVF, echocardiography is usually used method of choice.

In addition, magnetic resonance imaging (MRI) and scintigraphy techniques are also used.[10] Ejection fraction (EF), tissue Doppler imaging (TDI) and Doppler strain

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are the most commonly used methods in the calculation of LVF.[11] Although, EF is the most commonly used index in LVF assessment, subjectivity and variability depending on the clinician are disadvantages. The most important limitations of the TDI and Doppler strain is limited spatial resolution and angle dependence.[12]

Two-dimensional strain imaging is a newly used method providing both objective and quantitative assessment of left ventricular (LV) functions. In addition, limitations of EF, TDI and Doppler strain are not included in this two-dimensional strain imaging. Thus, two-dimensional strain imaging has been used more frequently in recent years.[13,14]

Many reports evaluated the left ventricular functions in women with PCOS by echocardiographic imaging.[15] Yet, there is no study that investigates the LV functions in lean women with PCOS by two -dimensional speckle tracking echocardiography (2D-STE) method. In the present study we aimed to evaluate subclinical LV functions in lean women with PCOS by 2D-STE method.

METHODS

The study was carried out with the permission of the Adana City Training and Clinical Researches Ethics Committee (Date: 01.05.2024, Decision No: 115). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study population consisted 60 lean women with PCOS who were referred from Department of Obstetrics and Gynecology (mean age, 24.14±5.07) and 30 healthy subjects as controls (mean age, 25.11±7.78 years). The diagnosis of PCOS was defined according to the criteria of 2003 Rotterdam European Society of Human Reproduction and Embryology / American Society for Reproductive Medicine (ESHRE/ASRM).[2] Age, body mass index (BMI) and biochemical blood parameters; and high-sensitivity C-reactive protein (hs-CRP) levels were recorded. The demographic characteristics and clinical data of the patients and the controls are collected.

The control subjects had no history of cardiovascular or other organ system diseases. Their physical examinations, chest X-rays, electrocardiograms, and two-dimensional and Doppler echocardiograms were all normal. Exclusion criteria included diabetes mellitus, renal failure, hypertension, coronary artery disease, chronic obstructive pulmonary disease, thyrotoxicosis, left ventricle ejection fraction below 50%, moderate or severe valvular stenosis and/or regurgitation, a QRS duration over 120 MS, and cardiac arrhythmias. Additionally, patients with poor echocardiographic image quality were excluded. The study was approved by the local ethics committee, and all participants provided written informed consent.

Echocardiographic Measurements

Left ventricular ejection fraction (EF) was calculated using the Simpson method.[16] Pulmonary artery pressure was estimated using the simplified Bernoulli equation, inferior vena cava abundance, and tricuspid regurgitation was estimated using jet velocity.[17]

The patients' left ventricular masses and left ventricular mass index were determined in grams with the widely used formula based on the echocardiographic parameters developed by Devereux and Reichek.[18] Again, body surface area was calculated by taking the height and weight of the patients. Left ventricular mass indexes were calculated by dividing the left ventricular mass by the body surface area. It was calculated with the formula SVK (gr)=0.8 x (1.04 (SVDSç +PDk+IVSk(^{3}-(SVDSç)^3)+0.6.18 Diastolic dysfunctions were categorized according to early and late diastolic mitral inflow (E/A ratio) velocities.[19] Grade 3 diastolic dysfunction was defined by an E/A ratio greater than 2, a Dt less than 140 milliseconds, and an E/E' ratio exceeding 10.[20] All imaging assessments were conducted by two cardiologists who were blinded to the participants' clinical information

Two-Dimensional Echocardiography

Evaluation of two-dimensional echocardiography images was performed using left ventricular (LV) apical four-chamber (4C), long-axis (LAX), and two-chamber (2C) views. All images were captured during a breath hold and stored in cine-loop format from three consecutive beats.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) program for Windows Version 27.0 (SPSS, Inc., Chicago, IL, USA) was utilized for the statistical analysis. Results were reported as the mean±SD, and categorical variables were presented as percentages. The chi-squared test was applied for the statistical analysis of categorical variables. The Mann–Whitney U-test was used for differences between lean women with PCOS and the healthy group. Correlation analyses were used. Additionally, Bland–Altman analysis was used to assess inter- and intra-observer variability in left ventricular deformation parameters. A p-value of <0.05 was considered statistically significant for all statistical analyses.

RESULTS

The demographic characteristics, clinical features, laboratory results, and medications of the study groups are presented in Table 1. The PCOS patients and healthy subjects were similar in age, body mass index (BMI), fasting glucose, fasting insulin, HOMA-IR, cholesterol levels, smoking habits, and alcohol consumption. However, the mean±SD hs-CRP values were significantly higher in lean patients with PCOS compared to the healthy subjects (2.34±1.07 mg/L vs. 1.13±0.54 mg/L; p<0.01).

The baseline echocardiographic values are detailed in Table 2. There were no significant differences in ejection fraction (EF), left ventricular mass (LVM) index, left ventricular (LV) diameter, or left atrium diameter between patients with PCOS and healthy controls. However, diastolic dysfunction was observed in three (10.0%) of the control subjects and in 18 (30.0%) of the PCOS patients, with all 18 PCOS patients displaying Grade 1 diastolic dysfunction and none showing Grade 2 or 3 diastolic dysfunction. Lean women with PCOS had elevated values for isovolumetric relaxation time (IVRT), deceleration time (Dt), peak A velocity, and E/E' ratio. In contrast, the control group exhibited a higher E/A ratio

Table 1. The demographic and clinical characteristics, as well as laboratory findings, in lean women with PCOS and control subjects

	PCOS (n=60)	Control group(n=30)	p
Age, years, mean±SD	24.14±5.07	25.11±7.78	NS
Body mass index, kg/m2, mean±SD	21.4±2.1	22.5±2.3	NS
Smoking, n(%)	13 (18.1)	4 (12.9)	NS
Alchol, n(%)	4 (5.5)	3 (9.6)	NS
Total cholesterol mg/dl, mean±SD	158±21	164±32	NS
LDL cholesterol, mg/dl, mean±SD	120±21	116±19	NS
HDL cholesterol, mg/dl, mean±SD	35±8	33±7	NS
Plasma triglyceride, mg/dl, mean±SD	163±38	148±32	NS
hs-CRP, mg/L, mean±SD	2.34±1.07	1.13±0.54	<0.01
Fastıng glucose, mg/dl	84.4±1.1	87.2±9.7	NS
Fasting insulin, Miu/Liter	10.4±3.4	9.8±2.6	NS
HOMA-IR	2.16±0.7	2.11±0.4	NS

HDL: High-density lipoprotein, hs-CRP: High-sensitivity C-reactive protein, HOMA-IR: Homeostatic model assessment-insulin resistance, LDL: Low-density lipoprotein NS: Non-significant (p>0.05)

Table 2. Echocardiographic findings in lean women with PCOS and control subjects

	PCOS group (n= 60) Mean±SD	Control group (n=30) Mean±SD	p
LV end-diastolic dimension, cm	2.68±0.39	2.65±0.33	NS
LV end-systolic dimension, cm	4.64±0.39	4.58±0.35	NS
IVSD, cm	0.99±0.09	0.99±0.065	NS
LVPWD, mm	0.99±0.09	0.99±0.06	NS
LA, mm	32.3±2.8	31.4±3.8	NS
Ejection fraction, %	64.14±2.43	64.67±2.53	NS
LV mass index, g	146.2±28	145.9±30	NS
E, cm/s	75.9±10.9	77.2±11.4	NS
A, cm/s	76.2±10.8	70.1±12.2	<0.01
E/A ratio	1.06±0.28	1.17±0.18	<0.01
Deceleration time, ms	216±32	178±29	<0.01
IVRT, ms	98±13	80±8	<0.01
E/E' ratio	8.3±1.8	7.4±1.3	<0.01

A: Late diastolic mitral inflow, E: early diastolic mitral inflow velocity, E/E0: Ratio of early diastolic mitral inflow velocity to early diastolic annular velocity, IVRT: Isovolumetric relaxation time, IVSD: Interventricular septum diameter, LA: Left atrium, LV: Left ventriculi, LVPWD: Left ventricular posterior wall diameter. NS: Non-significant (p>0.05)

When comparing data between the control and PCOS groups, it was found that left ventricular global strain (LV-GS), four-chamber longitudinal strain (4C-LS), long-axis longitudinal strain (LAX-LS), and two-chamber longitudinal strain (2C-LS) values were significantly lower in the lean PCOS group. Additionally, all strain rate (SR) values were significantly reduced in patients with PCOS compared to healthy subjects (Table 3).

A multiple regression model was established with global strain (GS) as the dependent variable, along with hs-CRP, EF, E/A ratio, and E/E' ratio as independent variables. The analysis showed that GS was independently associated with hs-CRP (β=0.31, P=0.04), E/E' ratio (β=0.33, p=0.01), and EF (β=0.35, p=0.01). Similarly, in a multiple regression model for global strain rate (GSR) with hs-CRP, E/A ratio, E/E' ratio, and EF, GSR was independently associated with EF (β=0.32, p<0.01) and E/E' (β=0.31, p<0.01) (Table 4).

Table 3. Left ventricular two-dimensional strain and strain rate measurements in lean women with PCOS and control subjects

	PCOS group (n= 60) Mean±SD	Control group(n=30) Mean ± SD	p
2C-SR, per s	1.31±0.32	1.52±0.34	0.02
LAX-SR, per s	1.26±0.27	1.46±0.32	<0.01
4C-SR, per s	1.29±0.35	1.65±0.40	<0.01
GS, %	16.2±1.3	19.1±1.8	<0.01
GSR, per s	1.42±0.24	1.54±0.32	<0.01
2C-LS, %	15.9±1.2	19.4±1.2	<0.01
LAX-LS, %	16.3±1.3	19.2±1.5	<0.01
4C-LS, %	17.0±1.1	19.2±1.4	<0.01

2C: Two-chamber, 4C: Four-chamber, GS: Global strain, GSR: Global strain rate, LAX: Parasternal long axis, LS: Longitudinal strain; SR: Strain rate.

Table 4. Correlations between echocardiographic parameters and global strain (GS) and global strain rate (GSR) values

	Global strain				Global strain rate			
	p	p-value	B	p-value	p	p-value	B	p-value
Hs-CRP	0.32	0.01	0.31	0.04	0.33	0.01	0.28	0.06
E/A ratio	-0.32	0.03	-0.25	0.07	-0.31	0.02	-0.23	0.06
E/E' ratio	-0.34	<0.01	-0.33	0.01	-0.30	<0.01	-0.32	<0.01
EF	0.41	0.01	0.35	0.01	0.37	<0.01	0.31	<0.01

EF: Ejection fraction, E/A: Ratio of early to late diastolic mitral inflow velocities, E/E': Ratio of early diastolic mitral inflow velocity to early diastolic annular velocity.

DISCUSSION

In this study, we investigated left ventricular function using two-dimensional strain imaging in lean PCOS patients. Our findings revealed that lean PCOS women have reduced LV systolic longitudinal function compared to the healthy group.

PCOS patients generally characterized by obesity, hypertension, insulin resistance, and dyslipidemia. Frequent occurrence of cardiovascular risk factors suggests that this is associated with increased risk of cardiovascular system (CVS) in PCOS patients.[6,15,21]

Studies on CVS morbidity and mortality in PCOS are not yet sufficient. In United Kingdom, women with PCOS followed for 30 years, and increased mortality was observed in the CVS.[22] In contrast, in patients with menstrual irregularities in the Nurses' Health study had an increased fatal or non-fatal CVS risk.[23] Additionally, in a study angiography results of postmenopausal women who are at risk of ischemia revealed that women with PCOS have increased CVD incidence.[24]

High-sensitivity CRP is a sensitive marker of inflammation. It is used to predict and diagnose low-grade inflammatory conditions. Its increase seems to be related to the extent of tissue injury and severity of inflammation. In patients with PCOS, levels of hs-CRP are expected to be high as a result of chronic inflammation. Also, CRP, predictor of CVD, was found to be increased in patients with PCOS.[25-27] Consistent with these findings, in our study CRP levels were found to be higher in PCOS patients. After adjustment for BMI in PCOS patients, some studies reported no difference in CVD mortality and some reported increased CVD mortality.[28,29] Also, in the present study, we determined a decrease in left ventricular functions in PCOS patients with BMI.

Numerous echocardiographic studies were attempted to investigate the presence of subclinical CVD in patients with PCOS. Diastolic LV dysfunction is known to be related to CVD risk. It is found that PCOS patients had a decrease in left ventricular diastolic function.[30] Sub clinic myocardial dysfunction may occur in PCOS patients. 2D-STE can be useful to show subclinical myocardial dysfunction.[31] It has been scientifically demonstrated that strain imaging, which has been widely used in recent years, more clearly demonstrates subclinical left ventricular dysfunction that conventional echocardiography cannot detect.[32] Erdogan et al.[33] used 2D-STE method and reported an impairment in left ventricular diastolic function and a reduction in global strain values. In their study, the average BMI of patients is 29.4+8.5. Obesity itself increases the risk of CVD. Although our study population was consisted of lean women with PCOS, GLS values were found to be increased. Moreover, a correlation was found between hs-CRP, which indicates subclinical inflammation, and GLS.

Left ventricular ejection fraction (LVEF) is usually measured to evaluate for LV systolic function.[31,34] In the current study, we found no differences in LV diameter, EF, left atrium diameter and LVM index between subjects with and without PCOS. However, in patients with PCOS, diastolic dysfunctions were detected more frequently. Additionally, LV strain and all SR values were found to be significantly lower in patients with PCOS than in control subjects.

As the experience of operator, image quality and LV geometry's assumption, C-echo gives limited data to us. The mechanism of 2D-STE is founded to following of characteristic speckle patterns occurred by initiative of ultrasonographic beams from myocardium. Speckle tracking is superior to evaluate for longitudinal function of left ventricle to basal segments. Longitudinal contraction is used to evaluate the subendocardial function in subclinical cardiovascular diseases like PCOS. While the LVEF of lean women with PCOS were normal using C-echo, LVEF values also in the same group were impaired using 2D-STE compatible with our knowledge mentioned above.

Limitations

The major limitation of our study is relatively small number of study population. Because of case control study, we could not have opportunity to evaluate echo results of drugs administrated in PCOS. Therefore, we do not know what will be the outcome of subclinical echo results in the future. Also, technical limitations of speckle echo can be seen our study.

CONCLUSION

This study highlights significant cardiac involvement in lean women with PCOS, demonstrating that these patients exhibit impaired left ventricular function as evidenced by lower peak longitudinal strain values in the 2-chamber, 4-chamber, and long-axis views. The findings also indicate that global strain is independently associated with elevated hs-CRP levels, increased E/E' ratio, and decreased ejection fraction (EF). These results suggest that even lean women with PCOS, who might be considered at lower risk due to their body mass index, are nonetheless at a heightened risk for cardiovascular complications. Early detection and monitoring of cardiac function using advanced imaging techniques like speckle tracking echocardiography can be crucial for managing and mitigating the cardiovascular risks associated with PCOS.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Adana City Training and Clinical Researches Ethics Committee (Date: 01.05.2024, Decision No: 115)

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

REFERENCES

1. Guan M, Li R, Wang B, et al. Healthcare professionals' perspectives on the challenges with managing polycystic ovary syndrome: a systematic review and meta-synthesis. *Patient Educ Couns*. 2024;123(1):108197.
2. Rotterdam EA-SPCWG. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertility and steril*. 2004;81(1):19-25.
3. Liang X, He H, Zeng H, et al. The relationship between polycystic ovary syndrome and coronary heart disease: a bibliometric analysis. *Front Endocrinol*. 2023;8(14):1172750.
4. Barber TM, Franks S. Obesity and polycystic ovary syndrome. *Clin Endocrinol* . 2021;95(4):531-541.
5. Karateke A, Dokuyucu R, Dogan H, et al. Investigation of therapeutic effects of erdosteine on polycystic ovary syndrome in a rat model. *Med Princ Prac*t. 2018;27(6):515-522.
6. Gozukara IO, Pinar N, Ozcan O, et al. Effect of colchicine on polycystic ovary syndrome: an experimental study. Arch Gynecol Obstet. 2016; 293(3):675-680.
7. Çakır E, Özbek M, Şahin M, Delibaşı T. Polycystic ovary syndrome and the relationship of cardiovascular disease risk. *Turk J Med Sci*. 2013;17 (1):33-37.
8. Henney AE, Gillespie CS, Lai JYM, et al. Risk of type 2 diabetes, MASLD and cardiovascular disease in people living with polycystic ovary syndrome. *J Clin Endocrinol Metab*. 2024;11(1):481.
9. Nandakumar M, Das P, Sathyapalan T, Butler AE, Atkin SL. A cross sectional exploratory study of cardiovascular risk biomarkers in non-obese women with and without polycystic ovary syndrome: association with vitamin D. *Int J Mol Sci*. 2024;25(12).6330.

10. Stegger L, Heijman E, Schafers KP, Nicolay K, Schafers MA, Strijkers GJ. Quantification of left ventricular volumes and ejection fraction in mice using PET, compared with MRI. *J Nucl Med*. 2009;50(1):132-138.
11. Han Y, Ahmed AI, Saad JM, et al. Ejection fraction and ventricular volumes on rubidium positron emission tomography: validation against cardiovascular magnetic resonance. *J Nucl Cardiol*. 2024;32(1):101810.
12. Gupta VA, Nanda NC, Sorrell VL. Role of echocardiography in the diagnostic assessment and etiology of heart failure in older adults: opacify, quantify, and rectify. *Heart Fail Clin*. 2017;13(3):445-466.
13. Baktir AO, Sarli B, Altekin RE, et al. Non alcoholic steatohepatitis is associated with subclinical impairment in left ventricular function measured by speckle tracking echocardiography. *A natol J Cardiol*. 2015;15(2):137-142.
14. Hamabe L, Mandour AS, Shimada K, et al. Role of two-dimensional speckle-tracking echocardiography in early detection of left ventricular dysfunction in dogs. *Animals*. 2021;11(8):2361.
15. Mirzohreh ST, Panahi P, Zafardoust H, et al. The role of polycystic ovary syndrome in preclinical left ventricular diastolic dysfunction: an echocardiographic approach: a systematic review and meta-analysis. *Cardiovasc Endocrinol Metab*. 2023;12(4):0294.
16. Otterstad JE. Measuring left ventricular volume and ejection fraction with the biplane Simpson's method. *Heart*. 2002;88(6):559-560.
17. Beghetti M. Echocardiographic evaluation of pulmonary pressures and right ventricular function after pediatric cardiac surgery: a simple approach for the intensivist. *Front Pediatr*. 2017;29(5):184.
18. Devereux RB, Alonso DR, Lutas EM, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol*. 1986;57(6):450-458.
19. Bruch C, Schmermund A, Bartel T, Schaar J, Erbel R. Tissue doppler imaging: a new technique for assessment of pseudonormalization of the mitral inflow pattern. *Echocardiography*. 2000;17(6):539-546.
20. Kuznetsova T, Bogaert P, Kloch-Badelek M, et al. Association of left ventricular diastolic function with systolic dyssynchrony: a population study. *Eur Heart J Cardiovasc Imaging*. 2013;14(5):471-479.
21. de Groot PC, Dekkers OM, Romijn JA, Dieben SW, Helmerhorst FM. PCOS, coronary heart disease, stroke and the influence of obesity: a systematic review and meta-analysis. *Hum reprod update*. 2011;17(4): 495-500.
22. Heald AH, Livingston M, Holland D, et al. Polycystic ovarian syndrome: assessment of approaches to diagnosis and cardiometabolic monitoring in UK primary care. *Int J Clin Pract*. 2018;72(1):11.
23. Vinnikov D, Saktapov A, Romanova Z, Ualiyeva A, Krasotski V. Work at high altitude and non-fatal cardiovascular disease associated with unfitness to work: Prospective cohort observation. *PLoS One*. 2024;19 (7):0306046.
24. Prabakaran S, Vitter S, Lundberg G. Cardiovascular disease in women update: ischemia, diagnostic testing, and menopause hormone therapy. *Endocr Pract*. 2022;28(2):199-203.
25. Keskin Kurt R, Okyay AG, Hakverdi AU, et al. The effect of obesity on inflammatory markers in patients with PCOS: a BMI-matched case-control study. *Arch Gynecol Obstet*. 2014;290(2):315-319.
26. Tola EN, Yalcin SE, Dugan N. The predictive effect of inflammatory markers and lipid accumulation product index on clinical symptoms associated with polycystic ovary syndrome in nonobese adolescents and younger aged women. *Eur J Obstet Gynecol Reprod Biol*. 2017;214(1):168-172.
27. Asimi Z, Burekovic A, Dujic T, Bostandzic A, Semiz S. Incidence of prediabetes and risk of developing cardiovascular disease in women with polycystic ovary syndrome. *Bosn J Basic Med Sci*. 2016;16 (4):298-306.
28. Ollila MM, Arffman RK, Korhonen E, et al. Women with PCOS have an increased risk for cardiovascular disease regardless of diagnostic criteria-a prospective population-based cohort study. *Eur J Endocrinol*. 2023;189(1):96-105.
29. Forslund M, Landin Wilhelmsen K, Brannstrom M, Dahlgren E. No difference in morbidity between perimenopausal women with PCOS with and without previous wedge resection. *Eur J Obstet Gynecol Reprod Biol*. 2023;28581):74-78.
30. Garvey WT, Mechanick JI, Brett EM, et al. American association of clinical endocrinologists and American college of endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity. *Endocr Pract*. 2016;22(3):1-203.
31. Keskin Kurt R, Nacar AB, Guler A, et al. Menopausal cardiomyopathy: does it really exist? A case-control deformation imaging study. *J Obstet Gynaecol Res*. 2014;40(6):1748-1753.
32. Edvardsen T, Sarvari SI, Haugaa KH. Strain imaging from Scandinavian research to global deployment. *Scand Cardiovasc J*. 2016;50(5):266-275.
33. Erdogan E, Akkaya M, Bacaksiz A, et al. Subclinical left ventricular dysfunction in women with polycystic ovary syndrome: an observational study. *Anadolu Kardiyol Derg*. 2013;13(8):784-790.
34. Kurt M, Tanboga IH, Aksakal E. Two-Dimensional strain imaging: basic principles and technical consideration. *Eurasian J Med*. 2014;46(2):126-130.