RESEARCH ARTICLE

DOI: 10.4274/ijca.2025.28247
Int J Cardiovasc Acad 2025;11(3):125-132

De Ritis Ratio as a Prognostic Marker for Mid-term Mortality in Femoropopliteal Artery Disease

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Abstract

Background and Aim: Peripheral arterial disease (PAD) is recognized as an increasing cause of cardiovascular (CV) morbidity and mortality with advancing age, affecting millions of people worldwide. CV mortality and all-cause mortality may be predicted by aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels in patients with PAD. We examined the effect of the AST/ALT ratio on mid-term prognosis in PAD.

Materials and Methods: A retrospective, single-center, observational study was conducted between January 2023 and December 2024. 156 patients with femoropopliteal artery lesions who underwent endovascular intervention were evaluated, and 150 patients with similar demographic characteristics and no history of PAD were included in the control group. De Ritis ratio (DRR) was calculated as the AST/ALT ratio on admission. A *P*-value < 0.05 was considered statistically significant in all analyses.

Results: The study participants were divided into three groups: survivors (n=135, 44.1%), non-survivors (n=21, 6.8%), and the control group (n=150, 49%). The average follow-up period was 20.50±9.56 months. During follow-up, 21 deaths occurred, 12 (57.1%), due to cardiac causes and 9 (42.9%), due to non-cardiac causes. A significant difference was observed in the DRR levels between the survivor (1.27±0.59) and non-survivor (1.66±0.98) groups ($P = 0.002$). For the DRR, the optimal cut-off value was found to be 1.78. In multivariate logistic regression analysis high DRR was an independent predictor of cardiac ($P < 0.001$), non-cardiac ($P = 0.023$), and all-cause mortality ($P = 0.004$)

Conclusion: DRR is a simple and effective inflammation-related marker that can be used to determine future adverse CV events in patients with PAD. These findings indicate that an elevated DRR may be a manifestation of systemic conditions rather than isolated liver damage.

Keywords: Peripheral arterial disease, mortality, De Ritis ratio, inflammation, angioplasty

INTRODUCTION

Peripheral arterial disease (PAD) has been identified as a major contributing factor to cardiovascular (CV) morbidity and mortality, affecting millions of people worldwide, particularly among the aging population.[1] It is well established that classical atherosclerotic risk factors, including advanced age, hyperlipidemia, diabetes mellitus (DM), hypertension, and smoking, exhibit a strong correlation with an increased risk of PAD.[1] Although PAD has received less attention than other atherosclerotic diseases, the increased interest in PAD in recent years has led to new insights into the association between thrombosis and inflammation. Inflammation has been identified as a pivotal factor in the development and progression of systemic atherosclerosis, and many studies have linked inflammatory biomarkers to PAD.[1] Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are easily obtainable, practical, and routinely measured values in

To cite this article: Çağlayan HÇ, Baytuğan NZ. De Ritis ratio as a prognostic marker for mid-term mortality in femoropopliteal artery disease. Int J Cardiovasc Acad. 2025;11(3):125-132

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Received: 28.03.2025
Accepted: 10.07.2025
Publication Date: 15.09.2025

clinical practice. These enzymes play crucial roles in systemic processes. ALT is primarily located in the hepatocyte cytoplasm. In contrast, AST is abundant in many organs and systems and is expressed in the mitochondria.[2] Serum AST and ALT levels are altered by oxidative stress and hepatocyte damage.

The De Ritis ratio (DRR) (AST/ALT ratio) was initially developed by De Ritis et al.[3] in 1957 for the prognostic evaluation of several liver diseases. The DRR is a complex and valuable parameter that provides important data about the metabolic status of the patient. In healthy humans, the release of AST and ALT into plasma is typically maintained at a constant rate due to the programmed regeneration of hepatocytes, with a DRR slightly less than one.[4] Recent findings suggest that DRR is associated with many adverse CV outcomes, such as acute coronary syndromes, atherosclerotic CV disease, acute and chronic heart failure, cardiac arrest, hypertension, and acute ischemic stroke.[5-12] However, the relationship between DRR and prediction of the mid-term prognosis of patients with PAD is not well established.

We aimed to evaluate the DRR level during percutaneous transluminal angioplasty (PTA) for PAD lesions and its association with mid-term cardiac and all-cause mortality.

METHODS

We conducted a retrospective, single-center study from January 2023 to December 2024. The study population comprised 177 patients with femoropopliteal artery (FPA) lesions who underwent endovascular intervention in our catheterization laboratory. However, 21 patients for whom sufficient follow-up data were unavailable were excluded, and finally 156 patients were evaluated. In addition, 150 patients with similar demographic characteristics and no history of PAD were included in the control group.

In the management guidelines for patients with PAD, we used the resting ankle-brachial index (ABI) as the primary diagnostic tool. ABI ≤0.90 in both limbs is diagnostic for PAD.[13] All patients enrolled before the procedure were symptomatic for PAD, had an ABI <0.90, and showed evidence of severe PAD on non-invasive testing (B-mode Doppler ultrasonography and/or computed tomography angiography). Laboratory findings were obtained from an electronic database. Complete blood counts and biochemical parameters, including fasting blood glucose, AST, ALT, creatinine, high-sensitivity C-reactive protein (hs-CRP), and D-dimer levels, were evaluated on admission. DRR was calculated as the ratio of AST to ALT levels. Blood samples were collected in standard tubes containing ethylenediaminetetraacetic acid to obtain complete blood cell counts. Patients aged <18 years were excluded: unavailable follow-up data, malignancy, chronic inflammatory disease, hematologic disease, chronic liver disease, hepatitis, and fatty liver disease. This study was conducted in accordance with the principles of the Declaration of Helsinki. In addition, approval was obtained from the local Ethics Committee University of Health Sciences Türkiye, Kocaeli City Hospital (approval number: 2024-55, date: 13.06.2024). A signed informed consent form was obtained from each patient enrolled in the study.

Clinical Data Collection and Follow-up

The clinical condition of the patients, their additional disease history, smoking status, mortality, and specific cause of death were recorded. The causes of death were determined by analyzing the death certificates available for all deceased individuals. The classification of deaths as cardiac or non-cardiac was determined using death certificates based on the International Classification of Diseases, 9th revision. After the procedure, the patients were referred for follow-up visits at the 1st, 3rd, 6th, and 12th months. During these visits, physical examinations were conducted and patients were asked about any symptoms they might have experienced.

Background

Angiographic Procedure

Prior to the implementation of the procedure, Doppler ultrasound evaluations were conducted for all patients to visualize the extent and morphology of the FPA lesion. Following the insertion of a 6-8F introducer sheath and diagnostic angiography, intravenous heparin was administered at a dose of 100 µg/kg. An antegrade contralateral strategy was employed, utilizing a Judkins right catheter (5-6F) with a hydrophilic guide wire to successfully traverse the lesions. In most cases, the standard guide wire utilized was 0.018 inches in diameter.

Statistical Analysis

Statistical analyses were performed using number cruncher statistical system (NCSS) 2020 Statistical Software (NCSS LLC, Kaysville, Utah, USA). Chi-squared and Fisher's exact tests were used to compare categorical variables, which are presented as absolute and relative frequencies. The data were evaluated for conformity to a normal distribution using the Shapiro-Wilk test and box plots. No significant deviations from normality were detected. Data was expressed as mean ± standard deviation, and an unpaired Student's t-test was used to assess the statistical significance of differences. One-way analysis of variance was used for comparisons of three or more groups, and the Games-Howell test was used to determine the groups contributing to the differences in the outcome. The optimal cut-offs for DRR's capacity to predict cardiac and all-cause mortality were established using receiver operating characteristic (ROC) curve analyses. Kaplan-Meier survival analysis was used to

assess survival outcomes. The parameters were analyzed using univariate and multivariate logistic regression models. Univariate and multivariate Cox proportional hazards regression analyses were conducted to determine the factors influencing mortality. Multivariate logistic regression analysis was performed using a backward selection method. The results were analyzed with a 95% confidence interval, and the significance level was set at $P < 0.05$.

RESULTS

The study included 306 participants, comprising 156 patients in the study group and 150 patients in the control group. Among the participants, 235 (76.8%) were men and 71 (23.2%) were women. The median age of the patients was 64±12.5 years. The study participants were divided into three groups: survivors (n=135, 44.1%), non-survivors (n=21, 6.8%), and the control group (n=150, 49%) (Table 1). 12 (57.1%) deaths were due to cardiac causes, whereas 9 (42.9%) deaths were due to non-cardiac causes. The basic clinical, demographic, and laboratory characteristics of the patients are presented in Table 1. The average follow-up period was 20.50±9.56 months.

Drug-coated balloons were used in 90.9% of the patients. A comparison of the characteristics of survivors and non-survivors revealed that the non-survivors were older ($P < 0.001$), but the two groups did not differ significantly in terms of other chronic diseases or smoking status (Table 1). Statistically significant correlations were identified between ABI ($P = 0.026$), the severity of stenosis ($P = 0.033$), and mortality ($P = 0.026$).

Hematological tests showed that non-survivors had lower levels of hemoglobin, hematocrit, and lymphocytes, but higher WBC, neutrophil, and monocyte counts (Table 2). Platelet count and red cell distribution width values were similar. A comparative analysis of biochemical parameters revealed higher levels of AST, ALT, hs-CRP, creatinine, and D-dimer in non-survivors. However, fasting blood glucose and uric acid levels were similar (Table 2).

DRR and Survival Analysis

A statistically significant difference was observed in the DRR levels between the survivor (1.27±0.59) and non-survivor (1.66±0.98) groups ($P = 0.002$). (Table 2 and Figure 1). All non-survivor groups, stratified by cardiac and non-cardiac causes of death, had higher DRR levels than survivors. (Table 2). The study identified a cut-off value of 1.78 as the optimal metric for determining DRR. Out of the total patients, 47 exhibited DRR levels greater than 1.78, accounting for a prevalence of 30.1%. Kaplan-Meier analysis demonstrated that patients with a DRR ≥1.78 exhibited a significantly higher rate of all-cause mortality than those with a DRR <1.78 ($P = 0.002$) (Figure 2).

ROC curve analysis revealed that the area under the curve (AUC), specificity, and sensitivity of the DRR for all-cause mortality were 0.67, 89.88%, and 41.5%, respectively ($P = 0.001$) (Figure 3A). Furthermore, the DRR for cardiac mortality had an AUC, specificity, and sensitivity of 0.74, 91.1%, and 47%, respectively ($P = 0.001$). (Figure 3B). Univariate and multivariate Cox proportional hazard regression analyses were

Table 1: The demographic and clinical characteristics of the patients

	Control (n=150)	Survival (n=135, 86.5%)	Non-survival (n=21, 13.4%)	*P*-value
Gender (female), n (%)	34 (22.6)	31 (22.9)	6 (28.5)	0.335
Age	64.33±10.21	63.19±11.20	77.07±16.29	0.001
Smoking, n (%)	47 (31.3)	44 (32.6)	8 (38.1)	0.474
Follow-up time (mounts)	20.11±6.33	21.33±13.41	19.61±10.31	0.341
Residual lesion	-	30.0±15.0	25.0±10.0	0.660
Degree of stenosis	-	85.0±5.50	95.0±10.0	0.033
Total balloon	-	101	20	-
Drug eluting balloon, n (%)	-	94 (93.0)	16 (80.0)	0.013
ABI	-	0.85±0.37	0.73±0.41	0.026
Past medical history				
DM, n (%)	63 (42.0)	45 (35.5)	7 (33.3)	0.821
HT, n (%)	59 (39.3)	58 (42.9)	9 (42.8)	0.902
HL, n (%)	35 (23.3)	35 (25.9)	7 (33.3)	0.102
Previous CAD, n (%)	28 (18.6)	23 (17.0)	5 (23.8)	0.699
AF, n (%)	5 (3.3)	6 (4.4)	1 (4.7)	0.443

ABI: Ankle-brachial index, AF: Atrial fibrillation, CAD: Coronary artery disease, DM: Diabetes mellitus, HT: Hypertension

Table 2: Laboratory values of study population

	Control (n=150)	Survival (n=135)	Non-survival (n=21)	*P*-value
Hemoglobin, g/dL	12.88±2.44	12.92±2.18	10.40±1.78	0.021
Hematocrit	38.01±6.55	38.76±5.74	31.90±4.63	0.033
WBC x 103/mL	9350.7±2451.4	8977.4±2445.8	13431.5±7562.2	0.022
Platelet x103/L	255.28±42.12	249.78±68.62	257.90±101.75	0.640
Lymphocyte x103/µL	2.44±0.17	2.17±0.81	1.47±0.77	0.001
Neutrophil x103/µL	5.87±3.10	5.65±1.92	10.68±7.39	0.001
Monocyte x103/µL	0.66±0.14	0.76±0.24	0.89±0.35	0.038
RDW	13.03±3.13	13.61±1.86	13.86±2.71	0.904
Creatinine, mg/dL	1.09±0.71	1.18±0.92	1.77±1.23	0.001
Glucose mg/dL	146.6±57.15	158.68±84.13	157.72±76.1	0.677
AST mg/dL	26.10±18.30	21.50±18.49	39.05±55.22	0.001
ALT mg/dL	25.44±13.77	18.81±13.89	36.77±90.36	0.001
De Ritis ratio	1.09±0.43	1.27±0.59	1.66±0.98	0.002
De Ritis ratio$^{\alpha}$	1.34±0.69	1.27±0.59	1.69±0.96$^{\beta}$	0.003
De Ritis ratio$^{\mu}$	1.34±0.69	1.27±0.59	1.62±0.55$^{\mu}$	0.013
D-dimer ng/mL	0.89±0.41	1.07±0.91	2.63±2.86	0.003
Uric acid, mg/dL	4.20±2.71	5.22±1.65	6.02±3.28	0.088
hs-CRP, mg/L	11.50±10.33	19.63±42.66	70.83±61.53	0.001

RDW: Red cell distribution width, ALT: Alanine aminotransferase, AST: Aspartate transaminase, hs-CRP: High sensitivity C-reactive protein, WBC: White blood cell, $^{\alpha}$: Cardiac causes, $^{\mu}$: Non-cardiac causes

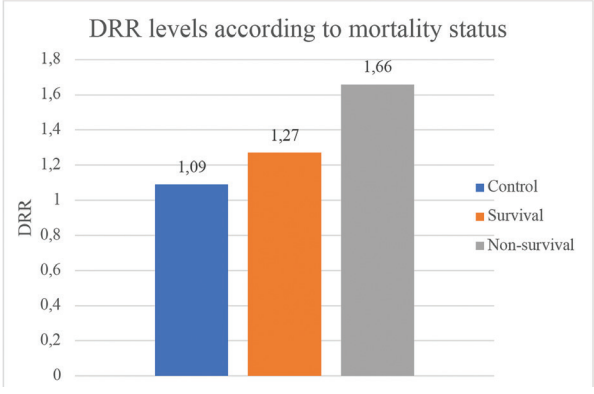

Figure 1. DRR levels according to mortality status
DRR: De Ritis ratio

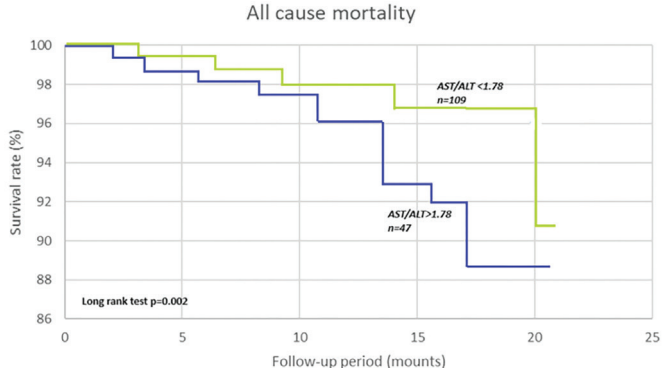

Figure 2. Kaplan-Meier analysis detecting for all-cause mortality
AST/ALT: Aspartate aminotransferase/alanine aminotransferase

performed to determine the factors influencing cardiac and all-cause mortality (Table 3). In univariate evaluations, DRR levels were significantly associated with all-cause, cardiac, and non-cardiac mortality (Table 3). After adjusting for confounding risk factors, multivariate Cox proportional hazards regression analysis showed that a high DRR was an independent predictor of cardiac ($P < 0.001$), non-cardiac ($P = 0.023$), and all-cause mortality ($P = 0.004$) (Table 3). The evaluation results were obtained using the backward-elimination method. Variables that were found to have significant or near-significant ($P < 0.200$) effects in the univariate evaluations were included in the multivariate evaluations (Table 4). We tested the independent association of DRR with the risk of all-cause, cardiac, and non-cardiac mortality using multivariate regression models that included a large number of risk factors and potential confounders (Table 4).

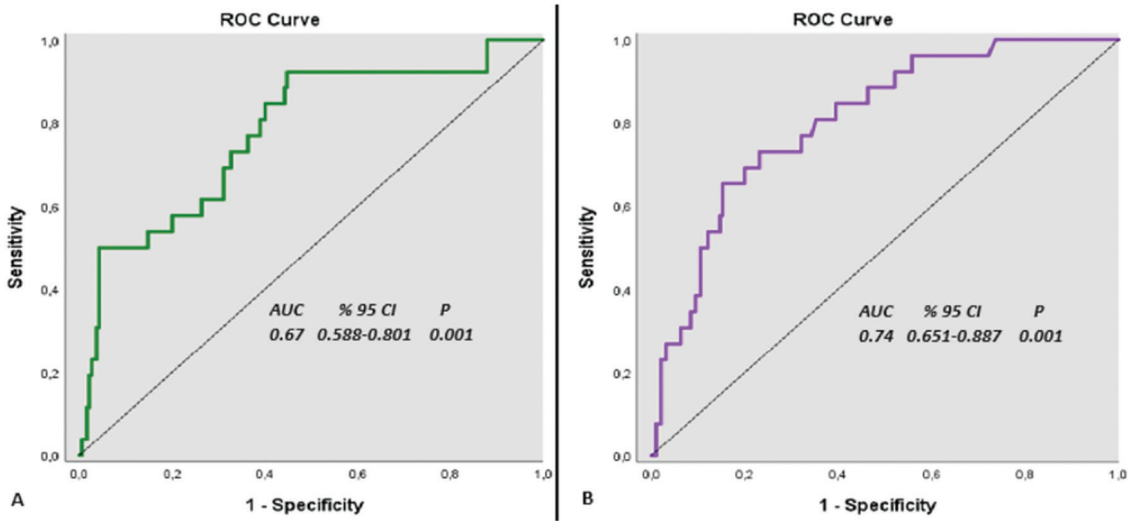

Figure 3: A) ROC curve analysis of DRR in predicting all-cause mortality B) ROC curve analysis of DRR in predicting cardiac mortality

ROC: Receiver operating characteristic, DRR: De Ritis ratio, AUC: Area under the curve, CI: Confidence interval

Table 3: Uni-variate Cox proportional hazard regression analysis of DRR for predicting cardiac, non-cardiac and all-cause mortality

Variables DRR >1.78	Unadjusted HR (95% CI)	*P*-value	Adjusted HR (95%CI)	*P*-value
All-cause mortality (n=21)	2.57 (1.51-4.70)	0.002	2.93 (1.33-5.07)	0.004
Cardiac mortality (n=12)	3.57 (0.94-7.52)	0.001	2.91[α] (1.52-3.85)	0.002
			2.56[µ] (1.75-4.31)	0.001
Non-cardiac mortality (n=9)	1.77 (0.89-3.44)	0.002	2.66[α] (1.44-4.63)	0.020
			1.58[µ] (0.96-4.05)	0.023

[α]: Adjusted for age, gender, ankle-brachial index, smoking, and diabetes mellitus, [µ]: Adjusted for age, gender, ankle-brachial index, D-dimer, and restenosis, CI: Confidence interval, DRR: De Ritis ratio, HR: Hazard ratio

Table 4: Cox multivariate analysis for predicting of all-cause, cardiac and non-cardiac mortality

	All-cause mortality			Cardiac mortality			Non-cardiac mortality		
	HR	(95% CI)	*P*-value	HR	(95% CI)	*P*-value	HR	(95% CI)	*P*-value
Female gander	1.78	1.24-3.62	0.039	1.55	0.51-3.62	0.669	1.44	0.76-2.77	0.418
Hypertension	2.55	1.98-4.78	0.076	2.27	1.23-4.01	0.034	2.09	1.44-3.68	0.311
Diabetes mellitus	1.79	0.87-2.88	0.224	1.03	0.48-1.71	0.020	0.97	0.55-3.67	0.032
Age	1.44	1.36-3.56	0.577	1.77	1.22-3.77	0.479	0.88	0.67-2.78	0.711
Smoking	0.21	0.15-1.06	0.709	0.78	0.56-1.79	0.088	2.35	1.66-4.75	0.041
hs-CRP	1.56	1.02-2.96	0.045	1.49	0.68-3.28	0.002	1.67	1.32-3.56	0.669
Hemoglobin	0.77	0.51-1.71	0.429	1.07	0.82-2.04	0.155	2.79	2.01-5.03	0.078

CI: Confidence interval, hs-CRP: High sensitivity C-reactive protein, HR: Hazard ratio

DISCUSSION

The present study examined the relationship between DRR levels during PTA and mid-term prognosis in patients with PAD. To the best of our knowledge, no studies have been conducted on this subject. Our results showed that higher DRR levels were significantly correlated with an increased risk of mid-term cardiac and all-cause mortality. This suggests that DRR may be a valuable tool for assessing the risk of adverse outcomes predicted by PAD.

The typical symptom of PAD is intermittent claudication in the lower limbs. It is characterized by muscle cramping, pain, and fatigue that occur during physical exertion and are typically relieved by rest. In patients with FPA, symptoms may occur in the buttock or thigh and generally correspond to the proximal level of occlusion. Medical approaches, PTA, and surgery are treatment options for FPA. Revascularization is the primary treatment option for lower extremity PAD. Endovascular intervention offers advantages over other treatment options; it is therefore increasingly recommended.[14]

Patients with symptomatic PAD have an increased risk of mortality. A meta-analysis of 16 studies involving 48,294 subjects found an association between ABI and mortality.[15] In the present study, an inverse correlation between ABI values and mortality was identified, which is consistent with the findings reported in previous literature. The higher risk of comorbidities, advanced age, and multiple organ failure in patients with low ABI may have led to an increased mortality rate.

Classic CV risk factors can affect all vascular beds and are associated with an increased risk of developing arterial disease. However, their effects vary among vascular beds.[16] PAD can be associated with other atherosclerotic diseases, such as coronary artery disease, carotid artery disease, and abdominal aortic aneurysms. Atherosclerosis is a chronic inflammatory vascular disease that affects the entire body. A significant connection exists between the immune system and inflammatory responses in the progression of atherosclerosis.[17] Recent studies have revealed that inflammation and lipid metabolism play important roles in PAD pathogenesis.[17] Masoudkabir et al.[18] showed that serum ALT and AST levels were independently associated with inflammatory conditions and subclinical atherosclerosis. This association remained independent of traditional CV risk factors and was positively correlated with the risk and severity of premature atherosclerotic disease. In addition, elevated hepatic transaminase levels indicate an increased burden of non-alcoholic fatty liver disease (NAFLD), liver fibrosis, and atherosclerotic disease.[19] In this respect, there is strong evidence of the "co-occurrence" of NAFLD, metabolic syndrome, and vascular disease. NAFLD is closely linked to classic coronary artery risk factors.[19,20] Zou et al.[21] demonstrated that NAFLD was linked to an elevated possibility of PAD following adjustment for demographic factors.

In our study, we found that inflammatory markers such as hs-CRP, D-dimer, and WBC increased with DRR in the non-survival group. These findings suggest that the DRR is an indicator of inflammatory responses. In addition, no significant differences were observed in the conventional risk factors for atherosclerotic CV disease among the groups. These results reveal the necessity for novel risk markers that extend beyond the traditional risk factors associated with PAD.

The liver accounts for only 2-3% of the total body weight but receives 25% of the cardiac output. The complex vascular system of the liver, combined with its high metabolic activity, increases its susceptibility to perfusion disorders, leading to several molecular and hemodynamic changes. Recent studies investigating the relationship between ALT and AST levels, AST/ALT ratio, and cardiac and all-cause mortality have yielded conflicting results. An analysis of the literature suggests that the DRR may predict adverse CV outcomes, particularly in selected patient groups. In contrast, a related study that concentrated on people aged ≥55 years found that ALT and AST were linked to death from all causes.[22] Furthermore, a recent meta-analysis that included information from over 9 million participants and 200,000 deaths found regional differences in the association between ALT levels and the risk of death from all causes in the general population, as well as a relatively weak relationship between AST levels and mortality.[23] In a 10-year follow-up cohort in the United Kingdom, Weng et al.[24] found an association between a high DRR and an increased risk of developing coronary artery disease in men. This association was not observed in women. In light of these findings, the authors recommended that DRR should not be included in CV disease risk prediction models for general primary care. In a long-term follow-up study in Japan, high DRR was determined to be an independent risk factor for CV mortality in the general population.[25] Similar results were obtained in 2529 DM outpatients who were followed up for 6 years. Increased DRR was significantly associated with an augmented risk of mortality from any cause and CV mortality.[26]

Liu et al.[27] analyzed data from 10,900 patients in the Chinese hypertension registry and revealed that the prevalence of PAD was 3.2%. Furthermore, the study indicated that DRR is independently associated with PAD risk, and that a DRR of ≥1.65 may be useful in identifying patients with high vascular risk.[27] In another study in which patients with PAD were followed for approximately 5 years, CV events were significantly higher in patients with DRR levels greater than 1.67.[28]

A recent study demonstrated a significant association between increased DRR and an elevated risk of all-cause mortality. We

also found that an optimal cut-off value of DRR ≥1.78 was a significant predictor of increased risk of cardiac and overall mortality in patients with PAD.

Study Limitation

This study has the following limitations. First, the study did not have a fixed follow-up period, which introduced variability and may have affected the accuracy of mortality estimates. The derived optimal DRR cut-off of 1.78 requires external validation in larger, independent cohorts. Its clinical utility is based on its reproducibility. Patients with chronic liver disease, hepatitis, and fatty liver disease were excluded. These conditions often coexist with CV disease; therefore, their exclusion may limit the study's applicability. Furthermore, the study was conducted at a single center and utilized a retrospective research design. The patient sample size was relatively small in this study. The duration of the subsequent period was comparatively brief.

CONCLUSION

The prevalence of PAD is increasing in tandem with the rise in patients exhibiting atherosclerotic risk factors and an aging population. Although many risk factors for PAD are similar to those of other atherosclerotic diseases, it is crucial to identify risk factors for disease progression and treatment. As patients with PAD have an elevated CV risk, the optimization of their treatment and/or different/stricter follow-ups are required. Furthermore, although DRR does not change the treatment approach, it can be considered an important new marker in patients with PAD. DRR is a simple and effective inflammation-related marker that can be used to determine future adverse CV events in patients with PAD. These findings indicate that an elevated DRR may be a manifestation of systemic conditions rather than isolated liver damage.

Ethics

Ethics Committee Approval: In addition, approval was obtained from the local Ethics Committee University of Health Sciences Türkiye, Kocaeli City Hospital (approval number: 2024-55, date: 13.06.2024).

Informed Consent: A signed informed consent form was obtained from each patient enrolled in the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: H.Ç.K., N.Z.B., Concept: H.Ç.K., Design: H.Ç.K., N.Z.B., Data Collection or Processing: N.Z.B., Analysis or Interpretation: H.Ç.K., Literature Search: H.Ç.K., Writing: H.Ç.K., N.Z.B.

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

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

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