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Research Article

Assessment of the Relationship Between JAK2 V617F Mutation Status and Plasma Viscosity in Polycythemia Vera Patients

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Abstract

Objectives: Polycythemia vera (PV) is a chronic myeloproliferative neoplasm characterized by the clonal proliferation of myeloid cells with variable morphologic maturity and hematopoietic efficiency. In this study, we aimed to evaluate the association between plasma viscosity, a potential risk factor for thrombotic complications, and the *JAK2* V617F mutation.

Methods: Patients were classified into two subgroups: *JAK2* V617F mutation-positive and *JAK2* V617F-negative patients. A total of 60 patients were enrolled in the study, of whom 31 were *JAK2* V617F-positive and 29 were negative. In addition, we evaluated fibrinogen, albumin, erythrocyte sedimentation rate, and C-reactive protein (CRP) levels.

Results: Plasma viscosity values in *JAK2* V617F mutation-positive patients and *JAK2* V617F mutation-negative patients were found to be 1.089±0.126 mPa·s and 1.098±0.111 mPa·s, respectively (p=0.782). There was no relationship between plasma viscosity levels and the *JAK2* V617F mutation in polycythemia vera. In correlation analyses, fibrinogen was correlated with plasma viscosity in both groups (r=0.30, r=0.15). In addition, the erythrocyte sedimentation rate was correlated with plasma viscosity in both groups (r=0.230, r=0.272).

Conclusion: We were unable to demonstrate a relationship between plasma viscosity and the *JAK2* V617F mutation in patients with polycythemia vera. This study shows that plasma viscosity is affected by fibrinogen and other acute-phase reactants.

Keywords: Plasma viscosity, *JAK2* V617F, fibrinogen, erythrocyte sedimentation rate, polycythemia vera

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Polycythemia vera is a chronic myeloproliferative disease that leads to an uncontrolled increase in red blood cell count and increased blood viscosity, resulting in a predisposition to thrombosis.[1] It was first described in the late 19th century and is primarily caused by mutations in the *JAK2* gene. Epidemiologically, PV predominantly affects adults over 60 years of age, with a slightly higher incidence in males.[2] According to the 2022 World Health Organization (WHO) diagnostic criteria, it is classified as a BCR-ABL1–negative myeloproliferative neoplasm.[3] Hemoglobin levels greater than 16.5 g/dL for men and greater than 16 g/dL for women, along with evidence of increased

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cellularity in the erythroid lineage from a bone marrow biopsy and the presence of the *JAK2* V617F mutation, are recognized as key diagnostic criteria.[4]

The *JAK2* V617F mutation is crucial in PV as it leads to the constant activation of the JAK-STAT signaling pathway, which in turn encourages unchecked proliferation of hematopoietic cells.[5] Plasma viscosity, a measure of the blood's resistance to flow, is clinically relevant in PV, as elevated viscosity contributes to vascular complications and impaired microcirculation. Studies on blood viscosity in patients with polycythemia vera (PV) have shown elevated levels compared to healthy individuals, reflecting increased blood cell mass and altered plasma composition.[6]

A substitution of valine for phenylalanine at position 617 characterizes the *JAK2* V617F mutation, leading to the persistent stimulation of the JAK-STAT cascade. This mutation is found in approximately 95% of PV patients and is a key indicator for diagnosis.[7]

Plasma viscosity refers to the thickness and stickiness of plasma, which affects its flow properties in the circulatory system. It is typically measured using viscometers that assess the resistance of the plasma to flow under controlled conditions.[8]

In a subset of PV patients, the *JAK2* V617F mutation was absent. Our research involved measuring plasma viscosity in individuals diagnosed with PV based on the WHO 2008 criteria who lacked the *JAK2* V617F mutation, and these findings were compared to those of patients possessing the *JAK2* V617F mutation.

This study sought to elucidate the relationship between the existence of the *JAK2* V617F mutation and changes in plasma viscosity among patients diagnosed with PV. Understanding this relationship is crucial because plasma viscosity plays a significant role in the pathophysiology of PV and its associated thrombotic risks. By investigating these factors, this study seeks to contribute valuable insights that may improve the clinical management and prognostic assessment of PV cases.

Materials and Methods

Patients and Ethical Approval

Individuals diagnosed with PV according to the updated 2008 WHO diagnostic criteria at our outpatient clinic were included in the study. Since plasma viscosity could be affected by several conditions, the exclusion criteria were defined as a history of smoking, coronary artery disease, hyperlipidemia, peripheral arterial disease, oral contraceptive use, diabetes mellitus, and the presence of other malignancies.

Before participating in the study, all patients and their legally authorized representatives provided written informed consent. The duration since PV diagnosis was not considered during patient enrollment. The study involved 60 patients who were categorized into two groups based on whether they tested positive or negative for the *JAK2* V617F mutation. Plasma viscosity measurements obtained from both groups were compared.

The Ethics Committee of Ankara University Faculty of Medicine received the study protocol and granted approval on April 4, 2013, under decision number KA13/70 Approval Date 04/04/2013.

The viscosity of plasma was determined using a Brookfield DV-II+ cone-plate viscometer (Brookfield, Stoughton, MA, USA). To ensure sample homogeneity, fasting blood samples were obtained from each patient simultaneously in the morning. Anticoagulant tubes were utilized to collect 5 mL of whole blood samples, which were subsequently subjected to a 5-minute centrifugation process at 3,000 rpm. The plasma was then separated and stored at –40 °C. On the day of analysis, all samples were simultaneously thawed. Immediately before measurement, the samples underwent another round of centrifugation at 3,000 rpm for 2.5 minutes.

The viscosity of the plasma samples was measured at 37 °C using a viscometer calibrated with distilled water, according to a water viscosity value of 0.68 mPa·s. Alongside measuring plasma viscosity, evaluations were conducted on serum levels of C-reactive protein (CRP), fibrinogen, erythrocyte sedimentation rate (ESR), high-density lipoprotein (HDL), low-density lipoprotein (LDL), total protein, albumin, and complete blood count parameters. These parameters were compared between the two groups based on the status of the *JAK2* V617F mutation, and their effects on plasma viscosity were evaluated.

We identified the *JAK2* V617F mutation in our patients through the use of real-time polymerase chain reaction (PCR).

Statistical Analysis

Data analysis was conducted using the Statistical Package for the Social Sciences (SPSS) for Windows, Version 16.0 (IBM SPSS Inc., Chicago, IL, USA). In the descriptive statistics, categorical variables were represented as counts and percentages, continuous variables with a normal distribution were shown as mean ± standard deviation, and those without a normal distribution were described using median and range values.

To evaluate pairs of data, the independent samples t-test was utilized for parametric distributions, whereas the Mann–Whitney U test was employed for non-parametric ones. In terms

of correlation analysis, Pearson's correlation coefficients were applied to parametric variables, while Spearman's correlation coefficients were used for non-parametric variables.

Results

Demographic Findings

This study involved 60 individuals who had been diagnosed with PV. The *JAK2* V617F mutation was positive in 31 patients and negative in 29 patients. The overall mean age of the patients was 57±17.9 years. The mean age was 70±10.6 years in the *JAK2* V617F mutation–positive group and 44±14.3 years in the *JAK2* V617F mutation–negative group (p<0.001).

In terms of gender distribution, there were 24 female patients, accounting for 40%, and 36 male patients, making up 60%. Among those with the *JAK2* V617F mutation, 19 out of 31 patients were female, representing 59%, while 12 were male, comprising 41%. Conversely, in the group without the *JAK2* V617F mutation, 24 of the 29 patients were male, which is 87%, and 5 were female, equating to 13% (Table 1).

Table 1. Patients age, sex and cytoreductive therapy status

	JAK2 V61F(+) n=31	JAK2 V617F(-) n=29
Sex (M/F)	12 (39%)/19 (61%)	24 (83%)/5 (17%)
Age (Years)	70±10.63	44.3±14.3
Cytoreductive therapy (receiving/not receiving)	27 (87.1%) / 4 (12.9%)	1 (3.4%)/28 (96.6%)

The number of patients who received cytoreductive therapy for PV was 28 (46.7%), while 32 (53.3%) did not. In the *JAK2* V617F mutation–positive group, 27 of 31 patients (87.1%) were receiving treatment. In contrast, only one of 29 patients (3.4%) in the *JAK2* V617F mutation–negative group was receiving treatment (p<0.001). Among the 28 patients receiving cytoreductive therapy, hydroxyurea was used in 22 patients, anagrelide in 4 patients, and hydroxyurea plus anagrelide in 2 patients.

Plasma Viscosity and Other Parameters

In our research, we utilized an independent samples t-test to compare plasma viscosity measurements between the two groups. The mean plasma viscosity was 1.089±0.12 mPa·s in the *JAK2* V617F mutation–positive group and 1.098±0.11 mPa·s in the *JAK2* V617F mutation–negative group. The two groups did not show any statistically significant differences (p=0.782) (Fig. 1).

Comparison of fibrinogen levels, which are known to affect plasma viscosity, revealed no significant differences between the groups (p=0.091). In the group without the *JAK2* V617F mutation, total protein levels were notably elevated (p=0.022). However, there was no statistically significant difference in albumin levels between the groups (p=0.078). Similarly, HDL and LDL levels did not show significant differences between the two groups (HDL:p=0.520; LDL:p=0.276). The difference in erythrocyte sedimentation rate (ESR) was also not statistically significant (p=0.382). However, in the group with the *JAK2* V617F mutation, C-reactive protein (CRP) levels were notably elevated (p=0.014).

Table 2. Laboratory results according to JAK2 V617F status

Parameters	JAK2 V617F (+)	JAK2 V617F (–)	p	Reference range
Plasma viscosity (mPa·s)	1.089±0.126	1.098±0.111	0.782	1.15–1.35 mPa·s
Hemoglobin (g/dL)	15.8±2.58	17.83±1.34	**0.001**	12–16 g/dL
Hematocrit (%)	48.5±7.64	53.4±3.38	**0.002**	34–45%
Leukocyte count (/µL)	11.160±5.660	9.260±3.110	0.117	4,000–10,000 /µL
Platelet count (/µL)	401.900±20.100	304.000±11.190	**0.025**	150,000–400,000 /µL
C-reactive protein (CRP) (mg/L)	5.5±1.16	2.37±0.35	**0.014**	0–5 mg/L
Fibrinogen (mg/dL)	327±77	296±62	0.091	190–400 mg/dL
High-density lipoprotein (HDL) (mg/dL)	45.1±8.3	46.6±9.9	0.520	40–60 mg/dL
Low-density lipoprotein (LDL) (mg/dL)	101±26.1	108±27.1	0.276	55–160 mg/dL
Total protein (g/dL)	7.16±0.50	7.41±0.30	**0.022**	6.0–8.7 g/dL
Albumin (g/dL)	4.02±1.20	4.10±0.89	0.078	3.5–5.0 g/dL
Erythropoietin (mIU/mL)	2.08±1.48	2.98±1.47	**0.022**	5–16 mIU/mL
Erythrocyte sedimentation rate (ESR) (mm/h)	8.41±6.60	6.92±6.37	0.382	0–20 mm/h

ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; HDL: High-density lipoprotein; LDL: Low-density lipoprotein.

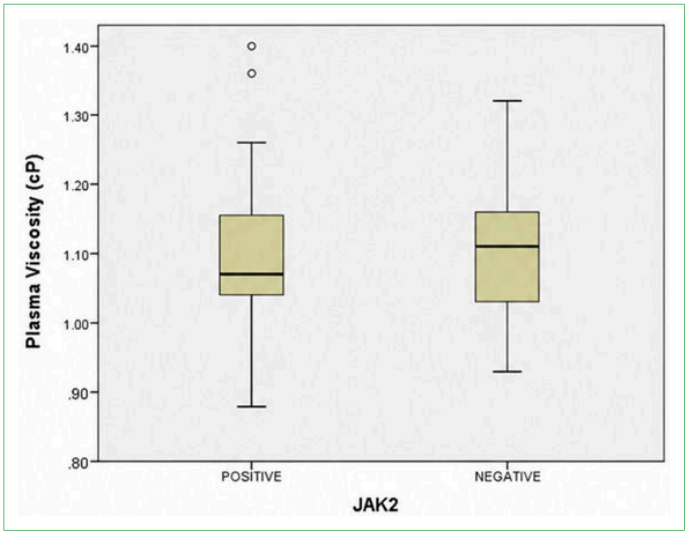


Figure 1. Comparison of plasma viscosity levels according to JAK2 V617F mutation status (p=0.782).

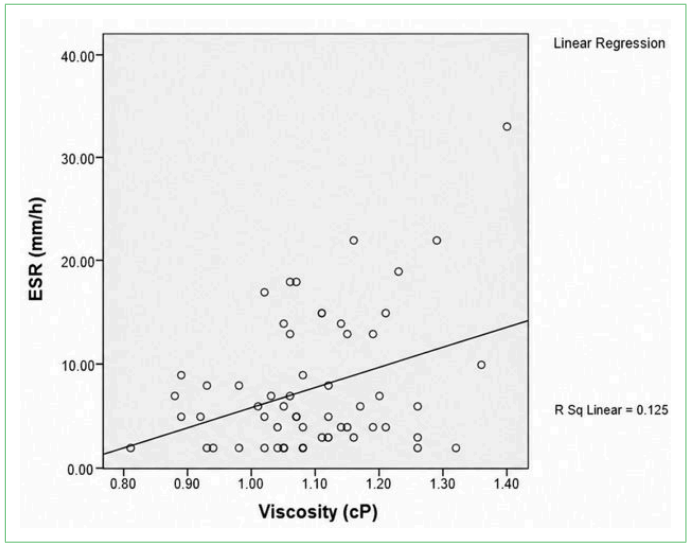


Figure 2. Positive correlation between ESR values and plasma viscosity in both groups (r=0.219).

In the group with the *JAK2* V617F mutation, erythropoietin (EPO) levels were notably lower compared to the group without the mutation (p=0.022) (Table 2).

Hemoglobin and hematocrit levels were higher in the mutation–negative group. However, the number of patients receiving cytoreductive therapy was significantly higher in the mutation-positive group (p<0.001). No significant difference was observed in leukocyte counts between the two groups (p=0.117). In contrast, the group with the mutation exhibited a notably increased platelet count (p=0.025). EPO measurements were lower in the *JAK2* V617F-positive group than the negative group (p=0.022).

In our study, the correlations between plasma proteins, CRP, ESR values, and plasma viscosity were evaluated (Fig. 2). Correlation analyses were performed between plasma viscosity and the variables within each group, and the relationships were assessed according to the correlation coefficient (r).

Fibrinogen levels were moderately correlated with plasma viscosity in the mutation-positive group (r=0.30). In the mutation-negative group, the correlation with plasma viscosity was weaker (r=0.150). ESR values were moderately correlated with plasma viscosity in both groups (r=0.23 and r=0.272, respectively).

There was no notable relationship found between LDL and HDL levels and plasma viscosity in either group (for LDL:r=-0.115 and r=0.02, respectively; for HDL:r=0.08 and r=-0.170, respectively). Total protein levels in the mutation-positive group indicated a moderate correlation with plasma viscosity (r=0.293). Similarly, albumin levels in the mutation-positive group were moderately correlated with

Table 3. Correlation of variables with plasma viscosity according to JAK2 V617F mutation status

Variables	JAK2 V617F (+)		JAK2 V617F (-)	
	r	p	r	p
Parametric variables				
HDL	0.08	0.968	-0.170	0.328
Fibrinogen	**0.30**	0.876	0.150	0.437
Total Protein	**0.293**	0.115	0.122	0.528
Albumin	**0.236**	0.135	0.132	0.456
Non-parametric variables				
CRP	-0.170	0.368	0.095	0.311
LDL	-0.115	0.262	0.120	0.533
ESR	**0.230**	0.903	**0.272**	0.153

ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; HDL: High-density lipoprotein; LDL: Low-density lipoprotein.

plasma viscosity (r=0.236) (Table 3). CRP levels demonstrated only a weak correlation with plasma viscosity in both groups (r=0.170 and r=0.095).

Discussion

It is well established that whole blood viscosity is increased in patients with PV, and this increase is associated with a higher incidence of thromboembolic complications. Unlike whole blood viscosity, plasma viscosity is not affected by parameters such as hematocrit, hemoglobin, leukocyte count, or platelet count. In contrast, plasma viscosity is more closely associated with inflammation and elevated plasma protein levels.[9]

Increased plasma viscosity is considered an important predictor of cardiovascular events in patients with hyperviscosity syndrome.[10] Elevated blood viscosity predominantly leads to stasis within the capillary beds and veins, characterized by a low blood flow velocity.

The *JAK2* V617F mutation negatively impacts the outlook for patients with PV. In a study conducted by Vannucchi et al.[11] involving 173 PV patients, *JAK2* V617F mutation positivity was associated with increased hematocrit and leukocyte counts, whereas platelet counts were decreased. However, approximately 5–10% of patients diagnosed with PV do not harbor this mutation after secondary causes of polycythemia have been excluded from consideration. Our study aimed to explore whether there is a difference in plasma viscosity between individuals with the *JAK2* V617F mutation and those without it, as the current literature offers limited data on this topic.

Our research found that the *JAK2* V617F mutation did not correlate with higher plasma viscosity when compared to patients without the mutation. Nevertheless, *JAK2* mutation positivity is associated with increased whole blood viscosity. In a meta-analysis published in 2024 by Chen et al.[12], patients harboring this mutation, particularly those with a high mutant allele burden, were found to have an increased risk of thrombosis, splenomegaly, myelofibrosis, and acute myeloid leukemia. Although our findings demonstrated no effect of mutation positivity on plasma viscosity, the clinical differences observed in mutation-positive patients are more likely attributable to increased whole blood viscosity.

Although we did not demonstrate an increase in plasma viscosity according to the *JAK2* V617F mutation status, other biochemical markers known to affect plasma viscosity were also evaluated in this study. One of these parameters is fibrinogen. The groups did not show any notable differences in fibrinogen levels. However, a positive relationship between fibrinogen and plasma viscosity was demonstrated. Similarly, erythrocyte sedimentation rate (ESR) values were evaluated, and no significant differences were found between the groups. Nevertheless, similar to fibrinogen, ESR demonstrated a positive correlation with plasma viscosity. These findings are consistent with previously established knowledge. Based on these results, it may be suggested that plasma viscosity is influenced more by acute-phase reactants such as fibrinogen and ESR rather than by the mutation status. Fibrinogen is known to increase erythrocyte aggregation and plasma viscosity.[13] Therefore, rather than mutation positivity alone, conditions associated with elevated plasma protein levels, such as chronic infections, smoking, and hypercholesterolemia, should be more carefully managed and treated in this patient population.

We also evaluated the complete blood count parameters in our study. The group with the mutation had lower hematocrit levels compared to the group without the mutation. Platelet counts were lower in the mutation-positive group. Under normal circumstances, patients with *JAK2* V617F mutation positivity are expected to exhibit higher hematocrit levels, and the mutant allele burden is known to play an important role in this association.[14] Therefore, these findings were not unexpected in our study, since 87% of mutation-positive patients had received cytoreductive therapy for PV, whereas this rate was only 3.4% among the mutation-negative patients. Most mutation-negative patients were primarily managed with phlebotomy alone.

Our study has some limitations. The study included patients who were diagnosed based on the 2008 WHO guidelines, which were valid at the time of the study. Currently, the 2022 WHO criteria are used for the diagnosis of PV, and bone marrow biopsy is considered a major diagnostic criterion. In patients diagnosed during the study period, secondary causes of polycythemia were excluded as thoroughly as possible from the study. In particular, erythropoietin levels were given greater consideration when establishing the diagnosis in mutation-negative patients. Although the current literature investigating the relationship between mutation positivity and plasma viscosity remains limited, it should also be noted that this study was conducted several years ago.

Conclusion

In conclusion, plasma viscosity did not vary according to the presence of the *JAK2* V617F mutation in our study. Although whole blood viscosity is known to increase in patients with PV, particularly in the presence of the *JAK2* V617F mutation due to erythroid lineage expansion, no significant alterations in plasma viscosity were observed. Plasma viscosity is predominantly influenced by plasma proteins and acute-phase reactants. Therefore, in this pa-

tient population, which already exhibits increased whole blood viscosity, factors that may promote inflammation and elevate acute-phase reactants should be avoided in treatment.

This research focused on examining the connection between the *JAK2* V617F mutation and plasma viscosity in individuals with PV. Plasma viscosity showed no correlation with the presence of *JAK2* V617F positivity. An increase in acute-phase reactants results in increased plasma viscosity. Elevations in ESR and fibrinogen levels lead to an increase in plasma viscosity. Plasma viscosity can act as an acute-phase reactant and serves as a significant risk factor for thrombotic events in patients with PV. During PV, conditions such as infection, inflammation, tissue injury, burns, and trauma may facilitate the development of thrombotic events.

Disclosures

Ethics Commitee Approval: The Ethics Committee of Ankara University Faculty of Medicine received the study protocol and granted approval on April 4, 2013, under decision number KA13/70 Approval Date 04/04/2013.

Conflict of Interest: All authors declare that there is no conflict of interest.

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Research Article

Retrospective Evaluation of Gastroscopic Findings in Colon Cancer Patients and Colonoscopic Findings in Gastric Cancer Patients

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Abstract

Objectives: The aim study is to detect gastroscopic lesions in colon cancer patients and colonoscopic lesions in gastric cancer patients.

Methods: This study is a single-center retrospective study. 101 colon cancer and 53 gastric cancer patients were included in the study. In colon cancer control group, 115 patients were selected who applied colonoscopy with no malignancy result. And in gastric cancer control group, 112 patients were selected who applied gastroscopy with no malignancy result.

Results: We observed colon cancer in 2 (%3,8) patients and totally 22 colon polyps in 13 (%24,5) patients from 53 gastric cancer patients. There was no colon cancer diagnosis and totally 36 colon polyps found in 27(%24,1) in control group (n=1l 2) patients. There was no statistically significance in both groups about the number and adenomatous polyps ratio (p>0.05). In colon cancer group (n=10l), 1 (%1) patient had severe dysplasia and 10(%9,9) patients had gastric polyp; but in control group (n=115), there was 1 (%0,8) mild dysplasia and 11(%9,6) gastric polyp. There was no statistically significance in both groups about the number and adenomatous of polyps.

Conclusion: We found no statistically significant difference between the groups. Prospective studies are needed for second primary cancer investigations.

Keywords: Gastric cancer, colon cancer, polyp, gastroscopy, colonoscopy

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Colorectal cancers are the third most common cancer worldwide, accounting for 10% of all cancer cases.[1,2] Gastric cancer is the sixth most common and the fourth leading cause of death. The presence of any primary malignancy predisposes a patient to an increased risk of developing secondary cancers in other regions. This clinical observation remains valid for both gastric and colon cancers. In regions with a high prevalence of gastric cancer, numerous studies have been conducted to facilitate both the early detection of this malignancy and the identification of potential second primary cancers. Efforts to find common etiological factors and establish cancer screening programs have been the focus of many studies to date.

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First described by Billroth in 1889, the definition of multiple primary cancers is used for cases where there are two or more primary cancers of origin with variations, without recurrence, metastasis or extension. Currently, the diagnostic criteria established by Warren and Gates are employed for the identification of second primary cancers. Accordingly, it is based on the histological determination of both tumors as the same tumor.[3] Numerous retrospective studies have reported a coexistence of colorectal and gastric cancers. Recognizing this association underscores the necessity of considering additional malignancies in patients undergoing cancer treatment. In a study conducted in South Korea, Oh et al.[4] investigated the presence of colon cancer in 105 patients with gastric carcinoma, identifying adenomatous polyps in 22.9% and colorectal adenocarcinoma in 9.5% of the cohort. Similarly, another study by Park et al.[5] examined the prevalence of colorectal cancer development in patients with gastric carcinoma; colorectal cancer was detected in 9% (3.5%) of 543 patients, while colonic adenomas were reported in 215 of these patients (39.6%).

Studies have been conducted not only with patients with gastric cancer but also with patients with colon cancer, and the frequency of gastric cancer in colon cancer patients has been investigated. In a study conducted by Lim et al.[6] in Korea in 2008, 1542 colorectal cancer patients were included in the study, and synchronous gastric carcinoma was detected in 31 (2.0%) of them. Of these detected gastric carcinoma patients, 26 (83.9%) were reported as having early stage and 5 as having advanced gastric carcinoma.

In addition to investigations into carcinomas within the gastrointestinal system, the presence of precancerous lesions has been the subject of numerous studies to date.[7-10] Patients with gastric mucosal non-malignant polyps have a significantly higher incidence of colon polyps compared to the primary control group, which supports the idea that gastric polyps are a risk factor for colon polyps.[11]

Although there is no implemented health policy in our country regarding the possibility of other gastrointestinal malignancies in colon and stomach cancer patients and the need for screening, there is a need for research on this subject, which is being investigated worldwide, and for studies to be conducted in our country to establish endoscopic screening programs.

Methods

The records of patients who applied to the endoscopy unit of the Gastroenterology Department at Ondokuz Mayıs University Faculty of Medicine between January 2006 and December 2011 were examined.

Patients diagnosed with colon cancer who underwent gastroscopy and those diagnosed with gastric cancer who underwent colonoscopy were identified. Patients whose phone numbers could be reached were included in the study. 53 gastric cancer patients who underwent colonoscopy and 101 colon cancer patients who underwent gastroscopy were included in the study. Patients' gender, age at diagnosis, comorbid diabetes, history of cholecystectomy, smoking and alcohol habits were all investigated. The study included patients whose histopathology revealed gastric and colon adenocarcinoma. Patients with colon and gastric cancer whose pathology revealed lymphoma, gastrointestinal stromal tumor, or neuroendocrine tumor, as well as patients with FAP, Peutz-Jeghers syndrome, ulcerative colitis, and Crohn's disease, were excluded. For both groups, non-cancer patients aged 18-83 years were selected to match the patient's age. 115 colon cancer patients served as the control group, and 112 gastric cancer patients served as the control group.

This study is a retrospective study conducted after written consent was obtained from the Ondokuz Mayıs University Faculty of Medicine Clinical Research Ethics Committee. Ethics committee approval number is B.30.2.ODM.0.20.08/965. The study was conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

The data obtained from the research were transferred to the computer and analyzed using SPSS version 15 (SPSS, Chicago, IL, USA). Descriptive characteristics of the data were expressed as mean, standard deviation, number, and percentage. Normality tests were performed for all measurement variables in the statistical analyses. Paired t-test was applied to the measurement variables that had a normal distribution, and Mann-Whitney U test was applied to those that did not conform to a normal distribution. Risk factors were evaluated with chi-square analysis, and the statistical significance level was accepted as $p<0.05$. Risk factors were evaluated using chi-square analysis, and the statistical significance level was accepted as $p<0.05$.

Results

Of the 53 patients with gastric cancer, 15 (28.3%) were female and 38 (71.7%) were male (Table 1). Twenty (37.7%) of the 53 patients were in the 60-70 age range, and 79.2% were over 50 years of age (Table 2). The mean age was 56.4±12.9 years for the 15 female patients and 59.3±12.3 years for the 38 male patients in the gastric cancer group, with no significant difference observed between them. Regarding habits, 54.7% of the patients with gastric cancer were smokers and 15.1% consumed alcohol. In the control group, the smoking rate was 29.5% ($p<0.05$). Additionally,

Table 1. Demographic characteristics of gastric cancer patients and control groups

Gastric cancer	Patient group n (%)	Control group n (%)	p
Gender			
Female	15 (28.3)	63 (56.3)	>0.05
Male	38 (71.7)	49 (43.8)	
Age			
Mean ± SD	58.5±12.5	55.2±16.0	>0.05
Diabetes	6 (11.3)	16 (14.3)	>0.05
Smoking	29 (54.7)	32 (29.5)	0.02
Alcohol	8 (15.1)	12 (10.7)	>0.05
Cholecystectomy	2 (3.8)	8 (7.1)	>0.05

6% of the patients had diabetes, and only 3.8% had undergone gallbladder surgery prior to the diagnosis of gastric cancer (Table 1). Aside from smoking, there were no significant differences between patient and control groups in terms of diabetes, cholecystectomy, and alcohol consumption. Of the 53 patients, 79.2% were stages III and IV, with gastric cancer most frequently detected in stage IV in both sexes. Furthermore, stage IV gastric cancer was most common in those over 50 years of age (59.5%) (Table 3). No significant association was found between diabetes, smoking, alcohol, cholecystectomy, and gastric cancer stages (p>0.05). Although stage IV gastric cancer was more common in those over 50, no statistically significant difference was found when compared to those under 50. In patients with stage III and stage IV gastric cancer, both nonneoplastic lesions and colon cancer were more common than in patients with stage I and stage II gastric cancer, but the difference was not statistically significant (Table 4). When the relationship between the histological type of gastric cancer and colon lesions was examined, nonneoplastic lesions and colon adenomas were more frequently observed in intestinal type gastric cancer, and the second primary colon cancer was more frequently observed in diffuse type gastric cancer (7.7%) (p>0.05) (Table 5).

Gastric cancer was most frequently observed in the distal stomach at a rate of 43.4%, with the frequency decreasing towards the proximal part of the stomach. Intestinal type gastric cancer was observed in 33 (62.3%) of the patients, and an increase in the frequency of intestinal type gastric cancer was detected towards the distal part (Table 6).

In both sexes, gastric cancer predominantly involved the distal part of the stomach. Intestinal type was the most

Table 2. Distribution of colon and gastric cancer by decade

Decade	Gastric cancer n (%)	Gastric cancer control n (%)	Colon cancer n (%)	Colon cancer control n (%)
<40	4 (7.6)	23 (20.6)	9 (8.8)	26 (22.6)
40–49	7 (13.2)	21 (18.8)	12 (11.9)	32 (27.8)
50–59	15 (28.3)	20 (17.8)	24 (23.8)	23 (20.0)
60–69	20 (37.7)	22 (19.6)	26 (25.7)	19 (16.5)
70–79	5 (9.4)	20 (17.8)	25 (24.8)	11 (9.6)
>80	2 (3.8)	6 (5.4)	5 (5.0)	4 (3.5)

Table 3. Demographic characteristics according to gastric cancer stages

	Stage I n (%)	Stage II n (%)	Stage III n (%)	Stage IV n (%)	p
Gender					
Female	2 (33.3)	1 (20.0)	3 (21.4)	9 (32.1)	>0.05
Male	4 (66.7)	4 (80.0)	11 (78.6)	19 (67.9)	
Age					
<50	2 (33.3)	2 (40.0)	4 (28.6)	3 (10.7)	>0.05
>50	4 (66.7)	3 (60.0)	10 (71.4)	25 (89.3)	
Diabetes	1 (16.7)	0 (0)	2 (14.3)	3 (10.7)	>0.05
Smoking	4 (66.7)	3 (60.0)	7 (50.0)	15 (53.6)	>0.05
Alcohol	2 (33.3)	1 (20.0)	1 (7.1)	4 (14.3)	>0.05
Cholecystectomy	0 (0)	0 (0)	2 (14.3)	0 (0)	>0.05

Table 4. Colonoscopy findings according to stages in the gastric cancer patient group

	Non-neoplastic n (%)	Adenoma n (%)	Cancer n (%)	Other n (%)	Normal n (%)	p
Stage I	1 (7.7)	1 (9.1)	0 (0)	0 (0)	4 (11.8)	>0.05
Stage II	2 (15.4)	0 (0)	0 (0)	1 (33.3)	2 (5.9)	>0.05
Stage III	2 (15.4)	3 (27.3)	1 (50.0)	1 (33.3)	9 (26.5)	>0.05
Stage IV	8 (61.5)	7 (63.6)	1 (50.0)	1 (33.3)	19 (55.8)	>0.05

Table 5. Histopathology of lesions detected during colonoscopy according to gastric cancer type

	Non-neoplastic n (%)	Adenoma n (%)	Cancer n (%)	Other n (%)	Normal n (%)	p
Diffuse type	2 (15.4)	0 (0)	1 (7.7)	1 (7.7)	9 (69.2)	>0.05
Intestinal	9 (24.4)	5 (13.5)	1 (2.7)	0 (0)	22 (59.4)	>0.05
Other	2 (15.4)	6 (46.1)	0 (0)	2 (15.4)	3 (23.1)	>0.05

Table 6. Relationship between gastric cancer localization and cancer histology

	Diffuse infiltrative type n (%)	Intestinal type n (%)	Other n (%)	Total n (%)	p
Proximal stomach	4 (30.8)	9 (69.2)	0 (0)	13 (100)	>0.05
Gastric corpus	5 (29.4)	8 (47.1)	4 (23.5)	17 (100)	>0.05
Distal stomach	4 (17.4)	16 (69.6)	3 (13.0)	23 (100)	>0.05

common histological type in both sexes, more frequent in male patients. While no significant relationship was found between histological type and gender, the occurrence of intestinal type gastric cancer in those over 50 years of age was significant (p=0.01) (Table 7). In 62.3% of colonoscopies performed on gastric cancer patients, the cecum was reached, while in the entire control group, the cecum was reached. Colonoscopies were performed on patients as early as 1 month and as late as 180 months after diagnosis, with an average of 12.3 months after the diagnosis of gastric cancer. Thirteen adenomas were detected in 11 of 53 patients, all of whom were over 50 years old. Benign lesions and adenomas were more frequently found in male patients. Of the 5 patients in whom malignant lesions were detected during colonoscopy, 3 were female and under 50 years of age (Table 8).

Colon cancer was detected in 2 out of 53 patients (3.8%), and in both cases the tumor was localized to the rectum. The patient who was diagnosed with colon cancer during a colonoscopy performed within 1 month of a gastric cancer diagnosis was a 68-year-old male with stage IV gastric cancer. In another patient, colon cancer was detected during a colonoscopy performed 48 months after a diagnosis of stomach cancer; this was a 40-year-old woman with stage III stomach cancer. The other three patients with malignancy in the colon had rectal metastases of stomach cancer. Compared to the control group, 61.3% of the gastric cancer patient group and 75.0% of the control group had no pathology on colonoscopy (p>0.05) (Table 9). In the gastric cancer patient group, one patient had both neoplastic and nonneoplastic colon polyps. When both groups were compared in terms of neoplastic and nonneoplastic polyps, no statistically significant difference was found between them. Although colon cancer and ulcerative colitis were more common in the gastric cancer patient group, there was no significant difference between them (p>0.05) (Table 9).

Regarding the distribution of colonic lesions, the number of adenomas was higher in the control group. However, compared to the patient group, adenomas in the right colon were detected more frequently in the control group than in the gastric cancer group (p=0.03). In the gastric cancer patient group, non-neoplastic lesions in the right colon were more prevalent than in the control group, and this difference was statistically significant (p<0.009). Colon cancer was detected only in patients with gastric cancer and was not observed in the control group. Furthermore, both the metastasis and the second primary colon cancer were found to be located in the left colon (Table 10). Colonic polyps were detected in 13 (24.5%) of the 53 patients with gastric cancer, and a total of 22 polypectomies were performed in these 13 patients. In the control group, polypectomies were performed on a total of 36 polyps in 27 patients. When compared in terms of the number of colonic polyps, a maximum of 3 polyps were detected in both

Table 7. Demographic characteristics according to gastric cancer type

	Diffuse type n (%)	Intestinal type n (%)	Other n (%)	p
Gender				
Female	5 (41.7)	6 (18.8)	4 (44.4)	>0.05
Male	7 (58.3)	26 (81.2)	5 (55.6)	
Age				
<50	6 (50.0)	**3 (9.4)**	2 (22.2)	**=0.01**
>50	6 (50.0)	**29 (90.6)**	7 (77.8)	
Diabetes mellitus	4 (33.3)	2 (6.3)	0 (0)	>0.05
Smoking	5 (41.7)	20 (62.5)	4 (44.4)	>0.05
Alcohol	2 (16.7)	5 (15.6)	1 (11.1)	>0.05
Cholecystectomy	2 (16.7)	0 (0)	0 (0)	>0.05

Table 8. Colonoscopy findings in gastric cancer patients

	Normal n (%)	Benign lesion n (%)	Adenoma n (%)	Malignant lesion n (%)
Total	33 (62.3)	8 (15.1)	7 (13.2)	5 (9.4)
Age				
<50	6 (18.2)	1 (12.5)	0 (0)	4 (80.0)
>50	27 (81.8)	7 (87.5)	7 (100)	1 (20.0)
Gender				
Female	10 (30.3)	0 (0)	2 (28.6)	3 (60.0)
Male	23 (69.7)	8 (100.0)	5 (71.4)	2 (40.0)
Smoking	19 (57.6)	7 (87.5)	4 (57.1)	0 (0)
Alcohol	6 (18.1)	2 (25.0)	0 (0)	0 (0)
Diabetes mellitus	5 (15.1)	1 (12.5)	0 (0)	0 (0)
Cholecystectomy	1 (3.0)	0 (0)	0 (0)	1 (20.0)

Table 9. Colonoscopy findings of gastric cancer patients and control group

Gastric cancer	Patient group n (%)	Control group n (%)	p
Polyp			
Non-neoplastic	7 (13.2) *	10 (8.9)	>0.05
Neoplastic	7 (13.2) *	15 (13.4)	>0.05
Cancer	2 (3.8)	0 (0)	>0.05
Ulcerative colitis	2 (3.8)	1 (0.9)	>0.05
Other	4 (7.5)	2 (1.8)	>0.05
No pathology detected	33 (62.3)	84 (75.0)	>0.05

*n: Number of patients: 1 patient has both nonneoplastic and neoplastic polyps.

groups; 1 polyp was identified in 11.3% of the gastric cancer patients and 17.8% of the control group (Table 11). However, there was no statistically significant difference. Regarding polyp size, all colonic polyps in both the gastric cancer and control groups were under 1 cm, and no significant difference was observed in terms of polyp size (Table 11). Ulcerative colitis limited to the rectum was identified in 2 (3.8%) of the 53 patients. Additionally, colonic metastasis of gastric cancer was detected in 3 (5.7%) of the 53 patients, all three of which had metastasized to the rectum. Of the 101 colon cancer patients, 40 (39.6%) were women and 61 (60.4%) were men (Table 12). Thirty (29.8%) of the 101 patients were over 70 years old, and 21 (20.7%) were under 50 years old (Table 2). Colon cancer was most common in the sixth decade, but occurred with almost equal frequency in decades after age 50. Sixty-fourth (64.4%) of the 101 patients were in stages 3 and 4, occurring in equal proportions. Forty-one (40.6%) of the patients were smokers and 15 (14.9%) were alcohol users. 14.9% of the patients were diabetic and only 8.9% had undergone gallbladder surgery before being diagnosed with colon cancer (Table 12). There were no significant differences between the colon cancer

Table 10. Location of pathological findings detected by colonoscopy in gastric cancer patients and control groups (n: number of lesions in the colon)

	Gastric cancer patient group n (%)*	Control group n (%)*	p
Left colon			
Benign	3 (10.3%)	9 (24.3%)	>0.05
Adenoma	7 (24.1%)	13 (35.1%)	>0.05
Cancer	2 (6.8%)	0 (0%)	>0.05
Other	6 (20.7%)	3 (8.2%)	>0.05
Right colon			
Benign	7 (24.1%)	1 (2.7%)	=0.009
Adenoma	4 (14.0%)	10 (27.0%)	=0.03
Cancer	0 (0%)	0 (0.0%)	>0.05
Other	0 (0%)	1 (2.7%)	>0.05

Table 11. Number and size of polyps detected during colonoscopy in gastric cancer patients and control groups

	Gastric cancer patient group	Gastric cancer control group	p
No polyps	40 (75.5%)	85 (75.9%)	p>0.05
1 polyp	6 (11.3%)	20 (17.8%)	p>0.05
2 polyps	5 (9.4%)	5 (4.5%)	p>0.05
3 polyps	2 (3.8%)	2 (1.8%)	p>0.05
Polyp size (cm) Mean ± SD	0.25±0.32	0.15±0.35	p>0.05

SD: Standard deviation.

Table 12. Demographic characteristics of colon cancer patients and control groups

	Colorectal cancer patient group n (%)	Control group n (%)	p
Gender			
Female	40 (39.6%)	65 (56.5%)	p>0.05
Male	61 (60.4%)	50 (43.5%)	
Age			
Mean ± SD	60.4±14.1	50.7±15.52	p=**0.001**
Diabetes mellitus	15 (14.9%)	10 (8.7%)	p>0.05
Smoking	41 (40.6%)	35 (30.4%)	p>0.05
Alcohol	15 (14.9%)	12 (10.4%)	p>0.05
Cholecystectomy	9 (8.9%)	4 (3.5%)	p>0.05

SD: Standard deviation.

and control groups in terms of smoking, alcohol, diabetes and cholecystectomy (p>0.05).

Colon cancer was most frequently detected in the left colon (56.4%), and within the left colon, it was most commonly found in the rectum (25.7%). Left colon involvement was more common in both patients under and over 50 years of age, but this difference was not statistically significant. Left colon involvement was more common in male patients, but there was no significant difference compared to the right colon. Furthermore, no significant association was found between smoking, alcohol, diabetes, and a history of cholecystectomy and the localization of colon cancer (Table 13). Gastroscopy was performed on colon cancer patients an average of 14 months later (1-120 months). In the colon cancer patient group, no gastroscopic pathology was detected in 64.4% of patients, while in the control group, gastroscopy was reported as normal in 74.8% of patients. Regarding gastric polyps and polyp pathology, no significant difference was found between the control and patient groups (Table 14).

Gastroscopic biopsies of colon cancer patients showed no significant difference in intestinal metaplasia and H. pylori positivity compared to the control group (p>0.05). In the colon cancer group, 1% of patients had severe dysplasia on gastroscopic biopsy. The patient was a 33-year-old woman who had been diagnosed with stomach cancer six months after her colon cancer diagnosis. She had stage III sigmoid colon cancer. When compared in terms of gastric polyps, 9.9% of the colon cancer group had gastric polyps, while 9.6% were detected in the control group (p>0.05). Regarding polyp localization, 60% of gastric polyps in the colon cancer group were located in the distal stomach, while 72% were located proximally, and particularly in the fundus, in the control group. There was no difference between the patient and control groups in terms of H. pylori and intestinal metaplasia (Table 15). Histopathological findings revealed the pres-

Table 13. Demographic characteristics of colon cancer patients according to cancer location

	Right colon n (%)	Left colon n (%)	p
Number (%)	44 (43.6)	57 (56.4%)	
Age			
<50	6 (13.6)	15 (26.3)	>0.05
>50	38 (66.4)	42 (73.7)	
Gender			
Female	19 (43.2)	21 (36.8)	>0.05
Male	25 (56.8)	36 (63.2)	
Smoking	17 (38.6)	24 (42.1)	>0.05
Alcohol	4 (9.1)	11 (20.0)	>0.05
Cholecystectomy	4 (9.1)	5 (9.8)	>0.05
Diabetes mellitus	4 (9.1)	1 (20.0)	>0.05

Table 14. Gastroscopy findings of the colorectal cancer patient group and the control group

Gastroscopy findings	Colorectal cancer patient group n (%)	Control group n (%)	p
Normal	65 (64.4%)	86 (74.8%)	>0.5
Peptic ulcer	11 (10.9%)	7 (6.1%)	>0.5
Cancer	1 (1.0%)	1 (0.9%)	>0.5
Esophagitis	14 (13.9%)	10 (8.7%)	>0.5
Gastric polyp			
Neoplastic	1 (1.0%)	1 (0.9%)	
Non-neoplastic	5 (5.0%)	10 (5.7%)	>0.5
Other	4 (4.0%)	0 (0%)	
Polyp size (cm)			
Mean ± SD	0.47±0.16	0.82±0.36	>0.5

SD: Standard deviation.

Table 15. Comparison of gastroscopic biopsies from colon cancer and control groups

Gastric pathology	Colorectal cancer patient group n (%)	Control group n (%)	p
Gastrointestinal metaplasia	24 (46.2%)	24 (39.3%)	>0.05
Dysplasia	1 (1.9%)	1 (1.6%)	>0.05
H. pylori gastritis	27 (51.9%)	36 (59.1%)	>0.05

ence of tubular adenomas and hyperplastic polyps in both groups, with no significant difference in distribution (Table 16). The control group had a 0.5 cm polyp located at the cardioesophageal junction with mild to severe dysplasia.

Discussion

The incidence of gastric and colorectal cancer varies significantly across different countries and regions.[12] Gastric cancer, which increases with age, is most commonly observed between the ages of 50 and 70.[13] In our study, 50.9% of gastric cancer patients were over 60 years old, while 7.6% were under the age of 40. Furthermore, consistent with other studies in the literature, gastric cancer was more frequent in the male gender.[5,7,14-16] Intestinal-type gastric cancer is not only more common but also tends to involve the distal stomach, with a higher prevalence in male patients. [13] Similarly, in our study, intestinal-type gastric cancer was identified in 62.3% of the patients and was found to be more frequent in males (90.6%). While some publications report that diffuse-type gastric cancer is more prevalent especially among females, it was observed at nearly equal rates in both genders in our study.[15] Over the last 30 years, the incidence of gastric cardia adenocarcinoma has increased 5- to 6-fold in developed countries. While distal gastric cancer is more common in developing countries, proximal gastric cancer exhibits higher rates in developed countries.[13] The eradication of H.pylori is cited as the primary reason for the decrease in distal gastric cancer incidence.[17] Additionally, the rise in obesity and reflux has been implicated as a factor in the increasing incidence of proximal gastric cancer.[18,19] In a retrospective study conducted by Vardar et al.[20] in Türkiye, the change in the localization of gastric adenocarcinomas in the Aegean Region was investigated, and no significant change was reported in the distal/proximal gastric cancer ratio. In our study, however, distal gastric cancer was found to be more prevalent than proximal gastric cancer.

Male gender and advanced age are two well-known risk factors for colorectal cancer.[21] In our study, 60.4% of colon

Table 16. Gastroscopic lesions detected in colon cancer patients and control groups, and their relationship with the demographic characteristics of the patients

	Colon cancer patient group				Control group				p
	No polyp	Benign polyp	Adenoma	Cancer	No polyp	Benign polyp	Adenoma	Cancer	
Age									
<50	18 (90.0%)	1 (5.0%)	0 (0%)	1 (5.0%)	57 (98.3%)	1 (1.7%)	0 (0%)	0 (0%)	>0.05
>50	72 (93.5%)	4 (5.2%)	1 (1.3%)	0 (0%)	46 (80.7%)	10 (17.5%)	0 (0%)	1 (1.8%)	
Gender									
Female	36 (90.0%)	3 (7.5%)	0 (0%)	1 (2.5%)	58 (89.2%)	7 (10.8%)	0 (0%)	0 (0%)	>0.05
Male	54 (94.7%)	2 (3.5%)	1 (1.8%)	0 (0%)	45 (90.0%)	4 (8.0%)	0 (0%)	1 (2.0%)	
Smoking	37 (41.1%)	4 (80.0%)	0 (0%)	0 (0%)	31 (30.1%)	2 (18.2%)	0 (0%)	0 (0%)	>0.05
Alcohol	11 (12.2%)	4 (80.0%)	0 (0%)	0 (0%)	12 (11.7%)	0 (0%)	0 (0%)	0 (0%)	>0.05
Cholecystectomy	7 (7.8%)	1 (20.0%)	1 (11.1%)	0 (0%)	4 (3.9%)	0 (0%)	0 (0%)	0 (0%)	>0.05
Diabetes mellitus	14 (15.6%)	1 (20.0%)	1 (6.3%)	0 (0%)	0 (0%)	1 (9.1%)	0 (0%)	0 (0%)	>0.05

cancer patients were male and 79.2% of all patients were over 50 years old.

In autopsy studies, colon cancer is most frequently seen in the left colon, and especially in the rectum.[22] In recent years, studies have been conducted that contradict this situation. In a prospective study by Thomas et al.[23], the rate of right colon cancer was found to be higher than left colon cancer. However, in our study, colon cancer was more common in the left colon (56.4%) than in the right. In addition, 25.7% of all colon cancers were in the rectum, making it the most frequent localization area. Insulin and IGF-1 levels play a role in carcinogenesis by affecting cell proliferation and apoptosis. While most studies consider diabetes to be a disease that increases the risk of colorectal cancer, some studies have claimed the opposite. This difference in the literature was examined by Larsson et al.[24] in a meta-analysis of 15 studies. In this meta-analysis, it was reported that diabetes increased the risk of colorectal cancer by 1.2-1.4 times, without distinction of gender and localization. Although diabetes was more prevalent in the colon cancer patient group compared to the control group in our study, it was not statistically significant. Studies on the effects of diabetes on gastric cancer have shown that gastric cancer mortality is higher in diabetic patients. However, there is no data to suggest that it increases the risk of gastric cancer.[25] In our study, there was no significant difference in diabetes mellitus between the control group and gastric cancer patients.

H. pylori infection, which is held responsible for the etiology of gastric cancer, has also been the subject of research concerning the etiology of colon cancer and colonic adenoma.[26] While some studies identify H. Pylori infection as a causative factor in the development of colonic neoplasia, others argue that there is no significant association between them.[27,28] In our study, the prevalence of H.pylori positivity in colorectal cancer patients did not differ significantly from the control group.Smoking, perhaps the most significant of all risk factors, is considered responsible for the etiology of both gastric and colorectal cancer. Compared to non-smokers, a higher frequency of p53 gene mutations has been detected in smokers.[29,30] In our study, the smoking rate was found to be significantly higher only in patients with gastric cancer.Another controversial topic in the etiology of gastric cancer is alcohol consumption. A meta-analysis evaluating 52 studies revealed that, based on current data, the relationship between gastric cancer and alcohol consumption remains clearly undefined.[31] The same situation applies to colorectal cancer. Franceschi et al.[32] evaluated 27 studies and stated that alcohol consumption, in parallel with low folate intake, increases the risk of colorectal cancer by 1–1.7 times. This finding has been supported by other meta-analyses.[31,33] In our study, no significant difference was found regarding alcohol consumption when gastric cancer and colorectal cancer groups were compared with the control groups.Cholecystectomy alters the bile acid content of the feces.[34] While some studies have shown an increased risk of proximal colon cancer specifically in women, other studies have additionally argued that the risk of rectal cancer also increases. Conversely, there are studies suggesting that cholecystectomy does not increase the risk of colorectal cancer.[35]

Early detection of gastric cancer makes curative surgery possible. In gastric cancer detected in the early stages, the 5-year survival rate is around 96%, and the 10-year survival rate is around 92%.[36] In our study, 79.2% of gastric cancer patients and 64.4% of colon cancer patients were detected in stages 3 and 4. In regions where gastric cancer is endemic, such as Korea and Japan, early detection of gastric cancer is common because screening programs have been established.[37] However, a screening program for gastric cancer has not yet been established in our country.

The first study on a second primary cancer was conducted in Japan in 1985 by Ikeda et al. [38] The study found an incidence of 2%. Subsequent studies have reported rates between 1.1% and 4.7%.[39] In another study by Ueno et al.[40], cancer patients were followed for a long period and the development of a second cancer was investigated. In this study, the development of a second malignancy was reported in 2/3 of the patients within the first 3 years after the development of the primary cancer. In East Asia, gastric cancer has a higher incidence among multiple primary cancers compared to other cancers, and it is reported to occur with colon cancer in most cases.[41] Studies in South Korea have also reported that multiple primary cancers are most frequently in the stomach.[42] In our study, gastric cancer was detected in 1 of the colon cancer patients, and this was detected during gastroscopy 6 months later. In patients with gastric cancer, colon cancer was detected in 2 patients; this was discovered during colonoscopies performed at 1 month and 48 months, respectively, and both tumors were localized to the rectum.

Studies conducted in the East have identified an increased frequency of gastric cancer among patients with colorectal cancer.[39-42] Some publications report that the prevalence of gastric cancer in colorectal cancer patients ranges between 0.2% and 2.9% [6,41–43]. In a study by Oh et al.[4], the risk of colorectal cancer in 105 patients with gastric cancer was found to be 9.5%, while colorectal cancer was detected at a rate of 0.7% in a control group of 269 patients without gastric cancer. In another prospective study by Oh et al.[4], colorectal cancer was detected in 2.4% of 723 gastric cancer patients; this value was reported to be 2.5

times higher than that of the healthy population, which was identified as 0.97%.However, some studies conducted in the West have demonstrated the exact opposite, reporting no increase in the development of gastric cancer among colorectal cancer patients compared to the general population.[44,45] In our study, while colorectal cancer was identified in 3.8% of gastric cancer patients, gastric cancer was detected in 1% of colorectal cancer patients. Although both cancers appeared more frequent in terms of percentage compared to the control group, this was not statistically significant. A likely reason for this is the limited number of patients. Furthermore, the rate of reaching the cecum via colonoscopy in the gastric cancer group was 62.3%, which suggests that the actual prevalence of colonic malignancy in these patients might be higher.It is well known that the presence of an adenoma in one part of the gastrointestinal tract is associated with the synchronous presence of an adenoma in another region.[10,11,46] Gastric polyps are generally asymptomatic and are often detected incidentally during endoscopic or radiological examinations at a rate of 1–5%. Gastric polyps can be divided into two groups: non-neoplastic (hamartomatous, inflammatory, and hyperplastic polyps) and neoplastic (adenomas and fundic gland polyps). Gastric polyps are found in 1–2% of the general population, and 7–10% of these are adenomatous polyps, which are premalignant lesions.[47,48] In a retrospective study by Cappell et al.[11] involving 41 patients with gastric polyps, a significantly higher rate of colonic polyps was detected compared to the control group. Similarly, in another retrospective study, colorectal adenomas were detected in 33% of the control group, whereas adenomas were found in 56% of patients with duodenal adenomas during colonoscopy. Additionally, when the rates of advanced colorectal adenoma and neoplasia were compared between the two groups, they were found to be 19% in the control group and 38% in the patient group.[46] Gastric polyps may also be associated with various polyposis coli syndromes.[49,50] It has been shown that the risk of colorectal cancer increases even in patients who only have duodenal adenomas or gastric fundic gland polyps.[51]

Patients with nonmalignant gastric mucosal polyps have a significantly higher incidence of colon polyps compared to the primary control group, supporting the idea that gastric polyps are a risk factor for colon polyps.[11,52] 53.
Watanabe et al.[53] reported that the presence of gastric polyps increased the risk of colon polyps fourfold, and the presence of colon polyps increased the risk of gastric polyps twentyfold. In a study conducted in Korea, Oh et al.[4] investigated colon cancer in 105 patients with gastric carcinoma. Colon adenomatous polyps were detected in 22.9% and colorectal adenocarcinoma in 9.5%. In another study conducted by Park and colleagues, the prevalence of colorectal cancer development in patients with gastric carcinoma in Korea was investigated. It was reported that colorectal cancer was detected in 19 (3.5%) of 543 gastric carcinoma patients, and adenoma in 215 (39.6%).[5] In our study, the rate of polyps in the colon was 39.6% in gastric cancer patients, while this rate was 29.5% in the control group. No significant difference was found between them in terms of polyp number and pathology. However, the fact that total colonoscopy was not performed in the gastric cancer group may have caused the data to be insufficient.

With the increasing elderly population, advances in diagnostic techniques for cancer mutations, and increased exposure to carcinogens, there has been an increase in the prevalence of multiple primary cancers. The gold standard technique for diagnosing colon cancer is colonoscopy, which also helps us detect precancerous lesions. However, many patients with gastric cancer are too debilitated to tolerate a total colonoscopy, and the technical difficulties of the procedure following prior surgery act as further deterrents. In our study, the low rate of cecal intubation may have hindered the detection of advanced adenomas or foci of cancer.

Screening programs exist in regions such as Japan, where gastric cancer is observed with high incidence. Through intensive screening, gastric cancer is detected at an early stage in asymptomatic populations, thereby reducing mortality rates. In studies conducted with asymptomatic individuals over the age of 50 in South Korea, where gastric cancer is common, colorectal cancer was detected at a rate of 1–4.1%.[46,54] In patients who have undergone surgery for colorectal cancer, primary cancer may recur, or second primary cancers and adenomatous polyps may develop. In this patient group, the average time for detecting metachronous adenomas after surgical resection is 19–32 months, whereas most recurrent adenocarcinomas (85%) are diagnosed within 3 years.[55] While colorectal carcinomas tend to localize in the sigmoid colon and rectum, data obtained in recent years indicate a relative increase in right-sided colon involvement, suggesting a shift in distribution. The detection of precancerous lesions in cancer development is crucial. Indirect evidence supporting the adenoma-carcinoma sequence exists; one such piece of evidence is the similarity in the prevalence and distribution patterns of colorectal cancer and colonic polyps in the general population.[4,5] Another is the frequent coexistence of benign adenomatous tissue with invasive cancer tissue in early-stage malignancies. Furthermore, the decrease in colorectal cancer incidence following endoscopic polypectomy supports the fact that polyps are indeed precancerous lesions.[56] A study by Bond et al.[57] in South Korea reported that the prevalence of colorectal adenoma increased with age, reaching 10% in the 30s, 22% in the 40s,

and 33% in the 50s. Adenomatous polyps carry a risk of malignant transformation.

The limitations of our study include its single-center design, the small sample size in both the gastric and colorectal cancer groups, the inability to perform colonoscopy sufficiently to reach the cecum in all patients, and the lack of control groups with similar age and gender characteristics.

Conclusion

In conclusion, the diagnosis of multiple primary cancers has become more common due to advances in diagnostic tests and the increasing elderly patient population. Considering the increase in life expectancy and the growing elderly population not only in our country but also worldwide, it is inevitable that cancer rates will increase day by day. Therefore, the importance of early detection of cancerous and precancerous lesions through complete cancer screenings and advanced evaluations of existing pathologies is highlighted. However, prospective studies with a larger number of patients are needed to create new cancer screening programs.

Disclosures

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Research Article

Inflammation-Based Risk Assessment in Acute Pulmonary Embolism: Diagnostic and Prognostic Implications of the Neutrophil-to-Lymphocyte Ratio

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Abstract

Objectives: Acute pulmonary embolism (PE) is a serious cardiovascular disorder that may lead to substantial morbidity and mortality if not recognized early. Timely diagnosis and accurate assessment of disease severity are essential for appropriate treatment planning. Although imaging techniques and cardiac biomarkers are commonly used in the diagnostic process, there remains a need for practical laboratory markers that are inexpensive, rapidly obtainable, and easily applicable in routine clinical settings. The neutrophil-to-lymphocyte ratio (NLR), derived from peripheral blood counts, has recently gained attention as an indicator of inflammatory activation. In this study, we investigated the diagnostic significance of NLR in acute PE and examined its association with clinical severity and mortality outcomes.

Methods: A total of 100 patients diagnosed with acute PE by computed tomography pulmonary angiography and 94 healthy individuals were retrospectively evaluated. Patients were categorized according to the 2014 European Society of Cardiology risk stratification model into low/intermediate-low-risk and intermediate-high/high-risk groups. Laboratory data obtained within the first 6 hours after hospital admission were analyzed. Receiver operating characteristic (ROC) curve analysis was used to determine the diagnostic performance of NLR.

Results: Patients with acute PE had significantly higher NLR values compared with healthy controls (5.7±4.3 vs. 2.08±1.6, p<0.001). ROC analysis demonstrated that NLR had favorable diagnostic performance for acute PE, with an area under the curve of 0.855. An NLR threshold above 2.56 provided 76% sensitivity and 84.6% specificity. Moreover, NLR levels were significantly greater in intermediate-high/high-risk patients compared with low/intermediate-low-risk patients (6.82±5.1 vs. 4.93±3.3, p=0.031). Although higher NLR values were observed among patients who died during follow-up, no statistically significant relationship was identified between NLR and short- or long-term mortality.

Conclusion: The present findings suggest that NLR may be a useful supportive biomarker in the early evaluation of acute PE. Elevated NLR levels were associated with increased disease severity. Although its prognostic value for mortality was not clearly demonstrated, NLR may still contribute to clinical risk assessment because of its rapid availability and ease of calculation.

Keywords: Inflammation, pulmonary embolism, mortality, neutrophil-to-lymphocyte ratio, risk stratification

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Acute pulmonary embolism (PE) is a serious cardiovascular condition caused by obstruction of the pulmonary arterial circulation, most commonly secondary to thrombi originating from the deep venous system of the lower extremities. Despite substantial progress in imaging modalities and anticoagulant treatment strategies, PE continues to be associated with considerable morbidity and mortality worldwide.[1–3] Clinical presentation may vary from mild nonspecific symptoms to circulatory collapse and sudden death. Because symptoms such as dyspnea, chest pain, syncope, and tachycardia are not unique to PE, establishing an early diagnosis may be difficult in routine clinical practice.[1,3]

Early identification of high-risk patients is essential for determining treatment strategy and predicting clinical outcomes. Current guideline recommendations support the use of clinical scoring systems, including the Pulmonary Embolism Severity Index (PESI) and simplified PESI (sPESI), together with imaging findings and cardiac biomarkers such as troponin and N-terminal pro-brain natriuretic peptide (NT-proBNP).[1,4] However, some of these approaches may not always be immediately available during the first assessment in emergency settings.

Recent studies have demonstrated that inflammatory mechanisms contribute significantly to the development and progression of venous thromboembolism. Endothelial dysfunction, platelet activation, cytokine release, leukocyte recruitment, and neutrophil extracellular trap formation are believed to participate in thrombus formation and pulmonary vascular injury.[5,6] Therefore, acute PE is increasingly recognized as a disorder involving both thrombosis and systemic inflammatory activation.

The neutrophil-to-lymphocyte ratio (NLR) is a readily available laboratory parameter derived from routine complete blood count measurements. Elevated NLR levels are considered to reflect both inflammatory activity and physiologic stress response.[7] Previous reports have demonstrated associations between increased NLR values and unfavorable outcomes in several cardiovascular and inflammatory diseases, including acute coronary syndromes, heart failure, ischemic stroke, and venous thromboembolism.[7,8]

Several investigators have evaluated the prognostic significance of NLR in acute PE. Higher NLR levels have been associated with greater disease severity, right ventricular dysfunction, and adverse short-term outcomes.[9,10] Nevertheless, evidence regarding its diagnostic value and long-term prognostic role remains limited and somewhat inconsistent. In addition, there is still a need for inexpensive and rapidly obtainable biomarkers that may support clinicians during the early evaluation of patients with suspected PE, particularly in emergency departments and resource-limited healthcare settings.[11,12]

In the present study, we aimed to investigate the diagnostic performance of NLR in patients with acute pulmonary embolism and to evaluate its association with disease severity and mortality outcomes.

Methods

Study Design and Population

We retrospectively evaluated adult patients diagnosed with acute pulmonary embolism (PE) between September 2015 and September 2017 at a tertiary referral center. Demographic characteristics, laboratory findings, and radiologic data were retrieved from institutional electronic medical records and archived patient files. To reduce potential selection bias, all eligible consecutive patients identified during the study period were included in the analysis.

The diagnosis of acute PE was established by computed tomography pulmonary angiography (CTPA). Only patients with segmental or more proximal pulmonary arterial involvement were included. Patients with isolated subsegmental embolism or chronic thromboembolic pulmonary disease were excluded from the study. Cases with missing clinical, laboratory, or imaging data required for statistical evaluation were excluded during the screening process.

Patients aged 18 years or older with laboratory measurements obtained within the first six hours after admission were considered eligible for inclusion. Evaluated laboratory parameters included complete blood count, D-dimer, arterial blood gas analysis, and cardiac biomarkers. Pregnant patients and individuals with incomplete clinical information were not included in the final cohort.

Risk stratification was performed according to the 2014 European Society of Cardiology (ESC) recommendations for acute PE. Clinical evaluation included assessment of the Pulmonary Embolism Severity Index (PESI), simplified PESI (sPESI), hemodynamic status, right ventricular dysfunction, and cardiac biomarker positivity. Echocardiographic findings suggesting right ventricular dysfunction included right ventricular dilatation, an RV/LV ratio greater than 0.9, or increased tricuspid regurgitation. Troponin I and NT-proBNP values obtained at admission were used for biomarker assessment.

A control group consisting of healthy individuals without known thromboembolic or acute inflammatory disease was included for comparison of neutrophil-to-lymphocyte ratio (NLR) values.

Peripheral venous blood samples collected before treatment initiation were analyzed using the hospital central

laboratory system. NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count.

The primary objectives of the study were to evaluate the diagnostic performance of NLR in acute PE and to investigate its relationship with disease severity. Secondary endpoints included 30-day and 1-year mortality. Mortality data were obtained from hospital records and national health databases.

Data analysis was conducted using SPSS version 20.0 (IBM Corp., Armonk, NY, USA) and MedCalc software. Continuous variables are presented as mean±standard deviation, whereas categorical variables are summarized as frequencies and percentages. Group comparisons were performed using the independent samples t-test or chi-square test, where appropriate. Receiver operating characteristic (ROC) curve analysis was applied to assess the diagnostic and prognostic performance of NLR, and cutoff values were determined using the Youden index. A two-sided p-value below 0.05 was considered statistically significant.

Results

Baseline Characteristics

A total of 100 consecutive patients with acute pulmonary embolism (PE) and 94 healthy controls were included in the study. The mean age of the PE group was 71.2±16.4 years, and 56% of the patients were female. The control group consisted of 51 women (54.3%) and 43 men (45.7%), with a mean age of 67.3±13.1 years. There was no statistically significant difference between the groups in terms of age or sex distribution (p>0.05).

The most common comorbid conditions among patients with PE were coronary artery disease (23%), chronic obstructive pulmonary disease (23%), congestive heart failure (23%), hypertension (48%), and diabetes mellitus (23%).

According to the 2014 ESC risk classification, 29 patients were categorized as low risk, 26 as intermediate-low risk, 36 as intermediate-high risk, and 9 as high risk. For further analyses, patients were grouped as low/intermediate-low risk (Group 1, n=55) and intermediate-high/high risk (Group 2, n=45). Baseline demographic and laboratory characteristics according to PE risk groups are summarized in Table 1.

Relationship Between NLR and Disease Severity

Patients in the intermediate-high/high-risk group demonstrated significantly higher NLR values compared with patients in the low/intermediate-low-risk group (6.82±5.1 vs. 4.93±3.3, p=0.031). Detailed laboratory comparisons between PE risk groups are shown in Table 1.

Similarly, D-dimer and NT-proBNP levels were significantly higher among patients with greater disease severity. Neutrophil counts were also significantly elevated in the higher-risk group, whereas lymphocyte counts were lower, although the difference in lymphocyte counts did not reach statistical significance.

ROC curve analysis evaluating the ability of NLR to differentiate low/intermediate-low-risk and intermediate-high/high-risk PE patients is presented in Figure 1.

ROC analysis of NT-proBNP for differentiating PE severity groups is shown in Figure 2.

Patients with higher-risk PE more frequently demonstrated right ventricular dysfunction and elevated cardiac biomarkers.

Although mean NLR values were numerically higher among non-survivors compared with survivors, the difference did not reach statistical significance. ROC analyses evaluating

Table 1. Baseline demographic and laboratory characteristics according to pulmonary embolism risk groups

Variable	Group 1 (n=55)	Group 2 (n=45)	p
Age	69.04±14.2	74.87±10.4	0.024
Female sex, n (%)	37 (67%)	28 (62%)	NS
D-dimer (ng/mL)	2969.64±2626.9	4514.73±4177.2	0.026
NT-proBNP (pg/mL)	313.42±931.2	733.66±1004.8	0.033
Leukocyte count (/mm^3)	9391±4238.1	11585.78±6729.6	0.061
Neutrophil count (/mm^3)	6803.64±3849.4	9215.33±6203.4	0.019
Lymphocyte count (/mm^3)	1728.27±824	1692.71±1195.8	0.861
NLR	4.93±3.3	6.82±5.1	0.031
Hemoglobin (g/dL)	11.22±2.2	10.76±2.5	0.347
Hematocrit (%)	34.05±6.5	32.31±8.8	0.263
Platelet count (/µL)	275056±113118	232435±109643	0.060

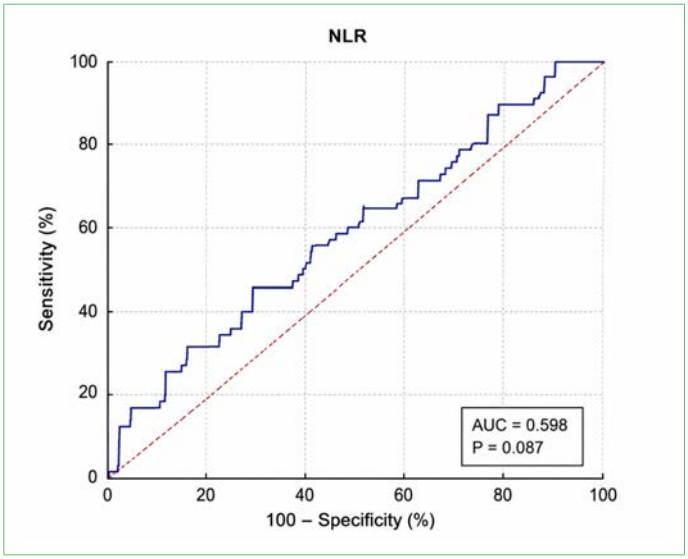


Figure 1. Receiver operating characteristic (ROC) curve of the neutrophil-to-lymphocyte ratio (NLR), showing limited and statistically nonsignificant discriminatory performance (AUC=0.598, p=0.087).

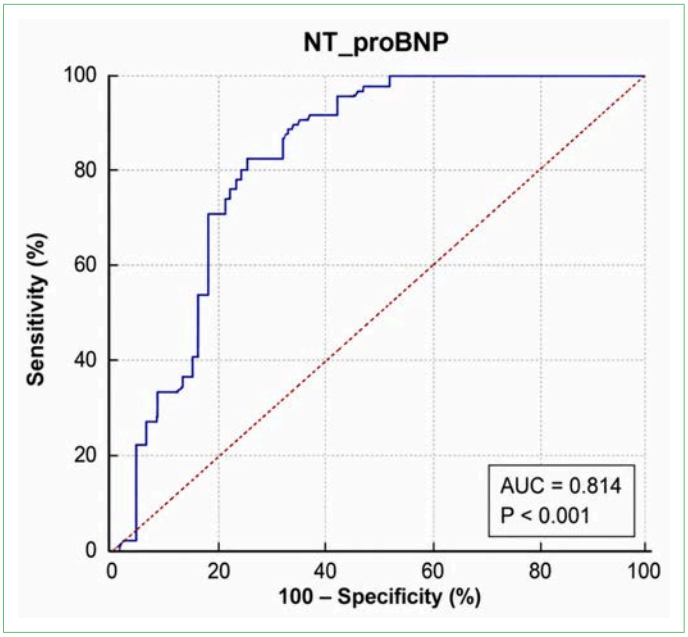


Figure 2. Receiver operating characteristic (ROC) curve of NT-proBNP, showing good and statistically significant discriminatory performance (AUC=0.814, p<0.001).

the prognostic performance of NLR for 30-day and 1-year mortality are presented in Figures 3 and 4, respectively.

Correlation Analyses

Elevated NLR values showed positive correlations with D-dimer and NT-proBNP levels, suggesting an association between systemic inflammatory response, thrombotic burden, and right ventricular strain in acute PE.

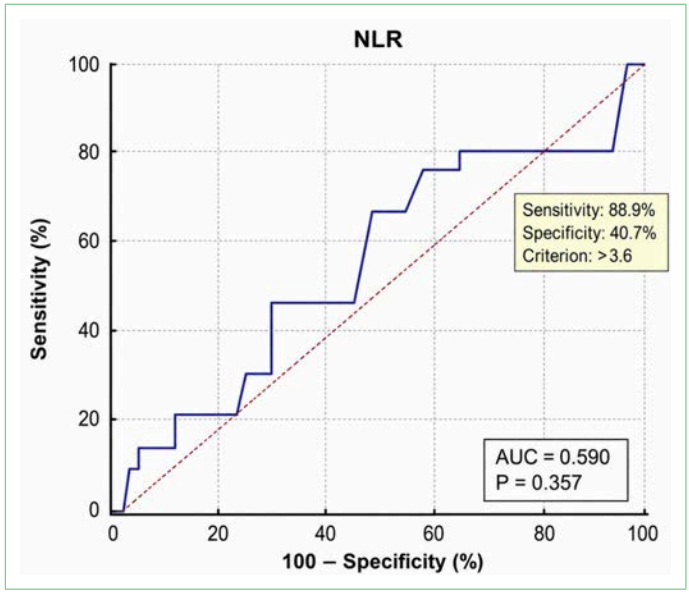


Figure 3. Receiver operating characteristic (ROC) curve of the neutrophil-to-lymphocyte ratio (NLR), showing limited and statistically nonsignificant discriminatory performance at a cutoff value of >3.6 (AUC=0.590, p=0.357).

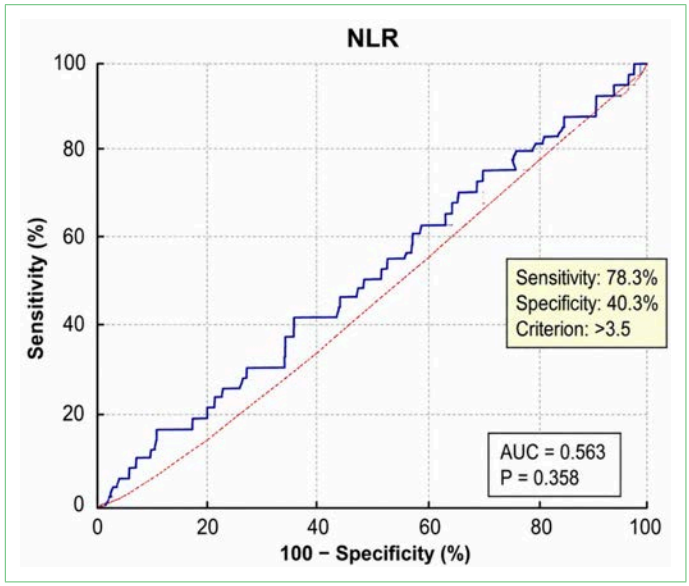


Figure 4. Receiver operating characteristic (ROC) curve of the neutrophil-to-lymphocyte ratio (NLR), showing limited and statistically nonsignificant discriminatory performance at a cutoff value of >3.5 (AUC=0.563, p=0.358).

Laboratory Findings and Diagnostic Performance of NLR

Comparisons of laboratory and demographic variables between low/intermediate-low-risk PE patients and healthy controls are summarized in Table 2.

Comparisons between intermediate-high/high-risk PE patients and healthy controls are summarized in Table 3.

Table 2. Comparison of group 1 pulmonary embolism patients and healthy controls

Variable	Group 1 (n=55)	Healthy Controls (n=94)	p
Age	69.04±14.2	67.3±10.9	0.047
Female sex, n (%)	37 (67%)	62 (66%)	NS
Leukocyte count (/mm^3)	9391±4238.1	6878.13±2099.5	0.032
Neutrophil count (/mm^3)	6803.64±3849.4	3945.27±1586.3	0.006
Lymphocyte count (/mm^3)	1728.27±824	2131.97±676.1	1.000
NLR	4.93±3.3	2.08±1.6	0.014
Hemoglobin (g/dL)	11.22±2.2	13.32±1.56	0.804
Platelet count (/µL)	275056±113118	248075±62337	0.059

Table 3. Comparison of group 2 pulmonary embolism patients and healthy control

Variable	Group 2 (n=45)	Healthy Control (n=94)	p
Age	74.87±10.4	67.3±10.9	<0.001
Female sex, n (%)	28 (62%)	62 (66%)	NS
Leukocyte count (/mm^3)	11585.78±6729.6	6878.13±2099.5	<0.001
Neutrophil count (/mm^3)	9215.33±6203.4	3945.27±1586.3	<0.001
Lymphocyte count (/mm^3)	1692.71±1195.8	2131.97±676.1	0.018
NLR	6.82±5.1	2.08±1.6	<0.001
Hemoglobin (g/dL)	10.76±2.5	13.32±1.56	<0.001
Platelet count (/µL)	232435±109643	248075±62337	0.059

Mean neutrophil-to-lymphocyte ratio (NLR) values were significantly higher in patients with acute PE compared with healthy controls, as shown in Table 4.

Receiver operating characteristic (ROC) analysis demonstrated good diagnostic performance of NLR for acute PE, with an area under the curve (AUC) of 0.855 (95% CI: 0.800–0.909, p<0.001). An NLR cutoff value >2.56 yielded 76% sensitivity and 84.6% specificity. Positive predictive value and negative predictive value were calculated as 40.4% and 96.9%, respectively (Fig. 5).

Mortality Outcomes

Thirty-day mortality was observed in 9 patients, whereas 1-year mortality occurred in 23 patients. Mortality outcomes according to PE risk groups are summarized in Table 5. Detailed mortality distributions between groups are presented in Table 5.

Table 4. Comparison of NLR between pulmonary embolism patients and healthy controls

Variable	PE patients (n=100)	Healthy controls (n=94)	p
NLR	5.7±4.3	2.08±1.6	<0.001

PE: Pulmonary embolism; NLR: Neutrophil-to-lymphocyte ratio.

Discussion

Acute pulmonary embolism (PE) continues to represent a major clinical problem despite advances in diagnostic

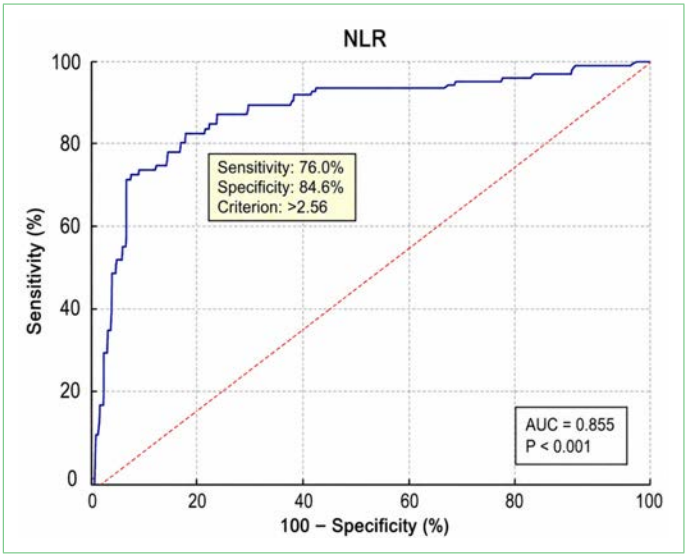


Figure 5. Receiver operating characteristic (ROC) curve of the neutrophil-to-lymphocyte ratio (NLR), showing good and statistically significant discriminatory performance at a cutoff value of >2.56 (AUC=0.855, p<0.001).

Table 5. Thirty-day and one-year mortality according to risk groups

Mortality	Group 1	Group 2	Total
30-day mortality	4	5	9
30-day survivors	51	40	91
1-year mortality	12	11	23
1-year survivors	43	34	77

approaches and anticoagulant therapies. Early identification of patients at increased risk for deterioration remains particularly important, especially among normotensive patients in whom the clinical course may initially appear stable.[1,2] Although patients presenting with hemodynamic instability are generally recognized rapidly, predicting adverse outcomes in clinically stable individuals is often more difficult.

Current risk assessment strategies are mainly based on clinical scoring systems, imaging findings related to right ventricular dysfunction, and cardiac biomarkers.[1,4] While these methods are well established, some may not be immediately accessible during the first evaluation in emergency settings. In addition, conventional biomarkers primarily reflect myocardial stress and may not fully demonstrate the inflammatory processes accompanying acute PE. For this reason, interest in simple laboratory parameters reflecting systemic inflammatory activation has increased in recent years.

Growing evidence suggests that inflammation plays an important role in the pathogenesis of venous thromboembolism. Endothelial injury, platelet activation, cytokine release, leukocyte recruitment, and neutrophil extracellular trap formation have all been implicated in thrombus formation and pulmonary vascular damage.[5,6] Accordingly, acute PE is now increasingly viewed as a condition involving both thrombotic and inflammatory mechanisms.

The neutrophil-to-lymphocyte ratio (NLR) is an easily obtainable marker derived from routine complete blood count analysis. Elevated NLR levels are considered to reflect both inflammatory activation and physiologic stress response.[7] Previous investigations have demonstrated associations between increased NLR values and adverse clinical outcomes in several cardiovascular and inflammatory disorders, including venous thromboembolism.[7,8]

In the present study, patients with acute PE had significantly higher NLR levels than healthy controls. In addition, patients classified in the intermediate-high/high-risk category demonstrated higher NLR values compared with lower-risk patients. These findings support the relationship between systemic inflammatory response and disease severity in acute PE.

Our results are generally compatible with previous reports evaluating the prognostic significance of NLR in PE. Earlier studies demonstrated that elevated NLR levels may be associated with right ventricular dysfunction, more severe clinical presentation, and poorer short-term outcomes.[9,10] Similarly, a recent meta-analysis suggested that inflammatory biomarkers, particularly NLR, may provide prognostic information in patients with acute PE.[12]

Another noteworthy finding of this study was the diagnostic performance of NLR in distinguishing patients with PE from healthy individuals. Although NLR cannot replace imaging modalities used for definitive diagnosis, it may provide supportive information during the early assessment of patients with suspected PE. This may be especially useful in emergency departments or situations in which immediate access to advanced imaging is limited.

We also observed positive correlations between NLR and established laboratory markers such as D-dimer and NT-proBNP. This observation may reflect the relationship between inflammatory activation, thrombotic burden, and right ventricular strain in acute PE. Therefore, NLR may represent a broader marker of physiologic stress associated with pulmonary vascular obstruction.

Unlike some previous studies, we did not observe a statistically significant relationship between NLR and mortality outcomes. Several factors may explain this finding. Mortality in acute PE is influenced by multiple clinical variables, including age, comorbid disease burden, cardiopulmonary reserve, clot extent, and treatment response. In addition, the relatively limited sample size may have reduced the ability to detect mortality-related differences.

This study has several limitations. First, its retrospective and single-center design may limit generalizability. Second, the number of patients included was relatively limited, particularly for mortality analyses. Third, serial measurements of NLR during follow-up were not available. Finally, the potential effects of accompanying inflammatory or chronic comorbid conditions cannot be completely excluded.

Despite these limitations, the study also has important strengths. Consecutive patient inclusion reduced the likelihood of selection bias, and laboratory measurements were obtained early after admission before treatment initiation. Moreover, no missing data were present in the final analytical cohort.

From a clinical perspective, NLR is an inexpensive, easily obtainable, and widely available laboratory parameter. Although it should not replace established diagnostic methods or cardiac biomarkers, it may provide additional support during early risk assessment in patients with acute PE.

Conclusion

The present study demonstrated that neutrophil-to-lymphocyte ratio levels were significantly increased in patients with acute pulmonary embolism and were associated with greater disease severity according to ESC risk categories. These findings support the relationship between inflammatory activation and the clinical presentation of acute PE.

Although NLR should not be used as an isolated diagnostic or prognostic marker, its rapid availability and low cost make it a potentially useful adjunctive parameter during the early assessment of suspected PE.

In routine clinical practice, a simple marker obtained from standard blood counts may provide additional information during the initial evaluation of patients with acute pulmonary embolism.

Disclosures

Ethical Committe Approval: The study protocol was approved by the Haydarpaşa Numune Training and Research Hospital Ethics Committee (Approval No: HNEAH-KAEK 2015/78 [487], Date: September 14, 2015).

Informed Consent: Due to the retrospective nature of the study, the requirement for informed consent was waived.

Conflict of Interest: The authors declare that they have no competing financial or non-financial interests.

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Use of AI for Writing Assistance: The authors declare that no artificial intelligence (AI)–assisted technologies (including large language models, chatbots, or image generation tools) were used in the preparation of this manuscript.

Author Contributions: Concept – BG; Design – FMT; Supervision – FMT; Findings – BG; Materials – BG; Data Collection and/or Processing – BG; Analysis and/or Interpretation – FMT; Literature Review – BÇG; Writing – BG; Critical Review – FMT, BÇG.

Peer-review: Externally peer-reviewed.

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Research Article

The Relationship Between Frailty, Hematological Parameters, and Mortality in Older Adults with COVID-19

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Abstract

Objectives: Frailty is a geriatric syndrome characterized by a decrease in physical and physiological reserve and increased vulnerability and susceptibility to external stressors. In this study, we aimed to investigate the relationship between mortality, hematological parameters, and frailty in hospitalized older adults with COVID-19.

Methods: In this prospective study, 154 patients who were hospitalized between 01.11.2020 and 31.12.2020 at the Şişli Hamidiye Etfal Health Practice and Research Center COVID-19 inpatient clinics were included. Frailty was evaluated with the FRAIL scale. Complete blood count, CRP, ferritin, D-dimer, and troponin T levels were included as hematological parameters.

Results: Forty-one of the 154 patients (26.6%) were categorized as frail. Troponin T levels were significantly higher in the frail patients compared with the non-frail patients ($p<0.001$). There was a statistically significant relationship between elevated troponin levels and mortality (1-month $p=0.015$, 3-month $p=0.011$).

Conclusion: In this study, there was no significant relationship between mortality and frailty status. A statistically significant relationship between elevated troponin levels and frailty was observed. There was also a significant relationship between elevated troponin levels and mortality in our study.

Keywords: COVID-19, frailty, laboratory, mortality

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The novel coronavirus infection has been affecting many people around the world for a few years. This impact is particularly greater in elderly patients. Morbidity and mortality due to coronavirus infection increase in elderly patients and those with chronic diseases.[1]

Frailty is a geriatric syndrome characterized by physiological decline in multiple systems and an increased susceptibility to adverse outcomes caused by stressors.[2] Frailty is most often seen in elderly patients, but it may not always be associated with age. Mortality is increased for many diseases and medical conditions in the frail population.

In this study, we aimed to prospectively screen patients over 60 years of age hospitalized due to COVID-19 and investigate whether there is a relationship between frailty, hematological parameters, and mortality.

Methods

This research included patients aged 60 years and over who were hospitalized in our hospital's COVID clinics between 10/11/2020 and 03/12/2020. Patients in intensive care, those who could not be contacted, and those who did not agree to participate in the study were excluded. The study

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was conducted prospectively. The protocol was approved by the Ethics Committee of Şişli Hamidiye Etfal Research and Education Hospital with decision number 2796 dated 12/05/2020.

Patients' demographic information, comorbidities, chronic medications they were using, COVID-19 treatments administered in the hospital, and hematological parameters were recorded.

Hematological parameters used included WBC, neutrophil, lymphocyte count and percentage, hemoglobin, CRP, ferritin, D-dimer, and troponin. Hemogram parameters were measured using a Mindray BC-6800 Plus device, D-dimer levels using a Coulter AU480 device, and CRP, ferritin, and troponin levels using Roche Diagnostics Cobas 8000 and Cobas 6000 Modular Analyzer devices.

The FRAIL frailty questionnaire was used to assess frailty. [3] Patients scoring 0 on the questionnaire were considered robust, those scoring 1–2 were considered pre-frail, and those scoring 3 and above were considered frail (Table 1). This study was conducted according to the Declaration of Helsinki.

Results

A total of 175 patients over 60 years of age were admitted to the COVID wards; 21 were excluded due to the inability to contact them, and 154 patients were included in the study. Our diagnostic criteria/inclusion criteria were being over 60 years of age, having ground-glass opacities consistent with COVID-19 pneumonia on chest CT, and/or having a positive SARS-CoV-2 PCR result. Mortality data were obtained from the hospital information management system and via telephone at the 1st and 3rd months.

The mortality rate at the 1st month was 19.6% (n=30), and at the 3rd month was 24.03% (n=37).

Cutoff values for hematological parameters were accepted as follows: lower limit for leukopenia, 4000×10^6/L; lower limit for platelet count, 150000×10^6/L; lower limit for lymphopenia, 800×10^6/L; lower limit for elevated CRP, 5 mg/L; lower limit for elevated ferritin, 500 µg/L; lower limit for elevated D-dimer, 1000 µg/L; and lower limit for elevated troponin T, 0.014 ng/L.

Statistical Analysis

Statistical analyses were performed using IBM SPSS version 17.0 (Illinois, USA). The normality of the variables was examined using histogram graphs and the Kolmogorov-Smirnov test. Descriptive analyses were presented using mean, standard deviation, median, minimum, and maximum values. Categorical variables were compared using the Pearson chi-square test. In cases where the data did not show a normal distribution, groups of two were evaluated using the Mann-Whitney U test, and groups of more than two were evaluated using the Kruskal-Wallis test. Spearman's correlation test was used to analyze the relationship between the measurement data. Kaplan-Meier analysis was used to determine the factors affecting patient survival. Cox regression analysis and binary logistic regression analysis, whichever was appropriate, were used to analyze the independent variables related to mortality. Cases where the p-value was below 0.05 were considered statistically significant.

Descriptive Statistics

A total of 154 patients were included in the study, 45.45% (n=70) of whom were female. The average age of the patients was 72±8.4 years.

Overall, 65% (n=102) of the patients had hypertension, 40% (n=62) had diabetes mellitus, 31.6% (n=49) had ischemic heart disease, 20% (n=31) had chronic kidney disease, and 14.2% (n=22) had chronic lung disease.

The median number of chronically used medications was 5 (min: 0, max: 14).

In total, 17.4% (n=27) of patients were using ACE inhibitors, 29% (n=45) ARBs, 37.4% (n=58) aspirin, 2.6% (n=4) warfarin, and 7.7% (n=12) NOACs.

Overall, 86.36% (n=133) of the patients included in the study tested positive for SARS-CoV-2 PCR.

In 77.92% (n=120) of the patients, chest CT scans showed

Table 1. FRAIL Questionnaire

1.	Fatigue	How much of the last 4 weeks did you feel tired?	Most of the time: 1, Other: 0
2.	Resistance	Do you have any difficulty walking up 10 steps without resting, alone and without assistance?	Yes: 1, No: 0
3.	Ambulation	Do you have any difficulty walking approximately 200 meters alone, without assistance and without difficulty?	Yes: 1, No: 0
4.	Illnesses	Presence of more than 5 of the following 11 diseases: HT, DM, COPD, MI, CHF, Angina, Asthma, Arthritis, Kidney Disease, Cancer (excluding minor skin cancers)	Yes: 1, No: 0
5.	Loss of weight	Have you lost 5% of your body weight in the last 1 year?	Yes: 1, No: 0

infiltration suggestive of COVID pneumonia. According to the FRAIL frailty questionnaire, 26.6% (n=41) of the patients were assessed as robust, 46.75% (n=72) as pre-frail, and 26.62% (n=41) as frail.

As part of COVID-19 treatment, 92.16% (n=141) of patients received enoxaparin, 96.03% (n=145) received favipravir, 55.2% (n=85) received dexamethasone, 4.5% (n=7) received methylprednisolone (1 mg/kg), 1.3% (n=2) received 250 mg methylprednisolone, 61% (n=94) received any steroid treatment, and 33.33% (n=51) received any quinolone during their hospitalization.

The median WBC count of the patients was 6560×10^6/L (min: 480, max: 116270), the median lymphocyte count was 930×10^6/L (min: 240, max: 100590), the median neutrophil count was 4870×10^6/L (min: 20, max: 28150), the median hemoglobin value was 12.2 g/dL (min: 5.4, max: 17.2), the median CRP value was 93 mg/L (min: 0.4, max: 706), the median ferritin value was 502 µg/L (min: 15, max: 25130), the median D-dimer value was 904 µg/L (min: 155, max: 10003), and the median troponin T value was 0.02 ng/L (min: 0, max: 2.75) (Table 2).

The mean follow-up period for patients was 81 days (min: 1, max: 97).

The median follow-up period in the hospital was 8.5 days (min: 1, max: 35).

The mortality rate at the 1st month was found to be 19.6% (n=30). The mortality rate at the 3rd month was calculated as 24.03% (n=37).

Frailty and Mortality-Related Factors (Univariate Analysis Results)

When the relationship between these groups and 1-month mortality was examined, no significant relationship was found between 1-month mortality and any group (p>0.05 for each group).

No statistically significant relationship was found between 1-month mortality and frailty status (robust, pre-frail, or frail) or frailty score (p=0.658 for frailty status, p=0.312 for frailty score).

No statistically significant relationship was found between mortality at 3 months and frailty status (robust, pre-frail, or frail) (p=0.173). A statistically significant relationship was found between frailty score and 3-month mortality (Table 3). Frailty score was higher in patients who died at 3 months compared with those who survived [median FRAIL score in deceased and surviving patients: 2 (1–3) vs. 1 (0–3); p=0.041].

When the relationship between frailty status and laboratory parameters was examined, a significant relationship was found between elevated troponin levels and frailty (p<0.001). As the level of frailty increased, a significant increase in troponin values was observed [median troponin values for robust, pre-frail, and frail groups, respectively: 0 (0–0.02), 0.02 (0–0.04), and 0.03 (0.02–0.05)]. No statistically significant relationship was found between frailty and other parameters.

Mortality and laboratory parameters were measured at 1 month and 3 months. Of the groups, only troponin elevation and mortality showed a significant correlation (p=0.015 for 1-month mortality, p=0.011 for 3-month mortality). No significant correlation was found between other parameters and mortality at months 1 and 3 (Table 3).

While a statistically significant relationship was found between frailty status and advanced age (p=0.001), no significant relationship was found between frailty status and sex, CT involvement, or PCR status.

Overall, 17.4% of the patients (n=27) were using ACE inhibitors, 29% (n=45) ARBs, 37.4% (n=58) aspirin, 2.6% (n=4) warfarin, and 7.7% (n=12) NOACs. When frailty status and chronically used drug groups were examined, no statistically significant relationship was found between drug groups and frailty.

A positive correlation was found between frailty score and age, number of chronic diseases, and number of chronically used medications, respectively (p=0.001, 0.001, and 0.001; r values: 0.322, 0.262, and 0.266, respectively).

Chronic diseases and frailty status (robust/pre-frail/frail) of the patients were examined. In these analyses, it was observed that patients with cerebrovascular disease (CVA) and dementia were more frail (p=0.001 and p<0.001, respectively). When the frailty status of the patients was categorized into two groups as frail and pre-frail/robust, patients with dementia, cerebrovascular disease (CVD), and

Table 2. Patients' laboratory values

	Mean
WBC (x10^6/L) (Min.-Max.)	8474.68 (480-116270)
Lymphocyte count (x10^6/L) (Min.-Max.)	1906.30(240-100590)
Lymphocyte % (Min.-Max.)	18.65(3-94)
Neutrophil count (x10^6/L) (Min.-Max.)	5823.05(20-28150)
Neutrophil % (Min.-Max.)	73.79 (4-95)
Hemoglobin (g/dL) (SD)	12.09±1.99
Platelet (x10^6/L) (Min.-Max.)	191798.70(700-476000)
CRP (mg/L) (Min.-Max.)	108.74(0.4-706)
Ferritin (µg/L) (Min.-Max.)	867.25(15-25310)
D-Dimer (µg/L) (Min.-Max.)	1276.54(155-10003)
Troponin T (ng/L) (Min.-Max.)	0.65(0-40)

Table 3. Relationship between laboratory parameters and 1-month and 3-month mortality

	1-month mortality		p
	No	Yes	
	Median (IQR)	Median (IQR)	
WBC (x10⁶/L)	6560 (5030-8960)	6825 (5530-9780)	0.475
Lymphocyte count (x10⁶/L)	940 (680-1410)	905 (590-1410)	0.613
Lymphocyte %	16.5 (11-22)	14.75 (9-23)	0.518
Neutrophil count (x10⁶/L)	4720 (3410-7210)	5165 (4480-7470)	0.180
Neutrophil %	76 (68-84)	79.5 (70-86)	0.323
Hemoglobin (g/dL)	12.2 (11.1-13.4)	12.45 (10.8-13.6)	0.925
Platelet (x10⁶/L)	183000 (145000-236000)	167000 (123000-210000)	0.177
CRP (mg/L)	90 (50-154)	105.5 (54-181)	0.388
Ferritin (µg/L)	462.5 (238-995)	621 (352-1426)	0.139
D-Dimer (µg/L)	839 (462-1530)	1027.5 (501-1700)	0.252
Troponin T (ng/L)	0.02 (0-0.04)	0.03 (0.02-0.07)	**0.015**
	3- month mortality		**p**
	No	**Yes**	
	Median (IQR)	**Median (IQR)**	
WBC (x10⁶/L)	6450 (5030-8580)	6930 (5530-10040)	0.277
Lymphocyte count (x10⁶/L)	930 (690-1390)	910 (590-1460)	0.779
Lymphocyte %	17 (11-22)	14,5 (9-22)	0.423
Neutrophil count (x10⁶/L)	4560 (3410-7030)	5170 (4480-7840)	0.105
Neutrophil %	76 (68-84)	79 (70-85)	0.317
Hemoglobin (g/dL)	12.2 (11.1-13.4)	12.3 (10.9-13.5)	0.973
Platelet (x10⁶/L)	183000 (149000-234000)	166000 (123000-210000)	0.145
CRP (mg/L)	85 (50-154)	111 (54-157)	0.387
Ferritin (µg/L)	480.5 (226.5-1009.5)	583 (347-1028)	0.203
D-Dimer (µg/L)	839 (462-1466)	1044 (501-1700)	0.202
Troponin T (ng/L)	0.02 (0-0.04)	0.03 (0.02-0.05)	**0.011**

chronic lung disease were found to be more frail (p<0.001, p<0.001, and p=0.031, respectively).

When the COVID-19 treatment received by patients during hospitalization was examined in relation to their frailty status, it was observed that non-frail patients received steroids more frequently (p=0.024).

When the relationship between sex and mortality was examined, no significant relationship was found between sex and 1-month or 3-month mortality.

Mortality Analysis

When the relationship between sex and mortality was examined, no significant relationship was found between sex and 1-month or 3-month mortality.

When the relationship between patients' chronic diseases and mortality was examined, it was observed that 1-month and 3-month mortality were higher in patients with hematological malignancies.

No significant relationship was found between mortality and other chronic diseases (for hematological malignancy, p=0.021 and p=0.003 for 1-month and 3-month mortality, respectively) (Table 4).

When the relationship between prognostic hematological parameters and mortality was examined, it was found that 3-month mortality was higher in patients with elevated troponin levels, while no significant relationship was found between mortality and other prognostic parameters (for troponin, p=0.022) (Table 4).

Table 4. Relationship between chronic disease, prognostic laboratory parameters, COVID-19 treatment administered during hospitalization and 1- month and 3-month mortality

Relationship between chronic diseases and mortality											
		1-month mortality				**p**	**3-month mortality**				**p**
		No		**Yes**			**No**		**Yes**		
		n	**%**	**n**	**%**		**n**	**%**	**n**	**%**	
CAD	No	84	(68.29)	21	(70.00)	0.857	78	(66.67)	27	(72.97)	0.473
	Yes	39	(31.71)	9	(30.00)		39	(33.33)	10	(27.03)	
HT	No	42	(34.15)	11	(36.67)	0.795	41	(35.04)	12	(32.43)	0.771
	Yes	81	(65.85)	19	(63.33)		76	(64.96)	25	(67.57)	
DM	No	74	(60.16)	18	(60.00)	0.987	69	(58.97)	23	(62.16)	0.730
	Yes	49	(39.84)	12	(40.00)		48	(41.03)	14	(37.84)	
COPD	No	106	(86.18)	25	(83.33)	0.690	101	(86.32)	31	(83.78)	0.700
	Yes	17	(13.82)	5	(16.67)		16	(13.68)	6	(16.22)	
Hematological malignancy	No	121	(98.37)	27	(90.00)	0.021	116	(99.15)	33	(89.19)	0.003
	Yes	2	(1.63)	3	(10.00)		1	(0.85)	4	(10.81)	
CKD	No	102	(82.93)	22	(73.33)	0.229	97	(82.91)	27	(72.97)	0.184
	Yes	21	(17.07)	8	(26.67)		20	(17.09)	10	(27.03)	
Relationship between prognostic laboratory parameters and mortality											
		1-month mortality				**p**	**3-month mortality**				**p**
		No		**Yes**			**No**		**Yes**		
		n	**%**	**n**	**%**		**n**	**%**	**n**	**%**	
Lymphopenia (<800 x 10^6/L)	No	78	(63.41)	18	(60.00)	0.729	74	(63.25)	22	(59.46)	0.678
	Yes	45	(36.59)	12	(40.00)		43	(36.75)	15	(40.54)	
At least a 10-fold increase in CRP	No	31	(25.20)	6	(20.00)	0.551	31	(26.50)	7	(18.92)	0.351
	Yes	92	(74.80)	24	(80.00)		86	(73.50)	30	(81.08)	
Ferritin>500 (µg/L)	No	64	(52.46)	12	(40.00)	0.221	60	(51.72)	16	(43.24)	0.369
	Yes	58	(47.54)	18	(60.00)		56	(48.28)	21	(56.76)	
D-Dimer> 1000 (µg/L)	No	72	(58.54)	14	(46.67)	0.240	69	(58.97)	17	(45.95)	0.164
	Yes	51	(41.46)	16	(53.33)		48	(41.03)	20	(54.05)	
Troponin T (ng/L)	Normal	43	(36.13)	6	(21.43)	0.137	43	(38.05)	6	(17.14)	0.022
	High	76	(63.87)	22	(78.57)		70	(61.95)	29	(82.86)	
Relationship between COVID-19 treatment administered during hospitalization and mortality											
		1-month mortality				**p**	**3-month mortality**				**p**
		No		**Yes**			**No**		**Yes**		
		n	**%**	**n**	**%**		**n**	**%**	**n**	**%**	
Enoxaaparin	No	8	(6.56)	4	(13.33)	0.218	8	(6.90)	4	(10.81)	0.441
	Yes	114	(93.44)	26	(86.67)		108	(93.10)	33	(89.19)	
Favipravir	No	5	(4.17)	1	(3.33)	0.835	5	(4.39)	1	(2.70)	0.649
	Yes	115	(95.83)	29	(96.67)		109	(95.61)	36	(97.30)	
Dexamethasone	No	57	(46.72)	11	(36.67)	0.321	56	(48.28)	12	(32.43)	0.091
	Yes	65	(53.28)	19	(63.33)		60	(51.72)	25	(67.57)	

Table 4. Continue

Relationship between COVID-19 treatment administered during hospitalization and mortality		1-month mortality				p	3-month mortality				p
		No		Yes			No		Yes		
		n	%	n	%		n	%	n	%	
1 mg/kg methylprednisolone	No	116	(95.08)	28	(93.33)	0.701	110	(94.83)	35	(94.59)	0.956
	Yes	6	(4.92)	2	(6.67)		6	(5.17)	2	(5.41)	
250 mg methylprednisolone	No	122	(100.00)	28	(93.33)	0.004	116	(100.00)	35	(94.59)	0.012
	Yes	0	(0.00)	2	(6.67)		0	(0.00)	2	(5.41)	
Did the patient receive steroids?	No	51	(41.80)	8	(26.67)	0.127	50	(43.10)	9	(24.32)	0.041
	Yes	71	(58.20)	22	(73.33)		66	(56.90)	28	(75.68)	
Did the patient receive any quinolone during admission?	No	84	(68.85)	17	(56.67)	0.205	80	(68.97)	22	(59.46)	0.285
	Yes	38	(31.15)	13	(43.33)		36	(31.03)	15	(40.54)	

The relationship between COVID-19 treatment received by patients during hospitalization and mortality was examined. It was observed that 1-month and 3-month mortality were higher in patients receiving 250 mg of prednisolone (p=0.004 and p=0.012 for 1-month and 3-month mortality, respectively). While no significant increase in 1-month mortality was detected in patients receiving steroids, 3-month mortality was found to be higher in patients receiving steroids (p=0.127 and p=0.041 for 1-month and 3-month mortality, respectively) (Table 4).

When the relationship between chronically used medication groups and mortality was examined, no association was found between any medication group and mortality (Table 4).

When the relationship between the number of chronic diseases, the number of chronically used medications, and mortality was examined, no significant relationship was found between mortality and the number of medications or diseases.

When the relationship between patients' age and mortality was examined, it was observed that 3-month mortality increased as patient age increased (p=0.220 and p=0.029 for 1-month and 3-month mortality, respectively).

Factors Independently Associated with Survival and Mortality (Kaplan-Meier and Regression Analysis Results)

Binary logistic regression analysis was performed to determine the factors affecting 1-month and 3-month mortality. According to the binary logistic regression analysis, age, frailty, elevated troponin, and the presence of hematological malignancy were not found to have a significant effect on 1-month mortality. However, a significant relationship was found between the presence of hematological malignancy and 3-month mortality (p=0.02) (Table 5).

Patients were divided into three categories based on their frailty status, and survival analysis was performed: Group 1: robust/pre-frail/frail; Group 2: robust or pre-frail/frail; Group 3: robust/pre-frail or frail.

Kaplan-Meier analysis was performed between 1-month mortality and frailty status, sex, prognostic parameters, and the presence of hematological malignancy. According to the results of the analysis, while survival was observed to be lower in patients with hematological malignancy (p=0.042), no statistically significant relationship was found for the other parameters (Table 6).

Kaplan-Meier analysis was performed between 3-month mortality and frailty status, sex, prognostic parameters, and the presence of hematological malignancy. According to the results of the analysis, it was observed that survival at 3 months was lower in the presence of hematological malignancy and elevated troponin (p<0.001 and p=0.024 for hematological malignancy and troponin, respectively) (Table 6).

When the effect of hematological malignancy on 1-month mortality was examined using Cox regression analysis, it was found that it had no statistically significant effect on mortality.

Table 5. Binary logistic analysis for 3-month mortality

	p	Exp(B)	95% CI for EXP(B)	
			Lower	Upper
Hematological malignancy	**0.020**	0.061	0.006	0.640

Table 6. Relationship between 1-month and 3rd-month mortality and frailty status, sex, prognostic parameters, and the presence of hematological malignancy

1-month mortality		Estimate	Std. error	95% Confidence interval		p
				Upper bound	Lower bound	
Sex	Male	21.712	1.677	18.425	24.998	0.833
	Female	20.282	1.894	16.570	23.995	
	All	21.072	1.265	18.593	23.552	
1.group	Robust	19.865	2.427	15.109	24.622	0.908
	Pre-frail	22.125	1.978	18.248	26.002	
	Frail	20.607	2.110	16.471	24.743	
	All	21.072	1.265	18.593	23.552	
2.group	Robust or pre-frail	21.416	1.578	18.322	24.510	0.774
	Frail	20.607	2.110	16.471	24.743	
	All	21.072	1.265	18.593	23.552	
3.group	Robust	19.865	2.427	15.109	24.622	0.834
	Pre-frail or frail	21.434	1.450	18.593	24.275	
	All	21.072	1.265	18.593	23.552	
Lymphopenia (<800 x 10^6)	No	20.247	1.709	16.898	23.597	0.448
	Yes	21.779	1.909	18.038	25.520	
	All	21.072	1.265	18.593	23.552	
Hematological malignancy	No	21.411	1.310	18.843	23.980	**0.042**
	Yes	14.800	6.172	2.704	26.896	
	All	21.072	1.265	18.593	23.552	
Increased CRP (>10 fold)	No	20.359	2.507	15.447	25.272	0.787
	Yes	21.117	1.434	18.307	23.927	
	All	21.072	1.265	18.593	23.552	
Ferritin > 500 µg/L	No	22.206	1.778	18.722	25.691	0.247
	Yes	20.150	1.738	16.744	23.556	
	All	21.066	1.265	18.586	23.546	
D-Dimer>1000 µg/L	No	20.050	1.792	16.537	23.564	0.636
	Yes	21.078	1.766	17.617	24.540	
	All	21.072	1.265	18.593	23.552	
Troponin T	Normal	21.236	2.818	15.713	26.759	0.651
	High	21.153	1.430	18.350	23.956	
	All	21.328	1.275	18.830	23.826	
3-month mortality		**Estimate**	**Std. Error**	**95% Confidence Interval**		**p**
				Lower Bound	**Upper Bound**	
Sex	Male	81.744	3.425	75.031	88.458	0.753
	Female	79.410	4.071	71.431	87.390	
	All	80.716	2.631	75.560	85.873	

Table 6. Continue

3-month mortality		Estimate	Std. Error	95% Confidence Interval		p
				Lower Bound	Upper Bound	
1.group	Robust	84.829	4.980	75.069	94.590	0.213
	Pre-frail	81.522	3.756	74.161	88.884	
	Frail	75.438	5.394	64.865	86.012	
	All	80.716	2.631	75.560	85.873	
2.group	Robust or pre-frail	82.684	2.990	76.824	88.544	0.093
	Frail	75.438	5.394	64.865	86.012	
	All	80.716	2.631	75.560	85.873	
3.group	Robust	84.829	4.980	75.069	94.590	0.276
	Pre-frail or frail	79.266	3.104	73.182	85.350	
	All	80.716	2.631	75.560	85.873	
Lymphopenia (<800 x 10^6)	No	81.617	3.339	75.072	88.161	0.662
	Yes	79.316	4.273	70.940	87.692	
	All	80.716	2.631	75.560	85.873	
Hematological malignancy	No	82.108	2.579	77.053	87.162	**<0.001**
	Yes	34.800	17.088	1.308	68.292	
	All	80.716	2.631	75.560	85.873	
Increased CRP (>10 fold)	No	81.184	5.412	70.577	91.792	0.323
	Yes	80.489	3.004	74.601	86.377	
	All	80.716	2.631	75.560	85.873	
Ferritin > 500 µg/L	No	82.793	3.457	76.017	89.569	0.298
	Yes	78.433	3.985	70.622	86.245	
	All	80.611	2.646	75.425	85.797	
D-Dimer>1000 µg/L	No	81.070	3.195	74.808	87.331	0.329
	Yes	78.520	4.259	70.171	86.868	
	All	80.716	2.631	75.560	85.873	
Troponin T	Normal	88.823	3.347	82.262	95.384	**0.024**

When the effects of hematological malignancy and elevated troponin on 3-month mortality were examined using Cox regression analysis, it was found that the presence of hematological malignancy increased 3-month mortality by 4.2 times, and elevated troponin increased it by 2.4 times, with a borderline significant p-value (p=0.02 for hematological malignancy, p=0.05 for elevated troponin) (Table 7).

Discussion

This prospective study included 154 patients with an average age of 72 years.

The average follow-up period for patients was 81 days (min: 1, max: 97). The average hospital stay was 8.5 days. The mortality rate at 1 month was found to be 19.61% (n=30). The mortality rate at 3 months was calculated as 24.03% (n=37).

When the relationship between frailty and mortality was examined, no statistically significant relationship was found between frailty status and mortality, while a statisti-

Table 7. Cox regression analysis for 3-month mortality

	B	SE	p	Exp(B)	95.0% CI for Exp(B)	
					Lower	Upper
Hematological malignancy	1.436	0.616	**0.020**	4.203	1.256	14.063
Troponin T	0.890	0.453	**0.050**	2.434	1.001	5.917

cally significant relationship was found between increased frailty score and 3-month mortality.

When the relationship between frailty status and laboratory parameters was examined, a significant relationship was found between elevated troponin and frailty.

Among the mortality and laboratory parameters examined at 1 and 3 months, only elevated troponin and mortality showed a significant relationship.

When we look at the studies in the literature examining the relationship between frailty and mortality in elderly COVID-19 patients, we see that different frailty scales are used in the studies and that the results are variable. In a study conducted by Kundi et al.[4] in 2020 in our country, using the hospital frailty risk score to examine the relationship between frailty and mortality in 18,234 hospitalized COVID patients, the average age of the patients was reported as 74.1. A total of 12,295 patients were classified as frail. The in-hospital mortality rate was stated as 18.2%. The study concluded that there was a statistically significant relationship between frailty and in-hospital mortality. This study has several weaknesses. The hospital frailty risk score only analyzes frailty based on the diagnoses available in the system. This scoring system evaluates frailty based on the number of illnesses rather than frailty parameters such as ambulation, walking speed, muscle strength, functionality, and malnutrition. Indeed, those with a low number of illnesses may also have higher disease severity, which can negatively affect frailty. Not taking disease severity into account is also among the limitations of the scale. As the authors have stated, the hospital vulnerability risk score is a scoring system that is difficult and inappropriate to apply to all patients and may give misleading results in terms of vulnerability.

Steinmeyer et al.[5] examined the clinical characteristics and disease outcomes of 94 hospitalized COVID patients in 2020. This retrospective study included patients from three geriatrics clinics. Frailty status was assessed using the Frail Non-Disabled Survey (FIND), which is very similar to the FRAIL questionnaire we used in our study. The mean age of the patients included in the study was 85.5, and 10 patients were classified as frail. According to multivariate regression analysis, increased age (>85 years), lymphopenia (<800), and respiratory failure were associated with mortality, while no significant relationship was found between frailty status and mortality.

Yang et al.[6] examined the relationship between frailty and mortality in hospitalized COVID patients in a meta-analysis in 2021. This meta-analysis included 4324 patients from 16 studies. Fourteen of the studies were retrospective cohorts, and two were prospective cohorts. The meta-analysis included 11 studies using the Clinical Frailty Scale, one using the Frailty Index, one using the FRAIL scale, one using the Palliative Performance Scale, one using the Hospital Frailty Risk Score, and one using the Frail Non-Disabled Survey. The meta-analysis found that frailty was associated with severe illness, prolonged hospital stay, mechanical ventilation, and increased mortality (RR: 1.81, $p<0.001$). One weakness of this analysis is that most of the studies included were retrospective. Furthermore, the mean follow-up period was not specified in the meta-analysis. As the authors also noted, converting OR to RR in the analysis may have contributed to the increased risk ratio.

Zhang et al.[7] conducted a meta-analysis in 2021 involving 23,944 studies to examine the relationship between frailty and mortality in COVID patients. This meta-analysis included 15 studies; seven were prospective and eight were retrospective. Of the studies included, 11 examined in-hospital mortality, three examined 30-day mortality, and one examined 60-day mortality. Thirteen of the patients included in the study were hospitalized, and two were nursing home residents. Eleven studies examined in-hospital mortality, three examined 30-day mortality, and one examined 60-day mortality. In 11 of these studies, the Clinical Frailty Scale was used; in one, the Frailty Index; in one, the Palliative Performance Scale; in one, the Hospital Frailty Risk Score; and in one, the Frail Non-Disabled Survey. As a result of the meta-analysis, frailty was found to be a risk factor for mortality. Of the studies included in the meta-analysis, 10 used OR (2.48) and five used HR (1.99) to examine the relationship between frailty and mortality (p-value not specified).

A meta-analysis conducted by Subramaniam et al.[8] in 2022 examined the relationship between frailty and in-hospital mortality or 30-day mortality and the need for invasive mechanical ventilation in hospitalized COVID patients. A total of 34,628 patients from 25 studies were included. For frailty, the Clinical Frailty Scale was used in 21 studies, the Frailty Index in one study, the Hospital Frailty Risk Scale in two studies, and the Frail Non-Disabled Survey in one study. The mean age of the patients was 73, the frailty rate was 57.9%, and the mortality rate was 26.2%. This meta-analysis found no significant relationship between frail and non-frail populations in terms of mortality. Furthermore, it was noted that frail patients had a lower need for invasive mechanical ventilation compared with non-frail patients and that non-frail patients had a higher rate of admission to the intensive care unit. The lower rate of intensive care unit admission in frail patients may be related to patient, family, or clinician preference. Of the studies included in the analysis, eight indicated mortality using HR, six using OR, and seven using other definitions. Four studies found no asso-

ciation between frailty and mortality. When frail patients were compared with non-frail patients, although univariate pooled mortality was higher in frail patients, frailty did not increase mortality when other covariates were considered (RR: 1.17). Based on 11 studies, it was also reported that the proportion of non-frail patients was higher in patients admitted to the intensive care unit (p=0.011) and that mortality was higher in non-frail patients (RR: 1.63). Although the majority of studies included in the meta-analysis (n=21) used the Clinical Frailty Scale, the large number of patients in studies using the Hospital Frailty Risk Scale may have skewed the results. Finally, the study observed that mortality was higher in patients with dementia, chronic renal failure, heart failure, diabetes mellitus, hypertension, and cerebrovascular disease.

Sablerolles et al.[9] retrospectively examined the relationship between frailty and in-hospital mortality in hospitalized COVID patients in their 2021 study, which included 2434 patients in 63 hospitals across 11 countries. In this study, which used the Clinical Frailty Scale and evaluated patients with an average age of 68 years, it was observed that frail patients had a higher rate of in-hospital mortality and that frailty was associated with increased intensive care unit admission (p<0.0001 for both cases).

Blomaard et al.[10] retrospectively examined the relationship between frailty and in-hospital mortality in 1376 hospitalized COVID patients in 15 hospitals in the Netherlands in 2021. In this study, which used the Clinical Frailty Score to assess frailty, the average age of the included patients was 78 years. As a result of this study, a significant relationship was found between increased frailty score and mortality (p<0.001; mortality was approximately three times higher in patients with Clinical Frailty Score 6–9 compared with patients with Clinical Frailty Score 1–3; OR: 2.8, CI: 1.8–4.3). In addition, it was shown that the time from the onset of symptoms to hospital admission was shortened as the frailty score increased (p<0.001). The authors interpreted this situation as frail patients being less tolerant of disease symptoms.

A literature review revealed that there are very few studies examining the relationship between mortality and laboratory parameters in elderly COVID patients.

In 2020, Wang et al.[11] conducted a study to determine the characteristics and prognostic factors of the disease in elderly COVID patients over a 4-week follow-up period. The study included 339 patients with an average age of 71 years. The results showed that increased WBC and neutrophil counts, decreased platelet count, prolonged aPTT, increased D-dimer, increased AST, increased creatinine, increased CK and troponin, increased CRP and IL-6, decreased CD4 and CD8, and increased procalcitonin were associated with mortality. In the Cox regression analysis performed, it was shown that increased WBC and prolonged aPTT (HR: 1.16 and 1.17, respectively; p<0.001 for both parameters) were associated with increased mortality, and decreased lymphocyte count was a strong factor in predicting poor disease outcome (p<0.001). Factors such as procalcitonin and troponin were also statistically significant, but it was noted that their predictive power was limited because their HR was around 1.

In our study, the only laboratory parameter associated with frailty and mortality was found to be increased troponin levels. Although no research directly investigating the relationship between frailty and troponin levels has been observed in the literature, Ticinesi et al.[12]'s study of elderly individuals presenting to the emergency department with suspected acute coronary syndrome showed that setting higher troponin threshold values (≥141 ng/L) in frail elderly patients with suspected acute coronary syndrome increased specificity (in the study, the upper limit of normal was 17.8 ng/L for men and 10.5 ng/L for women). In other words, it was observed that the relationship between troponin, MI, and frailty increased when the upper limit value for hsTroponin I was set higher. Based on this, it can be concluded that troponin levels may be somewhat higher in frail patients. The fact that no correlation was found between mortality and other laboratory parameters besides troponin in our study may be related to the limitation of evaluating only the parameters at the time of admission.

Our study has several strengths and limitations. Strengths include being one of the few studies to examine the relationship between frailty and mortality in COVID-19 patients using the FRAIL questionnaire, being the first to investigate the relationship between frailty and laboratory parameters, being one of the few studies to examine the relationship between laboratory parameters and mortality in elderly COVID patients, and being a prospective study. Weaknesses include the small number of patients included, the failure to assess vital signs and oxygen requirements upon hospital admission, the inability to examine other elements of a comprehensive geriatric assessment, such as malnutrition and sarcopenia, and being a single-center study. Furthermore, laboratory parameters were recorded upon initial hospitalization, and the analysis was performed only with parameters at admission; follow-up laboratory measurements were not included in the evaluation.

Conclusion

COVID-19 is an infectious disease that causes significant morbidity and mortality. Frailty, on the other hand, is a

condition that usually appears with advancing age, is characterized by decreased resistance to stressors, and is associated with increased mortality. In our study, we investigated whether there is a relationship between frailty and mortality in patients with COVID-19. While no statistically significant relationship was found between frailty status and mortality in patients with COVID-19, a significant relationship was found between frailty score and elevated troponin levels, as well as between mortality and elevated troponin levels. Based on these results, we recommend that frailty status, a significant cause of mortality and morbidity, be assessed and that troponin levels be checked in elderly hospitalized patients with COVID-19.

Abbreviations

ACE: Angiotensin converting enzyme
aPTT: Active partial thromboplastin time
ARB: Angiotensin receptor blocker
ARDS: Acute respiratory distress syndrome
BAL: Bronchoalveolar lavage
CD-3: Cluster of differentiation-3
CD-4: Cluster of differentiation-4
CD-8: Cluster of differentiation-8
CK: Creatinine kinase
COPD: Chronic obstructive pulmonary disease
COVID: Coronavirus disease
COVID-19: Coronavirus disease 2019
CRP: C reactive protein
CT: Computed tomography
CVA: Cerebrovascular accident
DL: Deciliter
DM: Diabetes mellitus
ESR: Erythrocyte sedimentation rate
G: Gram
HARC: Health application and research center
HR: Hazard ratio
HsTroponin: High sensitive troponin
HT: Hypertension
IL-6: Interleukin-6
IL-10: Interleukin-10
CAD: Coronary artery disease
CKD: Chronic kidney disease
L: Liter
LDH: Lactate dehydrogenase
MERS-CoV: Middle east respiratory syndrome–related coronavirus
MCG(µg): Microgram
MG: Milligram
Min: Minimum
Max: Maximum
mRNA: Messenger ribonucleic acid
NG: Nanogram
NOAC: Novel oral anticoagulant
OR: Odds Ratio
PCR: Polymerase chain reaction
RNA: Ribonucleic acid
RR: Risk ratio
SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2
SD: Standard deviation
USA: United States of America
WBC: White blood cell
WHO: World Health Organization

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Research Article

Comparative Evaluation of Fibrinolytic System Parameters in Newly Diagnosed Polycythemia Vera and Essential Thrombocythemia Patients

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Abstract

Objectives: Thrombotic complications are major determinants of morbidity and mortality in polycythemia vera (PV) and essential thrombocythemia (ET), yet the role of fibrinolytic dysfunction remains unclear. This study evaluated tissue plasminogen activator (tPA), plasminogen activator inhibitor-1 (PAI-1), and thrombin-activatable fibrinolysis inhibitor (TAFI) in newly diagnosed patients with PV and ET.

Methods: In this prospective, single-center, comparative cross-sectional study, 46 newly diagnosed patients with myeloproliferative neoplasms, including 17 with PV and 29 with ET, and 36 healthy controls were included. Serum tPA, PAI-1, and TAFI levels were measured by enzyme-linked immunosorbent assay and compared between groups.

Results: Among the fibrinolytic parameters, tPA levels differed significantly between groups (p=0.015). Both patients with PV and those with ET had lower tPA levels than healthy controls. No significant differences were observed in PAI-1 or TAFI levels.

Conclusion: Newly diagnosed patients with PV and ET showed reduced tPA levels, suggesting impaired fibrinolytic activation. These findings support a possible contribution of hypofibrinolysis to the prothrombotic tendency of myeloproliferative neoplasms.

Keywords: Essential thrombocythemia, fibrinolytic system, polycythemia vera

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Myeloproliferative neoplasms (MPNs) occur when a multipotential stem cell undergoes neoplastic transformation. According to the World Health Organization (WHO), MPNs are classified as chronic myeloid leukemia (CML), polycythemia vera (PV), primary myelofibrosis, essential thrombocythemia (ET), and other less common entities.[1]

Hemostatic disorders are an important cause of mortality and morbidity in patients with PV and ET.[2] The percentage of patients with thrombosis varies from 40% to 60% in PV and ET. In addition to thrombosis, bleeding is also frequently seen in such diseases. Thrombosis can occur at the arterial, venous, or microcirculatory levels, and hemorrhage is

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predominantly mucocutaneous. The pathophysiological mechanisms of thrombosis and hemorrhage in MPNs are not fully understood.[3] It is known that factors such as being over 60 years old, hypertension, diabetes, and smoking increase the risk of thromboembolic events.[4] It has been shown that erythrocytosis and thrombocythemia contribute to the increased risk of thrombosis by increasing blood viscosity. It has also been shown that platelets have not only numerical but also structural defects in MPNs. Especially in patients with ET, changes in von Willebrand factor (vWF) and FVIII levels have been detected.[5]

The fibrinolytic system is a physiological stabilizing mechanism within the coagulation process. The most crucial activator of plasminogen, the main enzyme of the fibrinolytic system, is tissue plasminogen activator (tPA). The two most important enzymes that reduce fibrinolytic activity by acting on the plasminogen-plasmin system are thrombin-activated fibrinolytic inhibitor (TAFI) and plasminogen activator inhibitor type 1 (PAI-1)[2].

We aimed to comparatively evaluate the parameters of the fibrinolytic system, including tPA, PAI-1, and TAFI, in newly diagnosed patients with PV, ET, and healthy controls. Therefore, we aimed to find potential differences between patients with PV and those with ET through subgroup analyses. Since the pathogenesis of PV and ET is quite different, it was planned to evaluate these diseases separately.

Methods

Study Design and Patient Selection

Our study was conducted as a prospective, single-center, comparative cross-sectional study. The first group of patients was admitted to the Bakırköy Dr. Sadi Konuk Training and Research Hospital Hematology outpatient clinic between January and October 2015 and was newly diagnosed with PV and ET. The second group consisted of healthy volunteers without hematologic disease, serving as the control group. The patient and control groups were similar in terms of age and gender. Participants were 18–80 years old and diagnosed with PV and ET according to the WHO 2008 criteria. Patients who met the following criteria were excluded: 1) use of drugs that affect the coagulation and fibrinolytic system, 2) use of drugs that affect platelet functions, 3) history of arterial or venous thrombosis, 4) presence of heart failure, 5) presence of different hematological diseases, and 6) presence of active malignancy.

Before the study, informed consent was obtained from the volunteers in the patient and control groups. The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol was approved by the Ethics Committee of Bakırköy Dr. Sadi Konuk Training and Research Hospital with decision number 2014/15/12, dated 10.11.2014.

Data Collection and Procedures

Demographic and clinical characteristics of eligible patients were collected. Hematological, biochemical, and hemostasis tests were performed and recorded. In addition, the presence of diabetes mellitus, hypertension, and dyslipidemia, which may increase thrombotic risk, was noted.

A total of 5 mL of blood was collected from the patient and control groups between 08:00 and 10:00 in the morning, after a 10–12-hour overnight fast, in a sitting position, into a vacuum gel tube. After the collected blood was kept at room temperature for about 30 minutes, it was centrifuged at 3000 rpm for 15 minutes, and the separated serum was stored at -80 °C until the day of analysis. Serum TAFI, tPA, and PAI-1 levels were analyzed by ELISA using YH Biosearch Laboratory, China, kits (Cat. Nos. YHB2957Hu, YHB3009Hu, and YHB2361Hu, respectively). The intra-assay CV values of the methods were 10%, and the inter-assay CV values were 12%.

PAI-1, TAFI, and tPA measurements were made using ELISA and biotin-labeled sandwich methods. After the serum samples were pipetted, the reaction was completed by incubation and washing steps, and the measurements were performed.

Statistical Analysis

The demographic features of the study population were stratified and recorded. SPSS version 23 (IBM Corp., Armonk, NY, USA) was used to analyze the patient groups' numerical data and generate statistics. Whether the distribution was normal was determined using the Kolmogorov-Smirnov test. The independent t-test was used to evaluate parameters with normal distribution, and the Mann-Whitney U test was used to evaluate parameters that did not show normal distribution. The ANOVA (Tukey) method was used to compare differences among the three normally distributed groups (PV, ET, and healthy controls), and the Kruskal-Wallis test was used to compare differences among the non-normally distributed groups. The chi-square test or Fisher's exact test was used to analyze categorical variables. A two-tailed p-value <0.05 was considered statistically significant.

Results

A total of 82 participants, 46 in the MPN group and 36 in the control group, were included. Among the MPN group, 17 (37%) patients were diagnosed with PV and 29 (63%) with ET. The clinical and laboratory findings of the participants are presented in Table 1. Parameters with abnormal distribution were described using the median, upper, and

Table 1. Clinical data of patients

Parameter (unit)	ET n=29	PV n=17	Control n=36	p
Age	53 (21- 81)	51 (26- 71)	52 (27-81)	0.395
Gender (F/M)	18/11	9/8	21/15	0.832
Hemogram Parameters				
WBC (mm^3)	9300 (3510- 15800)	8700 (5070-23100)	7700(5200-16850)	0.151
HGB (g/dl)	13.25±2.54	18.28±1.71	13.72±1.48	<0.01
HCT	39.6 (24.6-49.2)	52.8 (49.8-64.7)	41.3(23.5-48)	<0.001
PLT (mm^3)	748 (484-2092)	328 (176-2650)	252 (153-540)	<0.001
NEU	5490 (1680-10320)	5870 (3250-17700)	4327.5(2500-10000)	0.011
Biochemical & Lipid profiles				
LDH	248 (163-396)	218 (182-454)	190.5 (148-326)	<0.001
Erythropoietin	5.88 (1.6-48.5)	2.41 (0.76-16)	11.3 (1.89-30.7)	<0.001
Uric Acid	4.94±1.67	6.17±1.09	5.4±1.63	0.060
CRP	0.35 (0.02-9.2)	0.34 (0.07-1.4)	0.245 (0.05-1)	0.080
Vitamin B12	282 (100-1500)	258 (122-942)	301 (37-544)	0.666
Total Cholesterol	189.03±52.44	179.62±33.71	203.22±40.64	0.174
LDL	103 (41.6-208)	103 (24.6-160)	114 (63-255)	0.213
HDL	45.5 (13-76)	40.5 (29-55)	48 (28-97)	0.091
Triglyceride	129 (53-722)	167 (57-274)	133 (61-319)	0.088

Normal distribution parameters were presented as mean and standard deviation (X) ± (SD). Non-normal distributed parameters were presented as median values (M) and smallest (S). largest (L). (M)-(S-L). ET: Essential thrombocythemia; PV: Polycythemia vera; WBC: White blood cell; HGB: Hemoglobin; HCT: Hematocrit; PLT: Platelet count; NEU: Neutrophil count; LDH: Lactate dehydrogenase; CRP: C-reactive protein; LDL: Low-density lipoprotein; HDL: High-density lipoprotein.

lower values, and parameters with normal distribution were described using the mean and standard deviation values. Patient ages were similar across groups, and ET was more common in women.

Compared with the control group, hemoglobin was significantly higher in patients with PV, and the platelet count was significantly higher in patients with ET. Neutrophil counts and LDH values were higher in all patients with MPN compared with the healthy group. As expected, the erythropoietin (EPO) value was lower in the MPN group. These differences were statistically significant ($p<0.05$). Although the number of white blood cells was numerically higher in the MPN group, no statistical difference was observed. In addition, there was no significant difference between the groups in uric acid, C-reactive protein, and vitamin B12 values. Similarly, no difference was found in lipid profiles. However, in the subgroup analysis, high-density lipoprotein (HDL) values were found to be significantly lower in patients with PV compared with healthy subjects ($p=0.008$).

The evaluation and comparison of hemostasis parameters are summarized in Table 2. PT and aPTT durations were longer, and fibrinogen was lower in patients with MPN ($p<0.05$). There were no significant differences in factor VIII (FVIII), von Willebrand factor antigen (vWF), and ristocetin cofactor activity (vWF-Ris) values between the three groups.

In evaluating the fibrinolytic system, the tPA value was statistically significant among the three groups ($p=0.015$) (Table 2). tPA values were 10.261 (2.666–51.494) in the PV group, 9.517 (0.179–59.802) in the ET group, and 19.357 (6.125–67.1) in the control group. When the groups were evaluated separately, the PV and ET groups had lower values than the control group. The differences were statistically significant, respectively ($p=0.015$, $p=0.018$). The distributions of tPA levels are shown in Figure 1. However, there was no significant difference between the PAI-1 and TAFI values.

Discussion

In MPNs, thrombosis and hemorrhage are complications that are important in mortality and morbidity. In our study, tPA, the main activator of the fibrinolytic system, was significantly lower in MPNs compared with the control group. There was no significant difference in the other anti-fibrinolytic system parameters, PAI-1 and TAFI. When patients diagnosed with PV and ET were compared with a separate

Table 2. Comparison of hemostasis parameters

Parameter (Unit)	ET n=29	PV n=17	Control n=36	p
PT	12.5 (11.3-15.9)	12.9 (11.1-38.2)	11.9 (10.5-14.9)	0.02
aPTT	28.2 (21.5-39.6)	29.2 (23.2-43.5)	26.25 (21.4-29.8)	<0.001
Fibrinogen	266 (191-705)	229 (108-435)	292 (197-412)	0.043
FVIII	62.1 (20.7-164.1)	57.35 (11.6-112)	68.8 (19-210)	0.251
vWF	73.8 (17.4-294.7)	81.95 (15-172.5)	96.85 (18.3-229)	0.412
vWF Ris	57.6 (15-165.9)	61.25 (15-161.3)	73 (15-228)	0.200
PAI-1 (ng/ml)	15.762 (0.591-86.654)	11.348 (2.751-83.875)	18.7335 (3.674-93.812)	0.234
TAFI (%)	56.41 (15.262-558.166)	70.072 (10.831-532.181)	79.88 (7.647-611.961)	0.833
t-PA (ng/ml)	9.517 (0.179-59.802)	10.261 (2.666-51.494)	19.357 (6.125-67.1)	0.015

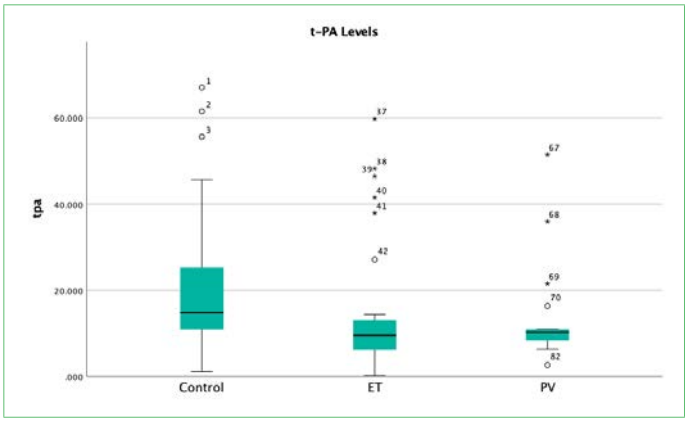


Figure 1. Distribution of tPA levels in ET, PV, and control groups.

control group and with each other, there was no difference in tPA levels among MPNs. Still, tPA levels were significantly decreased compared with the control group.

tPA is the primary activator of the fibrinolytic system; it converts inactive plasminogen to plasmin. PAI-1 limits fibrinolytic activity by inhibiting fibrinogen activators, including tPA and uPA. An increase in PAI-1 inhibits the fibrinolytic system, shifting the equilibrium toward procoagulation.[6] There are conflicting results regarding the fibrinolytic system in MPNs. In the study in which 20 patients diagnosed with ET were included by Bazzan et al.[7], similar to our study, tPA levels were lower in the healthy group compared with the patient group. Nevertheless, contrary to our study, PAI-1 values were significantly higher. As a result of the study, they stated that fibrinolytic imbalance might be a critical factor in thrombosis seen in patients with ET. However, in the study by Rosc et al.[8], in which tPA and PAI-1 values of 20 patients with CML, 17 with ET, and 5 with MF were compared with those of healthy volunteers, no significant difference was found in tPA levels. Nevertheless, in the subgroup analysis of this study, PAI-1 levels increased significantly in patients with ET compared with the control group. It has been suggested that the increase in PAI-1 levels may be due to vascular endothelial damage caused by proteolytic enzymes and cytokines secreted by leukocytes, especially neutrophils, and by granulocyte elastase, which are significantly increased in patients with MPN.[8]

In another study in which a total of 112 patients with MPN, including 63 with ET, 29 with PV, 11 with CML, and 9 with PMF, were included, tPA levels were higher in the MPN group, and statistically significant D-dimer elevation accompanied tPA elevation between the patient and control groups. It has been noted that elevated tPA and D-dimer levels in patients with MPN may be due to secondary activation in the fibrinolytic system. In addition, contrary to our study, PAI-1 levels of patients with ET and PV were higher than those in the control group. It has been suggested that the increase in PAI-1 may be due to increased production of activated platelets and vascular endothelial damage.[2] Similarly, PAI-1 levels of 19 patients with PV and 14 with ET were significantly increased compared with those of healthy volunteers in another study. There was a more significant increase in those with a history of thrombosis than in those who were asymptomatic or had a history of hemorrhage. They also found that PAI-1 levels correlated with platelet count in patients with PV and ET. They emphasized that fibrinolytic activity was significantly reduced in patients with MPN compared with the control group.[9]

TAFI activity has been shown to cause hypofibrinolysis.[10,11] However, our study observed no significant difference in TAFI activity between healthy controls and patients with MPN. Studies evaluating TAFI activity in patients with MPN are very few in the literature. In a study in which TAFI activity and susceptibility to thrombosis were measured in 21 patients diagnosed with ET and 21 healthy controls, TAFI was significantly higher in patients with ET. They emphasized that hypofibrinolysis, caused by increased TAFI activity, better explains the susceptibility to thrombosis in patients with ET.[12]

Our study has limitations. Although the study was designed as a prospective study, it was cross-sectional and lacked follow-up, so the relationships between fibrinolytic system parameters and thrombosis could not be determined. In 2015, the WHO 2008 criteria were still used to diagnose PV and ET. Since it was designed in 2015, patients were included according to the WHO 2008 criteria. However, since bone marrow biopsies were performed on all newly diagnosed patients, they also met the WHO 2016 criteria. Molecular tests such as CALR and MPL status are unknown, as they were not widely used at the time of data collection. The low number of patients has meant that the fibrinolytic system has not been evaluated in larger populations. The lack of standard measurements and cut-off values for tPA, PAI-1, and TAFI, which we evaluated in the study, is another limitation.

Conclusion

In conclusion, our study found that tPA levels, the main activator of the fibrinolytic system, were lower in patients with PV and ET than in the healthy control group. These results suggest that fibrinolytic system activity is reduced in patients with PV and ET. The number of studies on fibrinolytic system activity in patients with MPN is limited, and the studies are small in size. Although some studies are contrary to our results, the detection of a decrease in tPA and an increase in PAI-1 in most studies supports our finding that fibrinolytic system activity decreases in patients with PV and ET. We think that a decrease in fibrinolytic system parameters is a condition that predisposes to thrombosis.

Disclosures

Ethics Committee Approval: The protocol was approved by the Ethics Committee of Bakırköy Dr. Sadi Konuk Training and Research Hospital with decision number 2014/15/12, dated 10.11.2014.

Informed Consent: Written informed consent was obtained from all participants.

Conflict of Interest: The authors declare that they have no competing financial or non-financial interests.

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Research Article

Is Young-Onset Breast Cancer a Distinct Clinical Entity?

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Abstract

Objectives: Women under 40 are not included in routine screening programs, which may delay early detection. This study aimed to evaluate the clinicopathological characteristics, treatment patterns, and survival outcomes of young breast cancer (BC) patients.

Methods: This retrospective study included 140 premenopausal women aged 18–40 years diagnosed with BC between January 2018 and December 2023. Medical records were reviewed for histopathological features, treatments, and survival data. Patients were divided into very young (≤35 years) and young (>35 years) groups.

Results: Of 140 patients, 55.7% were very young and 44.3% were young. Most cases were symptom-detected (97.9%). Invasive ductal carcinoma predominated in both groups. Grade 2 and 3 tumors were observed in 42.9% and 27.9% of cases, respectively (p=0.005). Estrogen and progesterone receptor negativity rates were 21.4% and 30%. Early-stage disease was more frequent in the young group, while advanced tumors and node positivity were higher in very young patients. Adjuvant chemotherapy rates were similar, but anthracycline-based regimens were more common in very young patients. Mean disease-free and overall survival were 124 and 170 months.

Conclusion: Young BC patients present with more advanced disease and unfavorable prognostic features. The lack of routine screening remains a critical issue, and larger prospective studies are needed.

Keywords: Breast cancer, Clinicopathological features, Young-onset

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Among all cancer types affecting women, breast cancer (BC) ranks first in terms of incidence and second only to lung cancer as a cause of cancer-related mortality.[1] In the adolescent and young adult (AYA) population—defined as individuals between 15 and 39 years of age—BC is also the most frequently diagnosed malignancy, representing roughly 5.6% of all invasive breast tumors.[2] When BC occurs in younger women, it tends to display more aggressive pathological features, such as larger tumor dimensions, poor differentiation, a greater likelihood of lymph node metastasis, overexpression of human epidermal growth factor receptor 2 (HER2), and a lack of hormone receptor expression.[3] Although different age thresholds have been used, "young" patients are most frequently defined as those under 40 years of age.[4]

AYA women are more likely than their older counterparts to carry inherited genetic mutations that predispose them to cancer, to be diagnosed with larger tumors, to present with unfavorable biological markers, and to have worse clinical outcomes [2]. Delayed diagnosis is common in this population, partly due to low clinical suspicion and the lack of routine screening programs.[5,6] Mammography, for instance,

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has not proven cost-effective in this age group.[7] According to data from the National Cancer Database, women under 35 years of age often present with more advanced disease and experience lower 5year survival rates.[8] They are also more frequently diagnosed with aggressive molecular subtypes, including triple-negative and HER2-positive breast cancer.[9] Pathogenic variants in *BRCA1*, *BRCA2*, or *TP53* are found in nearly 50% of AYA women.[10] For those with *BRCA1/2* mutations, risk-reducing bilateral salpingooophorectomy is advised after the completion of childbearing, and PARP inhibitors have emerged as a promising therapeutic option.[11,12]

While chemotherapy protocols do not differ substantially across age groups, young women present unique clinical challenges.[13] Most are of reproductive age, and cancer treatments can adversely affect fertility. Consequently, it is essential to discuss fertility preservation strategies before initiating systemic therapy.[13–15] In this context, early-stage detection and the use of less aggressive treatment regimens are particularly important. The present study therefore aimed to describe the clinicopathological features, treatment approaches, and survival outcomes of young patients diagnosed with breast cancer.

Methods

Study Design and Patient Selection

This retrospective investigation included 140 premenopausal women diagnosed with breast cancer between January 2018 and December 2023 at Gazi Yasargil Training and Research Hospital. All patients were aged 18–40 years at diagnosis. We excluded individuals who had either a second primary malignancy or insufficient data in their medical charts. The following clinical and pathological variables were collected from the hospital's electronic health records: age, marital status, smoking history, family history of breast/ovarian cancer, surgical approach, tumor laterality, histological type and grade, *BRCA1/2* mutation status, estrogen/progesterone receptor status, HER2 status, molecular subtype, TNM stage, tumor size, treatments received, recurrence status, last follow-up date, and survival outcomes. Subsequently, the study population was split into two age categories for comparison: very young (≤35 years) and young (>35 years).

Disease staging was determined according to the 8th edition of the American Joint Committee on Cancer (AJCC) tumor–node–metastasis (TNM) classification system. The study was approved by the Ethics Committee of the University of Health Sciences Gazi Yasargil Training and Research Hospital and was conducted in accordance with the Declaration of Helsinki (approval date: 29/09/2023; decision no: 527).

Pathological Evaluation

Immunohistochemical data extracted from pathology reports were used to determine estrogen receptor (ER), progesterone receptor (PR), HER2, and Ki67 expression levels. Positivity for ER and PR was defined as ≥1% nuclear staining on IHC at 10× magnification. For HER2, an IHC score of 3+ was classified as positive; cases with a score of 2+ required confirmation via fluorescence in situ hybridization (FISH) to assess gene amplification. A Ki67 index of ≥15% was considered high.

Tumor molecular subtyping was performed according to the four markers listed above. The luminal A category comprised ER- and/or PR-positive, HER2-negative tumors with a Ki67 ≤14%. Luminal B tumors were ER- and/or PR-positive with a Ki67 >14%, regardless of HER2 status (positive or negative). HER2-positive (HER2-enriched) tumors lacked both ER and PR but expressed HER2. Finally, triple-negative breast cancers were negative for ER, PR, and HER2.

Treatment

Patients were categorized according to the treatments received. Those who underwent neoadjuvant or adjuvant chemotherapy were further stratified based on receipt of anthracycline-based regimens. Hormonal therapy was classified into three groups: tamoxifen alone, aromatase inhibitors alone, or sequential therapy with tamoxifen followed by aromatase inhibitors. Patients who received adjuvant radiotherapy were recorded. Surgical management included breast-conserving surgery (BCS), modified radical mastectomy (MRM), and simple mastectomy (SM). All patients with HER2-positive disease received trastuzumab, and treatment was completed for a duration of one year.

Statistical Analysis

Statistical analysis was performed using SPSS (version 24.0; IBM Corporation, Armonk, NY, USA). Data normality was tested with the Shapiro–Wilk procedure, and Levene's test served to evaluate equality of variances. Student's t-test was applied for continuous data following a normal distribution; otherwise, the Mann–Whitney U test was used. Categorical variables were compared by means of the Pearson chisquare or Fisher's exact test, depending on the expected frequencies. Descriptive statistics for continuous variables are shown as either mean with standard deviation (SD) or median together with the minimum–maximum range. Categorical variables are expressed as counts and percentages (n/%). To assess survival, we used the Kaplan–Meier method, and group differences were tested with the logrank test. DFS was defined as the period from initial diagnosis to the first recurrence, whereas OS was defined as the period from diagnosis to death or last known follow-up. All analy-

ses were performed with a 95% confidence level, and p-values less than 0.05 were considered statistically significant.

Results

A total of 140 patients were included in the study; 78 (55.7%) were aged ≤35 years and 62 (44.3%) were >35 years. The median age at diagnosis was 35 years (range, 19–39). The predominant histological subtype was invasive ductal carcinoma (IDC), accounting for 72.9% (n=112) of cases. Tumor grading revealed 20% grade 1, 42.9% grade 2, and 27.9% grade 3 tumors. Estrogen receptor, progesterone receptor (PR), and HER2 positivity rates were 78.6%, 70%, and 40%, respectively. At diagnosis, 12.9% of patients were stage I, 48.6% stage II, 20.7% stage III, and 17.9% stage IV. A family history of breast and ovarian cancer in first- and second-degree relatives was present in 9.3% and 7.9% of patients, respectively, with no significant differences between age groups (p=0.30 and p=0.53, respectively). *BRCA* mutation status was available for 50 patients; 12.9% harbored a mutation, with similar frequencies between the two age groups (p=1.00). Regarding marital status, 67.1% of patients were married and 30% were single. A significantly higher proportion of patients aged $>$35 years were married compared to those ≤35 years (79% vs. 62.8%, p=0.03, respectively). Diagnosis was predominantly symptom-driven (97.9%), with no difference between age groups (p=0.58).

Surgical management included breast-conserving surgery in 44.3%, modified radical mastectomy in 40.7%, and simple mastectomy in 5% of patients. The median tumor size was 30 mm (range, 9–80), with no significant difference between age groups (p=0.75). The median Ki-67 proliferation index was 20%, also comparable between groups (p=0.74).

The frequency of IDC was 76.9% in patients aged ≤35 years and 67.7% in those >35 years (p=0.17). Notably, grade 3 tumors were significantly more common in the younger group (40.8% vs. 17.9%, p=0.005). Estrogen receptor positivity was significantly lower in patients ≤35 years compared to those >35 years (70.5% vs. 88.7%, p=0.009), whereas PR positivity showed a non-significant trend (64.1% vs. 77.4%, p=0.08). HER2 positivity was similar between groups (p=0.53) (Table 1).

Molecular subtype distribution was as follows: luminal B (62.9%), luminal A (17.1%), HER2-enriched (10.7%), and triple-negative (9.3%), with no significant difference between age groups (p=0.06). Tumor T stage distribution was 20.7% T1, 65% T2, 13.6% T3, and 0.7% T4. Among patients $\le$35 years, 80.8% were T1–T2 and 19.2% were T3–T4, compared to 91.9% and 8.1%, respectively, in patients >35 years (p=0.06). Nodal status was N0 in 22.1%, N1 in 49.3%, N2 in 23.6%, and N3 in 5% of patients. Node positivity was observed in 83.3% of patients aged ≤35 years and 71% of those >35 years, without a statistically significant difference (p=0.08). Stage distribution by age group showed no significant differences (Table 2).

Adjuvant chemotherapy was administered to 54.3% of patients, with no difference between age groups (p=0.57). However, anthracycline-based chemotherapy was used significantly more frequently in younger patients (p=0.04). Adjuvant radiotherapy was delivered in 71.4% of cases and hormonal therapy in 79.3%, with no significant differences between groups (p=0.17 and *p*=0.10, respectively) (Table 3).

The mean disease-free survival (DFS) was 124±6.09 months; 125 months in patients ≤35 years and 103 months in those >35 years, with no significant difference (p=0.79). The 3-year DFS rates were 89% and 86%, respectively (Fig. 1). The mean overall survival (OS) was 176±6.00 months; 177 months in the younger group and 122 months in the young group, also without a significant difference (p=0.59). The 3-year OS rates were 90% and 94%, respectively (Fig. 2). The overall recurrence rate was 13.6%, including 2.1% local recurrence and 10% systemic recurrence.

Discussion

This analysis compared two age groups of breast cancer patients (18–40 years): those aged 35 years or younger ("very young") and those older than 35 years ("young"). The primary aim was to assess differences in clinicopathological features and survival outcomes. Our results indicate that the very young subgroup had more aggressive tumor characteristics, particularly a significantly higher frequen-

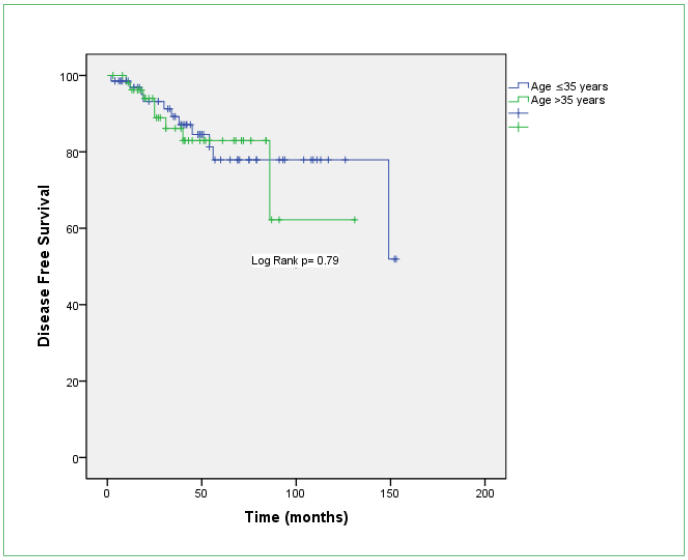


Figure 1. Disease-free survival curve between the ≤35 age group and the >35 age group according to Kaplan–Meier analysis.

Table 1. Demographic and pathological characteristics

Feature	Category	Overall (n=140)	≤35 years (n=78)	>35 years (n=62)	p
Family history of breast cancer	Yes	13 (9.3%)	9 (11.5%)	4 (6.5%)	0.30
	No	127 (90.7%)	69 (88.5%)	58 (93.5%)	
Family history of ovarian cancer	Yes	11 (7.9%)	5 (6.4%)	6 (9.7%)	0.53
	No	129 (92.1%)	73 (93.6%)	56 (90.3%)	
Marital status	Married	94 (67.1%)	47 (60.3%)	47 (75.8%)	0.03
	Single	42 (30.0%)	29 (37.2%)	13 (21.0%)	
	Divorced	4 (2.9%)	2 (2.6%)	2 (3.2%)	
Initial presentation	Symptomatic	137 (97.9%)	77 (98.7%)	60 (96.8%)	0.58
	Screening	3 (2.1%)	1 (1.3%)	2 (3.2%)	
Smoking status	Active Smoker	15 (10.7%)	12 (15.4%)	3 (4.8%)	0.12
	Passive Smoker	21 (15.0%)	12 (15.4%)	9 (14.5%)	
	Non-Smoker	104 (74.3%)	54 (69.2%)	50 (80.6%)	
Tumor localization	Right	84 (60.0%)	44 (56.4%)	40 (64.5%)	0.29
	Left	52 (37.1%)	32 (41.0%)	20 (32.3%)	
	Bilateral	4 (2.9%)	2 (2.6%)	2 (3.2%)	
Histological subtype	IDC	102 (72.9%)	60 (76.9%)	42 (67.7%)	0.17
	ILC	5 (3.6%)	1 (1.3%)	4 (6.5%)	
	Other	32 (22.9%)	16 (20.5%)	16 (25.8%)	
	Unknown	1 (0.7%)	1 (1.3%)	0 (0.0%)	
Histological grade	G1	28 (20.0%)	12 (15.4%)	16 (25.8%)	0.005
	G2	60 (42.9%)	30 (38.5%)	30 (48.4%)	
	G3	39 (27.9%)	29 (37.2%)	10 (16.1%)	
	Unknown	13 (9.3%)	7 (9.0%)	6 (9.7%)	
Lymphovascular invasion	Negative	81 (57.9%)	45 (57.7%)	36 (58.1%)	0.12
	Positive	43 (30.7%)	26 (33.3%)	17 (27.4%)	
	Unknown	16 (11.4%)	7 (9.0%)	9 (14.5%)	
Perineural invasion	Negative	108 (77.1%)	59 (75.6%)	49 (79.0%)	0.12
	Positive	16 (11.4%)	12 (15.4%)	4 (6.5%)	
	Unknown	16 (11.4%)	7 (9.0%)	9 (14.5%)	
Estrogen receptor	Negative	30 (21.4%)	23 (29.5%)	7 (11.3%)	0.009
	Positive	110 (78.6%)	55 (70.5%)	55 (88.7%)	
Progesterone receptor	Negative	42 (30.0%)	28 (35.9%)	14 (22.6%)	0.08
	Positive	98 (70.0%)	50 (64.1%)	48 (77.4%)	
HER2 status	Negative	84 (60.0%)	45 (57.7%)	39 (62.9%)	0.53
	Positive	56 (40.0%)	33 (43.3%)	23 (37.1%)	

IDC: Invasive ductal carcinoma; ILC: Invasive lobular carcinoma; HER2: Human epidermal growth factor receptor 2.

cy of grade 3 tumors and a lower rate of estrogen receptor (ER) positivity. Despite these adverse pathological findings, no significant differences were observed between the two groups in terms of diseasefree survival (DFS) or overall survival (OS). Although the younger cohort showed a tendency toward more frequent lymph node involvement and more advanced disease stages, these differences did not achieve statistical significance. Taken together, these findings suggest that while younger age at diagnosis is linked to more aggressive tumor biology, it does not necessarily

Table 2. Molecular subtypes, tumor (t) stage, and nodal (n) stage

Feature	Category	Overall (n=140)	≤35 years (n=78)	>35 years (n=62)	P
Molecular subtype	Luminal A	24 (17.1%)	10 (12.8%)	14 (22.6%)	0.06
	Luminal B	88 (62.9%)	47 (60.3%)	41 (66.1%)	
	HER2 positive	15 (10.7%)	10 (12.8%)	5 (8.1%)	
	Triple negative	13 (9.3%)	11 (14.1%)	2 (3.2%)	
Tumor (T) Stage	T1	29 (20.7%)	15 (19.2%)	14 (22.6%)	0.06
	T2	91 (65.0%)	48 (61.5%)	43 (69.4%)	
	T3	19 (13.6%)	14 (17.9%)	5 (8.1%)	
	T4	1 (0.7%)	1 (1.3%)	0 (0.0%)	
Nodal (N) Stage	N0	31 (22.1%)	13 (16.7%)	18 (29.0%)	0.08
	N1	69 (49.3%)	40 (51.3%)	29 (46.8%)	
	N2	33 (23.6%)	20 (25.6%)	13 (21.0%)	
	N3	7 (5.0%)	5 (6.4%)	2 (3.2%)	

HER2: Human epidermal growth factor receptor 2.

lead to worse survival. This may reflect the effectiveness of current multimodal treatment protocols in offsetting the impact of unfavorable tumor features.

Breast cancer is responsible for a significant proportion of cancers diagnosed in adolescents and young adults.[16] Compared to older patients, this population typically presents with more aggressive disease and a poorer prognosis.[17] This unfavorable pattern is associated with a higher prevalence of adverse features, including high histological grade, ER negativity, and HER2 positivity.[16] Moreover, aggressive subtypes like triplenegative and HER2-positive breast cancer occur more frequently in younger women and are commonly detected at later stages.[9]

A family history of BC is a well-established risk factor and has gained further importance with the identification of hereditary genetic mutations.[18] McAree et al.[19] reported that 27.1% of patients aged 18–40 years had a family history of breast or ovarian cancer. Similarly, another study reported a family history rate of 37%.[20] In a cohort of 628 patients under 40, the prevalence of breast or ovarian cancer history was 31%.[21] In contrast, our study observed considerably lower rates: 9.3% for breast cancer and 7.9% for ovarian cancer family history. Pathogenic variants in *BRCA1* and *BRCA2* are well-established genetic risk factors, conferring a lifetime breast cancer risk of approximately 72% and 69%, respectively.[22] In a large cohort study by Copson

Tablo 3. Neoadjuvant therapy, adjuvant chemotherapy, and adjuvant radiotherapy

Feature	Category	Overall (n=140)	≤35 years (n=78)	>35 years (n=62)
Neoadjuvant therapy	No	79 (56.4%)	46 (59.0%)	33 (53.2%)
	Yes	61 (43.6%)	32 (41.0%)	29 (46.8%)
Neoadjuvant anthracycline-based therapy	Yes	55 (39.3%)	28 (35.9%)	27 (43.5%)
	Non- anthracycline -based	6 (4.3%)	4 (5.1%)	2 (3.2%)
	No Therapy	79 (56.4%)	46 (59.0%)	33 (53.2%)
Adjuvant chemotherapy	No	64 (45.7%)	34 (43.6%)	30 (48.4%)
	Yes	76 (54.3%)	44 (56.4%)	32 (51.6%)
Adjuvant anthracycline -based therapy	Yes	53 (38.0%)	35 (44.9%)	18 (29.0%)
	Non- anthracycline -based	23 (17.0%)	10 (12.8%)	13 (22.6%)
	No Therapy	64 (45.0%)	33 (42.3%)	31 (50.0%)
Adjuvant radiotherapy	No	37 (26.4%)	24 (30.8%)	13 (21.0%)
	Yes	100 (71.4%)	52 (66.7%)	48 (77.4%)
	Unknown	3 (2.1%)	2 (2.6%)	1 (1.6%)

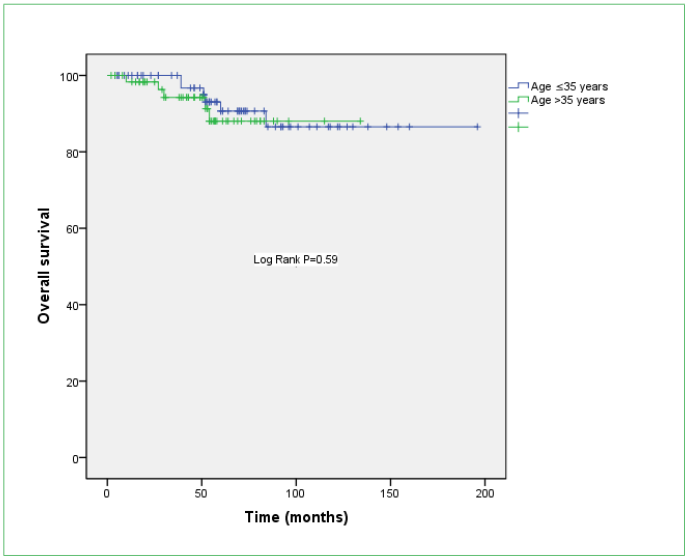


Figure 2. Overall survival curve between the ≤35 age group and the >35 age group according to Kaplan–Meier analysis.

et al.[23], *BRCA1/2* mutations were identified in 12 of 2,733 women under age 40. In our study, the mutation rate was 12.9%, which appears higher than previously reported series, although this finding should be interpreted with caution given the limited number of patients who underwent genetic testing. Individuals with *BRCA1/2* mutations are more likely to have a family history of early-onset breast or ovarian cancer; therefore, genetic testing and counseling should be strongly considered, particularly in patients with a relevant family history.[24]

Regarding sociodemographic characteristics, 30% of patients were single, 67.1% were married, and 2.9% were divorced. The proportion of married individuals was significantly higher in the young patients subgroup compared to very young patients (p=0.03). This finding has important implications for multidisciplinary management, particularly regarding psychosocial support. Furthermore, since many patients are within their reproductive years, marital status may also influence fertility preservation strategies and the management of treatment-related complications.

Since women under age 40 are not routinely included in population-based screening programs, BC in this group is more often diagnosed at a symptomatic stage. Avci et al.[20] reported that 62.9% of patients presented with a palpable mass. Similarly, another study found that 24.2% of patients aged 40–70 years were diagnosed through screening.[25] Consistent with the literature, 97.9% of patients in our cohort were diagnosed based on symptoms, while only 2.1% were detected through screening. These findings highlight the need for increased awareness and the development of tailored early detection strategies in younger populations.

With respect to tumor laterality, previous studies have reported right breast involvement in 59.7% of cases,[26] while two other studies demonstrated rates of 50.6% and 44.8%, respectively.[27,28] In our cohort, 60% of tumors were localized in the right breast, consistent with the existing literature.

Regarding histological subtype, IDC has been reported as the predominant subtype, with a frequency of 86% in one study.[20] Similarly, Ozmen reported that, in a large cohort of 11,385 patients, an IDC rate of 79% was observed.[29] In our study, IDC was observed in 72.9% of patients, with rates of 76.9% in the very young group and 67.7% in the older young group (p=0.17). Although no statistically significant difference was observed between age groups, the distribution and frequency of histological subtypes in our cohort were consistent with previously published data.

Avci et al.[20] reported grade 2 and grade 3 tumors in 44.3% and 43.2% of patients, respectively. The rate of grade 3 disease was 42.9% in very young patients and 43.5% in young patients. Another study reported a grade 3 tumor rate of 60% in patients under 40 years, compared to 48% in those aged ≥40 years.[29] Similarly, Copson et al.[30] demonstrated that 59% of tumors were grade 3 in patients younger than 40 years. In contrast, in a cohort of patients aged 45–69 years, grade 2 and grade 3 tumors were observed in 33% and 13% of cases, respectively.[31] Multiple studies have consistently shown that higher tumor grade is associated with poorer prognosis.[32] In our study, 42.9% of patients had grade 2 disease and 27.9% had grade 3 disease. Notably, the proportion of grade 3 tumors was significantly higher in very young patients compared to young patients (40.8% vs. 17.9%, p=0.005). These findings are consistent with the literature, indicating that younger patients tend to present with higher-grade tumors, while lower-grade tumors become more prevalent with increasing age. Furthermore, the higher frequency of grade 3 tumors in very young patients supports the concept that breast cancer diagnosed at an earlier age is associated with more aggressive tumor biology and a poorer prognostic profile.

In a study of patients under 40 evaluating receptor status, ER negativity was reported in 33.7% and HER2 positivity in 24% of cases.[30] In another study comparing very young and young patient groups, ER negativity rates were 38.8% and 21.6%, respectively, while PR negativity rates were 49.1% and 35.3%, with significantly higher hormone receptor negativity in the very young group (p<0.001 and p=0.0010, respectively).[8] Similarly, another study reported ER negativity in 39%, PR negativity in 43%, and HER2 positivity in 26% of patients under 40.[29] Poorolajal et al.[33] demonstrated that patients with ER-negative and

HER2-positive tumors had shorter survival than those with ER/PR-positive, HER2-negative disease. Furthermore, ER-positive tumors have been associated with improved five-year OS compared to ER-negative tumors.[30] In studies including older patient populations, ER and PR negativity rates were lower. For example, one study reported ER negativity in 14.2% and PR negativity in 20.4% of patients over 40,[34] while another study found both ER and PR negativity rates to be 25.9%.[35] In our cohort, 21.4% of patients were ER-negative and 30% were PR-negative, while HER2 positivity was observed in 40%. When stratified by age, ER negativity was significantly higher in the very young group compared to the young group (29.5% vs. 11.3%, p=0.005). Progesterone receptor negativity was also more frequent in the very young group (35.9% vs. 22.6%), although this difference did not reach statistical significance (p=0.08). The higher prevalence of hormone receptor negativity and relatively elevated HER2 positivity in younger patients supports the association between younger age and more aggressive tumor biology, and is consistent with previously reported findings.

Ozmen[29] reported molecular subtype distributions in patients under 40 as 56% luminal A, 18.5% luminal B, 8% HER2-positive, and 17% triple-negative. In the same study, among patients older than 40, 64% were luminal A and 14% were luminal B. In another cohort of patients under 40, subtype distribution was reported as 33% luminal A, 35% luminal B, 11% HER2-positive, and 21% triple-negative.[36] In studies including patients over 40, luminal A, luminal B, HER2-positive, and triple-negative subtypes were observed in 33%, 44%, 9.4%, and 13.5% of cases, respectively.[37] Furthermore, Sweeney et al.[38] demonstrated that the luminal B subtype was 2.48 times more frequent than luminal A in patients younger than 40. In our study, molecular subtype distribution was 17.1% luminal A, 62.9% luminal B, 10.7% HER2-positive, and 9.3% triple-negative. The relatively lower proportion of the favorable prognostic luminal A subtype, together with the predominance of luminal B tumors, supports the notion that younger patients tend to have more aggressive tumor biology. These findings are consistent with the literature and may partly explain the comparatively poorer prognosis observed in younger BC populations.

Since women under 40 are not routinely included in screening programs, BC in this population is often diagnosed at a symptomatic and more advanced stage. In the analysis by Avci et al.[20], 12.9% of patients under 40 had T3–T4 tumors and 61% were node-positive; in patients ≤35 years, these rates were 13.7% and 59.1%, respectively. Another study reported stage distribution as 2.5% stage I, 20.5% stage II, 55% stage III, and 22% stage IV.[39] Several studies have consistently shown that younger women tend to present with larger tumors, higher rates of lymph node involvement, and consequently more advanced-stage disease.[2,20,29] In our study, most patients presented with a palpable mass, and the proportion of T2 tumors was 65%. T3 and T4 tumors accounted for 13.6% and 0.7%, respectively, while in the very young subgroup, the proportion of T3–T4 tumors was 19.2%. The overall rate of node-positive disease was 77.9%, reaching 83.3% in the very young group. Stage distribution in the entire cohort was 12.9% stage I, 48.6% stage II, 20.7% stage III, and 17.9% stage IV. Although the very young group exhibited numerically higher rates of T3–T4 tumors and nodal involvement compared to the young group, these differences were at the borderline of statistical significance (p=0.06 and p=0.08, respectively). These findings are consistent with prior reports suggesting a tendency toward more advanced disease at presentation in younger patients.

In the study by Wang et al.[40], neoadjuvant therapy, adjuvant chemotherapy, adjuvant radiotherapy, and hormonal therapy rates were 38.1%, 89.7%, 27.4%, and 34.3%, respectively. In our cohort, 43.6% received neoadjuvant chemotherapy, 54.3% adjuvant chemotherapy, 71.4% adjuvant radiotherapy, and 79.3% adjuvant hormonal therapy. The relatively frequent use of both neoadjuvant and adjuvant treatments in younger patients is consistent with previous studies, which suggest that more intensive treatment strategies are often required in this population to reduce mortality and recurrence risk [40]. In our study, 37.9% of patients received anthracycline-based adjuvant chemotherapy. Notably, anthracycline use was significantly higher in the very young group compared to the young group (77.8% vs. 56.3%, p=0.04). This finding likely reflects the more aggressive tumor biology observed in younger patients and the consequent need for more intensive systemic therapy, consistent with the existing literature.

The main limitations of our study include its retrospective design and relatively small sample size. Consequently, subgroup analyses for all variables could not be performed with sufficient statistical power. Additionally, due to the limited number of events during follow-up, median survival outcomes could not be reliably estimated. The retrospective nature also precluded a comprehensive evaluation of established breast cancer risk factors. Furthermore, the heterogeneity of molecular subtypes among very young patients may contribute to variability in histopathological characteristics, potentially influencing stage at presentation and treatment outcomes. Despite these limitations, our study highlights important histopathological differences and treatment patterns in young BC patients. Since this population often presents with aggressive disease and is excluded from routine

screening, careful attention to these features is critical. Raising awareness and considering more intensive treatments could improve outcomes in this group.

Conclusion

In conclusion, this study shows that younger breast cancer patients frequently present with laterstage disease and a higher number of poor prognostic features. The ongoing debate about excluding this age group from standard screening protocols continues to lack resolution. Additionally, because few studies have focused specifically on this population, there is a clear need for wellpowered prospective research to develop standardized screening and treatment strategies for young women with breast cancer.

Disclosures

Ethics Committee Approval: All analyses were performed in accordance with the principles of the Declaration of Helsinki. Approval was obtained from the ethics committee of Gazi Yasargil Training and Research Hospital for the study (approval date: 29/09/2023; decision no: 527).

Informed Consent: All authors of the manuscript titled: 'Is Young-Onset Breast Cancer a Distinct Clinical Entity?' certify that they qualify for authorship because of substantial contribution to the work submitted. The authors undersigned declare that this manuscript has not been published nor is under simultaneous consideration for publication elsewhere. The authors agree to transfer the copyright to the 'Eurasian Journal of Medical İnvestigation' to be effective if and when the manuscript is accepted for publication and that the manuscript will not be published elsewhere in any other language without the consent of the Eurasian Journal of Medical İnvestigation. The final form of the manuscript has been seen and approved by all authors.

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Research Article

Association of End-of-Procedural Angiographic Response with 1-Year Mortality after Primary Percutaneous Coronary Intervention in ST-Segment Elevation Myocardial Infarction: A Retrospective Cohort Study

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Abstract

Objectives: We evaluated whether the final angiographic result after primary percutaneous coronary intervention (PCI) was associated with 1-year all-cause mortality in patients with ST-segment elevation myocardial infarction (STEMI).

Methods: This retrospective single-center cohort study included 222 consecutive patients with STEMI who underwent primary PCI between January 2013 and December 2015. Final thrombolysis in myocardial infarction (TIMI) flow, residual TIMI thrombus grade, and myocardial blush grade (MBG) were recorded at the end of the procedure. An end-of-procedural angiographic response phenotype was defined before survival modeling. Optimal response was defined as final TIMI flow 3, residual TIMI thrombus grade 0–1, and MBG 2–3. Suboptimal response was defined as any of the following: final TIMI flow <3, residual TIMI thrombus grade ≥2, or MBG ≤1. Vital status at 1 year was obtained from the national death registry (e-Nabız). Kaplan–Meier analysis and Cox proportional hazards regression were used.

Results: The mean age was 57.9±13.6 years, and 173 patients (77.9%) were male. The median overall follow-up was 620 days (interquartile range, 443–813 days), whereas survival analyses were restricted to the first 365 days after index PCI. In-hospital mortality occurred in 23 patients (10.4%), and 1-year all-cause mortality occurred in 33 (14.9%). Compared with survivors, patients who died by 1 year had lower final TIMI flow, higher residual TIMI thrombus grade, and lower MBG (all p<0.001). The suboptimal angiographic response phenotype was present in 50 patients (22.5%) and was associated with markedly higher 1-year mortality than optimal response (46.0% vs. 5.8%; log-rank p<0.001). In multivariable Cox analysis adjusted for age, diabetes mellitus, Killip class, and left ventricular ejection fraction (LVEF), suboptimal angiographic response remained independently associated with 1-year mortality (hazard ratio 8.50, 95% confidence interval 3.81–18.94; p<0.001).

Conclusion: Simple end-of-procedural angiographic markers were strongly associated with 1-year mortality after STEMI. A suboptimal angiographic response phenotype may support early post-PCI risk stratification in routine practice.

Keywords: Coronary Angiography, Mortality, Myocardial Infarction, No-reflow Phenomenon, Percutaneous Coronary Intervention, ST-elevation

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Primary percutaneous coronary intervention (PCI) is the standard reperfusion strategy for ST-segment elevation myocardial infarction (STEMI) when it can be delivered without delay.[1] Even after successful opening of the infarct-related artery, however, downstream tissue reperfusion may remain incomplete because of distal embolization, persistent thrombus burden, endothelial injury, and microvascular dysfunction.[2] These phenomena are clinically relevant because they are linked to larger infarct size, impaired myocardial recovery, and worse survival.[3]

The angiographic variables most often used to describe final reperfusion are the thrombolysis in myocardial infarction (TIMI) flow grade,[4] residual TIMI thrombus grade,[5] and myocardial blush grade (MBG).[6] These measures are available immediately at the end of primary PCI and are already familiar to interventional cardiologists. In daily practice, they may offer a practical way to distinguish patients with an apparently successful procedure from those who remain at high residual risk despite epicardial patency.

Recent work on no-reflow in STEMI has focused largely on pre-procedural or procedural prediction models.[7] Less attention has been given to the prognostic value of the final angiographic result as an integrated post-procedural phenotype. We therefore examined whether end-of-procedural angiographic response, defined by final TIMI flow, residual thrombus burden, and MBG, was associated with 1-year all-cause mortality after primary PCI in STEMI.

Methods

Study design and population

This retrospective observational cohort study included consecutive patients with STEMI who underwent primary PCI at Bagcilar Training and Research Hospital between January 2013 and December 2015. Patients with unavailable core angiographic data or unavailable survival status were excluded. The final study population consisted of 222 patients. The manuscript was prepared in accordance with the STROBE statement.[8] The approval for this study was obtained from the Bağcılar Training and Research Hospital Non-Invasive Clinical Research Ethics Committee (decision no: 2015-423, dated 26.11.2015, 38th board meeting). The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was waived because of the retrospective study design.

The diagnosis of STEMI, the decision to perform primary PCI, and intraprocedural pharmacologic management were made by the treating cardiology team according to the routine standards of the study period. Baseline demographic, clinical, laboratory, procedural, and angiographic variables were obtained from the institutional database.

Angiographic assessment

Epicardial flow was graded with the TIMI flow scale.[4] Thrombus burden was assessed with the TIMI thrombus grade classification.[5] Myocardial perfusion was graded with MBG.[6] The angiographic no-reflow variable was retained as recorded in the institutional dataset.

For the primary analysis, an exploratory end-of-procedural angiographic response phenotype was defined before survival modeling. Optimal angiographic response was defined as final TIMI flow 3, residual TIMI thrombus grade 0 to 1, and MBG 2 to 3. Suboptimal angiographic response was defined as any of the following: final TIMI flow below 3, residual TIMI thrombus grade 2 or higher, or MBG 1 or lower.

Follow-up and outcomes

The primary outcome was 1-year all-cause mortality. Survival status was ascertained through the national death registry (e-Nabız). Follow-up time was calculated from the index PCI date to the date of death or the date of the last confirmed status. Secondary outcomes were in-hospital mortality, cardiovascular death during follow-up, recurrent myocardial infarction, repeat revascularization, stroke, and heart failure hospitalization.

Because the study used retrospectively collected clinical and angiographic data, no additional intervention was performed for research purposes.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation or median (interquartile range), as appropriate, and categorical variables are presented as number (percentage). Group comparisons were performed with the Mann–Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables, as appropriate.

Kaplan–Meier curves were compared with the log-rank test. Cox proportional hazards regression was used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs). Given the limited number of events, the multivariable model was kept parsimonious and prespecified to include the angiographic response phenotype together with age, diabetes mellitus, Killip class, and LVEF. Survival analyses were restricted to the first 365 days after index PCI, although longer follow-up data were available for censoring. Statistical analyses were performed with Python 3.13, and a two-sided *p*-value $p<0.05$ was considered statistically significant.

Results

Cohort characteristics

The study cohort included 222 patients. The mean age was 57.9±13.6 years, and 173 patients (77.9%) were male. The

median overall follow-up duration was 620 days (interquartile range, 443–813 days). Thirty-three patients (14.9%) died within 365 days, and all observed deaths occurred during the first year of follow-up. Baseline clinical characteristics according to 1-year vital status are summarized in Table 1.

Patients who died by 1 year had more frequent cardiogenic shock at presentation (36.4% vs. 2.6%; p<0.001), higher Killip class (2.61±1.32 vs. 1.59±0.89; p<0.001), lower systolic blood pressure (109.09±25.07 vs. 125.07±19.98 mmHg; p<0.001), and lower LVEF (35.97±13.43% vs. 43.96±10.44%; p=0.001). Age, sex, diabetes mellitus, hypertension, previous myocardial infarction, previous PCI, chronic kidney disease, and heart rate were not significantly different between groups.

Procedural and angiographic findings

Procedural and angiographic findings are shown in Table 2. In-hospital mortality occurred in 23 patients (10.4%), and angiographic no-reflow occurred in 14 (6.3%). Pre-PCI TIMI flow and pre-PCI thrombus grade were similar between groups, whereas final angiographic metrics showed clear separation.

Compared with survivors, patients who died by 1 year had lower final TIMI flow (2.55±0.90 vs. 2.97±0.18; p<0.001), higher residual TIMI thrombus grade (2.03±1.40 vs. 0.46±0.70; p<0.001), lower MBG (1.42±1.06 vs. 2.71±0.45; p<0.001), more frequent angiographic no-reflow (24.2% vs. 3.2%; p<0.001), and more frequent suboptimal angiographic response (69.7% vs. 14.3%; p<0.001).

Clinical outcomes according to angiographic response phenotype

The exploratory suboptimal angiographic response phenotype was present in 50 patients (22.5%). Clinical outcomes according to angiographic response phenotype are presented in Table 3.

Patients with suboptimal response had substantially higher in-hospital mortality (46.0% vs. 0.0%; p<0.001) and 1-year all-cause mortality (46.0% vs. 5.8%; p<0.001) than those with optimal response. Cardiovascular death during follow-up was also more frequent in the suboptimal group (46.0% vs. 4.7%; p<0.001). Recurrent myocardial infarction, repeat revascularization, and stroke were numerically similar between groups, whereas heart failure hospitalization occurred more often in the suboptimal response group (22.0% vs. 9.3%; p=0.025).

Survival analysis

Kaplan–Meier analysis demonstrated early and persistent separation of the survival curves according to angiographic response phenotype (Fig. 1), with significantly lower 1-year survival in the suboptimal response group (log-rank p<0.001).

In univariable Cox analysis, suboptimal angiographic response was associated with 1-year mortality (HR 11.31, 95% CI 5.36–23.84; p<0.001). Killip class and systolic blood pressure were also associated with mortality, whereas higher LVEF was associated with lower risk. In the prespecified multivariable model, suboptimal angiographic response remained independently associated with 1-year all-cause mortality (adjusted HR 8.50, 95% CI 3.81–18.94; p<0.001). Killip class remained independently associated with higher risk (adjusted HR 1.48, 95% CI 1.11–1.98; p=0.007), and higher LVEF remained independently associated with lower risk (adjusted HR 0.97, 95% CI 0.94–1.00; p=0.043) (Table 4).

Table 1. Baseline clinical characteristics according to one-year vital status

Variable	Alive at 1 year (n=189)	Dead by 1 year (n=33)	p
Age, years	57.41±13.39	60.61±14.81	0.152
Male sex	146 (77.2)	27 (81.8)	0.654
Diabetes mellitus	55 (29.1)	10 (30.3)	1.000
Hypertension	104 (55.0)	14 (42.4)	0.192
Previous myocardial infarction	22 (11.6)	5 (15.2)	0.566
Previous PCI	22 (11.6)	5 (15.2)	0.566
Chronic kidney disease	18 (9.5)	2 (6.1)	0.745
Cardiogenic shock at presentation	5 (2.6)	12 (36.4)	<0.001
Killip class	1.59±0.89	2.61±1.32	<0.001
Systolic blood pressure, mmHg	125.07±19.98	109.09±25.07	<0.001
Heart rate, bpm	80.44±18.93	82.48±20.27	0.511
LVEF, %	43.96±10.44	35.97±13.43	0.001

Values are mean±standard deviation or number (percentage). LVEF: Left ventricular ejection fraction; PCI: Percutaneous coronary intervention.

Table 2. Procedural and angiographic findings according to one-year vital status

Variable	Alive at 1 year (n=189)	Dead by 1 year (n=33)	p
Multivessel disease	67 (35.4)	16 (48.5)	0.174
Thrombus aspiration	58 (30.7)	12 (36.4)	0.545
Glycoprotein IIb/IIIa inhibitor use	75 (39.7)	10 (30.3)	0.338
Pre-PCI TIMI flow	0.59±0.88	0.48±0.80	0.585
Final TIMI flow	2.97±0.18	2.55±0.90	<0.001
Pre-PCI TIMI thrombus grade	3.96±0.93	3.76±0.90	0.189
Residual TIMI thrombus grade	0.46±0.70	2.03±1.40	<0.001
Myocardial blush grade	2.71±0.45	1.42±1.06	<0.001
Angiographic no-reflow	6 (3.2)	8 (24.2)	<0.001
Suboptimal angiographic response*	27 (14.3)	23 (69.7)	<0.001

*Suboptimal angiographic response was defined as final TIMI flow <3, residual TIMI thrombus grade ≥2, or myocardial blush grade ≤1. TIMI: Thrombolysis in myocardial infarction; PCI: Percutaneous coronary intervention.

Table 3. Clinical outcomes according to end-of-procedural angiographic response phenotype

Outcome	Optimal response (n=172)	Suboptimal response (n=50)	p
In-hospital death	0 (0.0)	23 (46.0)	<0.001
1-year all-cause mortality	10 (5.8)	23 (46.0)	<0.001
Cardiovascular death during follow-up	8 (4.7)	23 (46.0)	<0.001
Recurrent myocardial infarction	7 (4.1)	3 (6.0)	0.698
Repeat revascularization	12 (7.0)	3 (6.0)	1.000
Stroke	5 (2.9)	2 (4.0)	0.656
Heart failure hospitalization	16 (9.3)	11 (22.0)	0.025

Suboptimal angiographic response was defined as final TIMI flow <3, residual TIMI thrombus grade ≥2, or myocardial blush grade ≤1.

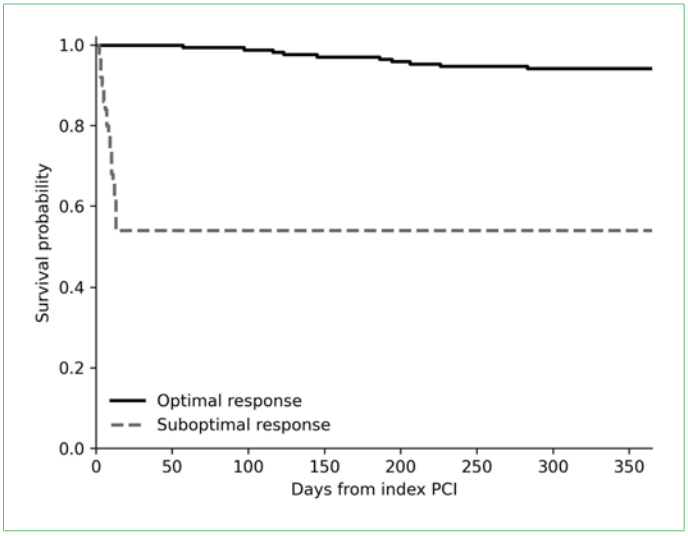


Figure 1. Kaplan-Meier estimate of 1-year survival according to end-of-procedural angiographic response phenotype. Suboptimal response was defined as final TIMI flow <3, residual TIMI thrombus grade ≥2, or myocardial blush grade ≤1.

Discussion

In this retrospective STEMI cohort treated with primary PCI, the final angiographic result was strongly associated with subsequent mortality. Patients with lower final TIMI flow, higher residual thrombus burden, and lower myocardial blush had worse outcomes, and the composite suboptimal angiographic response phenotype remained independently associated with 1-year all-cause mortality after adjustment for age, diabetes mellitus, Killip class, and LVEF.

These findings are biologically plausible. Final TIMI flow reflects epicardial reperfusion.[4] Residual thrombus grade reflects the remaining thrombotic burden after intervention.[5] MBG reflects tissue-level myocardial perfusion.[6] Persistent abnormalities in any of these domains may indicate incomplete reperfusion despite technically successful PCI, with ongoing distal embolization, microvascular obstruction, or impaired downstream flow. From a clinical perspective, the final angiographic picture therefore captures more than a procedural endpoint; it may summarize the residual

Table 4. Cox regression analysis for one-year all-cause mortality

Predictor	Univariable HR (95% CI)	p	Adjusted HR (95% CI)	p
Suboptimal angiographic response	11.31 (5.36-23.84)	<0.001	8.50 (3.81-18.94)	<0.001
Killip class	2.12 (1.60-2.80)	<0.001	1.48 (1.11-1.98)	0.007
Systolic blood pressure (per mmHg)	0.97 (0.95-0.98)	<0.001		
LVEF (per %)	0.94 (0.91-0.97)	<0.001	0.97 (0.94-1.00)	0.043
Age (per year)			1.02 (1.00-1.05)	0.097
Diabetes mellitus			1.32 (0.62-2.84)	0.473

HR: Hazard ratio; CI: Confidence interval.

ischemic and thrombotic risk carried by the patient after revascularization.

Our results are consistent with prior work showing adverse prognostic implications of residual thrombus burden in STEMI.[9] Adverse associations between no-reflow and clinical outcomes have also been reported in meta-analytic data.[10] The present study adds a practical post-procedural perspective by integrating these familiar angiographic markers into a simple phenotype that can be recognized immediately in the catheterization laboratory. Unlike more elaborate prediction models, this approach does not require additional testing or delayed risk assessment.

This has potential implications for early clinical decision-making. A patient with suboptimal angiographic response after primary PCI may merit closer hemodynamic surveillance, more cautious discharge planning, and more intensive follow-up after the index hospitalization. The phenotype could also be useful in future studies that aim to enrich high-risk post-PCI populations or evaluate tailored secondary prevention strategies.

Conclusion

The study has several limitations. It was retrospective and single-center, which introduces the possibility of selection bias and limits generalizability. The cohort was relatively modest in size, and the number of deaths constrained the complexity of multivariable modeling. Angiographic variables were obtained from the institutional dataset rather than from a blinded core laboratory. The cohort reflects practice from 2013 to 2015, so contemporary interventional techniques and adjunctive pharmacotherapy may differ. In addition, the composite angiographic response phenotype should be viewed as exploratory and requires external validation before broader adoption.

Despite these limitations, the signal observed in this cohort was large, clinically coherent, and based on variables that are readily available in routine care. In conclusion, end-of-procedural angiographic response was strongly associated with 1-year mortality after primary PCI in STEMI. A simple phenotype based on final TIMI flow, residual thrombus grade, and myocardial blush may help identify patients at increased residual risk immediately after the procedure.

Disclosures

Ethics Committee Approval: The approval for this study was obtained from the Bağcılar Training and Research Hospital Non-Invasive Clinical Research Ethics Committee (decision no: 2015-423, dated 26.11.2015, 38th board meeting). The study was conducted in accordance with the Declaration of Helsinki.

Informed Consent: Written informed consent was waived because of the retrospective study design.

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