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Gender-Stratified Hematological Predictors of Pulmonary Involvement in COVID-19: A Retrospective CT-Correlated Analysis

COVID-19'da Pulmoner Tutulumun Cinsiyete Göre Hematolojik Öngörücüleri: BT-Korelasyonlu Retrospektif Bir Analiz

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Objective: This study investigated the association between hematological parameters and thoracic computed tomography (CT) findings in coronavirus disease-2019 (COVID-19) patients with a focus on gender-specific platelet dynamics.

Methods: Four hundred thirty-seven patients who underwent both reverse transcriptase polymerase chain reaction and thoracic CT scans were analyzed retrospectively. Hemogram data, inflammatory markers, and CT findings were compared by sex.

Results: CT positivity was significantly associated with elevated neutrophil/lymphocyte ratio, C-reactive protein, D-dimer, and neutrophil counts, and with reduced lymphocyte, monocyte (MONO), eosinophil, and basophil (BASO) counts ($p < 0.01$). Mean platelet volume (MPV) showed a significant correlation with CT findings only in female patients ($p = 0.024$). Monocytopenia emerged as a strong predictor of CT positivity, explaining 9.4% of the variance in females and 17.6% in males.

CONCLUSION: These findings underscore the need for gender-specific approaches to COVID-19 triage and suggest that MPV and MONO counts may serve as cost-effective, readily accessible biomarkers of pulmonary involvement when imaging is unavailable.

Keywords: COVID-19, platelet, mean platelet volume, platelet activation, gender analysis, thorax CT, hematological markers.

Amaç: Bu çalışmada, koronavirüs hastalığı-2019 (COVID-19) tanılı hastalarda hematolojik parametreler ile toraks bilgisayarlı tomografi (BT) bulguları arasındaki ilişki, cinsiyete özgü trombosit dinamikleri odağında araştırılmıştır.

Yöntemler: Hem revers transkriptaz polimeraz zincir reaksiyonu hem de toraks BT incelemesi yapılan 437 hasta retrospektif olarak değerlendirilmiştir. Hemogram verileri, enflamatuvar belirteçler ve BT bulguları cinsiyete göre karşılaştırılmıştır.

Bulgular: BT pozitifliği; yüksek nötrofil/lenfosit oranı, C-reaktif protein, D-dimer ve nötrofil sayısı ile anlamlı şekilde ilişkili bulunmuş; düşük lenfosit, monosit (MONO), eozinofil ve bazofil sayıları ile ilişkilendirilmiştir ($p < 0,01$). Ortalama trombosit hacmi (MPV), BT bulguları ile yalnızca kadın hastalarda anlamlı korelasyon göstermiştir ($p = 0,024$). Monositopeni, BT pozitifliğinin güçlü bir öngörücüsü olarak ortaya çıkmış; kadınlarda varyansın %9,4'ünü, erkeklerde ise %17,6'sını açıklamıştır.

Sonuç: Bu bulgular, COVID-19 triyajında cinsiyete özgü yaklaşımların gerekliliğini ortaya koymakta ve görüntüleme imkânı bulunmadığında MPV ile MONO sayımlarının pulmoner tutulumun maliyet etkin ve kolay erişilebilir biyobelirteçleri olarak kullanılabileceğini düşündürmektedir.

Anahtar Sözcükler: COVID-19, trombosit, ortalama trombosit hacmi, trombosit aktivasyonu, cinsiyet analizi, toraks BT, hematolojik belirteçler

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INTRODUCTION

Coronavirus Disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, was initially found in Wuhan, China, in December 2019 and quickly spread worldwide (1). The World Health Organization declared COVID-19 a global public health danger on January 30, 2020 and gave pandemic status on March 11, 2020 putting enormous strain on healthcare systems around the world. This global health crisis has demonstrated the critical need for timely and precise diagnostic tools.

COVID-19, caused by the SARS-CoV-2 virus, exhibits a wide clinical spectrum, ranging from asymptomatic infection to critical lung infection. Lung involvement is the primary factor determining the prognostic course of COVID-19 and affecting mortality rates. Therefore, early recognition and management of respiratory complications has become a primary goal in the clinical approach (2-4).

Reverse transcriptase polymerase chain reaction (RT-PCR) examination of nasopharyngeal samples, which is regarded as the reference method in COVID-19 diagnosis, has become the standard practice in the field of molecular diagnosis. However, the RT-PCR approach has some drawbacks in clinical practice (5). According to published research, the RT-PCR test has lower sensitivity than thoracic computed tomography (CT) imaging. In patient groups with negative PCR findings, the discovery of COVID-19-specific pathological alterations on radiological imaging modalities emphasizes the importance of multi-parameter evaluation in the diagnostic approach. As a result, a multidisciplinary approach to COVID-19 diagnosis is advocated, with clinical symptoms, laboratory testing, and imaging modalities all being assessed simultaneously (6-8).

During the global health crisis, when maximum efficiency is required with limited resources, the demand for promptly accessible, cost-effective, and minimally invasive biomarkers for illness detection and prognosis has skyrocketed (9). In this critical moment, when health-care systems' capacities are stretched thin, developing diagnostic and monitoring methods based on cost-benefit analysis has become a strategic priority. Among the laboratory abnormalities observed in COVID-19 infection, decreases in lymphocyte (LYM) count, increases in acute phase reactant C-reactive protein (CRP) values, increases in iron storage protein ferritin concentrations, elevations in coagulation marker D-dimer levels, and increases in cellular damage marker lactate dehydrogenase activity are frequently reported (10).

In recent years, the importance of hematological parameters in the diagnosis and prognostic evaluation of COVID-19 has received increasing attention. The systemic inflammatory response induced by SARS-CoV-2 is reflected in characteristic hematological changes. In the meta-analysis by Henry et al. (4), leukocytosis, neutrophilia, lymphopenia, thrombocytopenia and high neutrophil/lymphocyte ratio (NLR) values were shown to be associated with poor prognosis in COVID-19 patients. Yang et al. (5) reported that NLR is an independent predictive factor in predicting COVID-19 severity, and its diagnostic value is as high as the area under the curve (AUC) of 0.841.

Mean platelet volume (MPV), a measure of platelet activation and reactivity, has been linked to increased inflammatory and prothrombotic states, such as those observed in COVID-19. Platelets in COVID-19 individuals are not only numerically but functionally changed, with hyperreactivity and procoagulant characteristics (11). High MPV levels have been linked to illness severity, intensive care unit admission, and mortality, according to research. However, there is limited information on the relationship between MPV and radiological abnormalities, particularly thoracic CT, which provides direct proof of pulmonary pathology (12).

Furthermore, the COVID-19 pandemic has highlighted gender-based immunological and hematological disparities. Sex hormones, notably estrogen and progesterone, alter coagulation pathways and platelet function, which may result in distinct biomarker patterns between males and females. Despite this, few studies have explored the gender-specific diagnostic or prognostic usefulness of platelet indices in COVID-19.

Previous research has primarily focused on general hematological markers or their correlation with disease severity scores (13-15). However, comprehensive studies evaluating the association between specific hemogram parameters—such as MPV, NLR, and monocyte (MONO) count—and thoracic CT findings, stratified by gender, remain scarce.

In this study, we aimed to investigate the relationship between hematological parameters and thoracic CT findings in COVID-19 patients, with a focus on platelet activation markers and gender-specific differences. We hypothesized that MPV, NLR, and MONO levels could serve as potential biomarkers for predicting pulmonary involvement, and that their diagnostic value may differ between male and female patients. Our findings may contribute to a more individualized and cost-effective diagnostic approach, especially in healthcare settings with limited access to advanced imaging.

MATERIALS AND METHODS

Study Design and Population

This retrospective, single-center study was conducted between October and December 2020 after obtaining ethical approval from the University of Health Sciences Türkiye, Dışkapı Yıldırım Beyazıt Training and Research Hospital Ethics Committee (approval number: 104-14, dated: 08.02.2021). The inclusion criteria were: age ≥18 years, simultaneous availability of thoracic CT and hemogram results, and either RT-PCR positivity or thoracic CT findings consistent with COVID-19. After excluding 31 patients because of extreme values that distorted the normal distribution, 437 patients were included in the final analysis.

Data Collection

Demographic information, RT-PCR results, and laboratory parameters—including complete blood count [white blood cells (WBC), neutrophils (NEU), LYM, MONO, eosinophils (EOS), BASO, MPV, and NLR]—were retrieved from electronic hospital records. Inflammatory and coagulation markers, such as CRP, procalcitonin, and D-dimer, were also recorded.

Thoracic CT scans were evaluated by two experienced radiologists who were blinded to the patients' laboratory and clinical data. CT findings were categorized as COVID-19 positive (CT+) or negative (CT–) based on standardized diagnostic criteria. CT positivity was defined by the presence of radiological features typical of COVID-19 pneumonia, such as bilateral ground-glass opacities, crazy paving patterns, and peripheral consolidations, in line with COVID-19 Reporting and Data System scores of ≥4. Reference ranges for all laboratory parameters were defined according to institutional standards.

Statistical Analysis

All statistical analyses were performed using SPSS version 23.0 (IBM Corp., Armonk, NY, USA). The normality of data distribution was assessed using the Kolmogorov–Smirnov test. Skewness and kurtosis coefficients were also examined to confirm the normality of the variables, allowing the use of parametric tests.

Descriptive statistics were presented as means ± standard deviation for continuous variables and as frequencies and percentages for categorical variables. Categorical variables were compared using the chi-square test, while continuous variables were compared using the independent-samples t-test and one-way analysis of variance, as appropriate. Point-biserial correlation analysis was conducted to assess the relationship between continuous hematological parameters and CT positivity (a dichotomous variable). Since the point-biserial correlation is mathematically equivalent to the Pearson product-moment correlation when one variable is dichotomous, it was computed using the Pearson correlation procedure in SPSS, yielding the same r coefficient. The coefficient of determination (r^2) was used to quantify the proportion of variance in CT positivity explained by each hematological parameter. Sex-stratified analyses were performed to explore potential sex-specific patterns. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of hematological parameters in predicting CT positivity. The AUC with 95% confidence intervals was calculated for each parameter. Optimal cut-off values were determined using the Youden index. Sensitivity and specificity were calculated for the selected thresholds. To assess potential gender-related differences, ROC analyses were conducted separately for males and females. Parameters of clinical relevance and those identified in preliminary analyses were included in the ROC analysis. The discriminatory power of each parameter was interpreted according to AUC values (0.5–0.6: poor, 0.6–0.7: fair, 0.7–0.8: acceptable, >0.8: excellent). A p-value <0.05 was considered statistically significant.

RESULTS

Patient Characteristics

A total of 437 COVID-19 patients were included in the study (Table 1). Approximately half of the patients (49.9%) were female and the mean age was 55.19 years. The majority of patients (64.1%) were aged 65 years or younger. The RT-PCR test was positive in 79.4% of patients, and thorax CT was positive in 71.6%. In the PCR-CT group distribution, the largest group was PCR (+)/CT (+) (51%), followed by PCR (+)/CT (-) (28.4%) and PCR (-)/CT (+) (20.6%).

Comparison of Hematological Parameters Between CT-Positive and CT-Negative Patients

Significant differences in hematological parameters were observed between patients with CT findings consistent with COVID-19 (CT-positive) and those without (CT-negative), as presented in Table 2. Inflammatory markers, including NEU count, NLR, CRP, and D-dimer levels, were significantly elevated in the CT-positive group (all $p < 0.05$). Conversely, immune cell-related parameters—LYM, MONO, EOS, and BASO counts—were significantly lower in CT-positive than in CT-negative patients *(all* p < 0.001). MPV values did not differ significantly between the two groups *(p* > 0.05).

Gender-Specific Analyses

Significant differences were observed in the stratified analysis according to sex (Table 3). In female patients, significant increases were detected in CT positivity and in WBC, NEU, MPV, NLR, CRP, and D-dimer values. In particular, MPV values showed a significant correlation with CT positivity only in females. In male patients, CT positivity, NLR, and CRP values increased significantly, whereas LYM, MONO, EOS, and BASO values decreased significantly. No significant relationship was detected between MPV and CT positivity in males. MPV values showed a significant correlation with CT positivity in females but not in males (p = 0.726).

Gender-Stratified Predictive Parameters

In the gender-stratified point-biserial correlation analysis, the parameters most strongly associated with CT positivity differed by sex, as reflected by their r^2 values (Table 4). Among female patients, MONO count explained 9.4% of the variance in CT positivity (r^2 = 0.094), BASO levels explained 7.0% (r^2 = 0.070), and NEU count explained 5.5% (r^2 = 0.055). Among male patients, MONO count demonstrated the highest explanatory value at 17.6% (r^2 = 0.176), followed by LYM count at 14.4% (r^2 = 0.144). These findings support the existence of gender-specific differences in the immune response to COVID-19. Monocytopenia showed the strongest association with CT positivity in both sexes, but its explanatory value was

Table 1. Patient characteristics.

Variable	n (%)
Gender	
Female	218 (49.9)
Male	219 (50.1)
Age groups	
≤65 years	280 (64.1)
>65 years	157 (35.9)
RT-PCR result	
Positive	347 (79.4)
Negative	90 (20.6)
Chest CT result	
Positive	313 (71.6)
Negative	124 (28.4)
PCR-CT group distribution	
PCR(+)/CT(+)	223 (51.0)
PCR(+)/CT(-)	124 (28.4)
PCR(-)/CT(+)	90 (20.6)
Total	437 (100.0)

RT-PCR: Reverse transcriptase polymerase chain reaction, CT: Computed tomography, PCR: Polymerase chain reaction.

Table 2. Comparison of hematological parameters according to CT results.

Parameter	CT-positive (n = 313)	CT-negative (n = 124)	p-value
WBC (×10³/μL)	6.35 ± 2.52	6.12 ± 2.12	0.363
RBC (×10⁶/μL)	4.86 ± 0.58	4.91 ± 0.60	0.430
HGB (g/dL)	13.68 ± 1.72	14.01 ± 1.77	0.074
HCT (%)	41.64 ± 4.73	42.26 ± 4.67	0.221
MCV (fL)	85.76 ± 5.70	86.28 ± 4.59	0.367
RDW (%)	13.59 ± 1.46	13.48 ± 1.15	0.454
PLT (×10³/μL)	224.36 ± 90.00	223.85 ± 57.51	0.953
MPV (fL)	10.40 ± 0.89	10.22 ± 0.91	0.063
PCT (%)	0.28 ± 0.95	0.22 ± 0.05	0.486
PDW (%)	12.03 ± 2.07	11.74 ± 1.98	0.181
NEU (×10³/μL)	4.52 ± 2.38	3.69 ± 1.79	0.001*
LYM (×10³/μL)	1.31 ± 0.57	1.68 ± 0.84	0.001*
MONO (×10³/μL)	0.46 ± 0.20	0.65 ± 0.25	0.001*
EOS (×10³/μL)	0.03 ± 0.06	0.06 ± 0.08	0.001*
BASO (×10³/μL)	0.01 ± 0.01	0.02 ± 0.02	0.001*
NLR	4.21 ± 3.12	2.81 ± 2.31	0.001*
Procalcitonin (ng/mL)	-0.93 ± 0.43	-0.91 ± 0.52	0.597
D-dimer (μg/mL)	-0.23 ± 0.35	-0.32 ± 0.38	0.016*
CRP (mg/L)	1.61 ± 0.46	1.32 ± 0.59	0.001*

*p < 0.05, BASO: Basophil count, CRP: C-reactive protein, CT: Computed tomography, EOS: Eosinophil count, HCT: Hematocrit, HGB: Hemoglobin, LYM: Lymphocyte count, MCV: Mean corpuscular volume, MONO: Monocyte count, MPV: Mean platelet volume, NEU: Neutrophil count, NLR: Neutrophil-to-lymphocyte ratio, PCT: Plateletcrit, PDW: Platelet distribution width, PLT: Platelet count, RBC: Red blood cell, RDW: Red cell distribution width, WBC: White blood cell.

approximately twice as high in males as in females. The predictive value of MPV was found to be significant only in females ($r^2 = 0.023$, $p = 0.024$), while no significant association was observed in males ($p = 0.726$).

ROC Curve Analysis

ROC curve analysis was performed to evaluate the diagnostic performance of selected hematological parameters for predicting CT positivity in female and male patients separately. The AUC, optimal cut-off values, sensitivity, specificity, and p-values were calculated for each parameter.

Among female patients, CRP demonstrated the highest diagnostic performance (AUC = 0.698, $p < 0.001$), followed by NLR (AUC = 0.641, $p < 0.001$) and D-dimer (AUC = 0.624, $p = 0.001$), indicating fair discriminatory ability. In contrast, WBC (AUC = 0.573, $p = 0.070$) and PLT (AUC = 0.484, $p = 0.699$) did not show statistically significant discrimination between CT-positive and CT-negative cases.

Similarly, among male patients, CRP (AUC = 0.654, $p < 0.001$), NLR (AUC = 0.680, $p < 0.001$), and D-dimer (AUC = 0.635, $p < 0.001$) demonstrated statistically significant discriminatory ability. NLR showed the highest AUC in males, suggesting a stronger predictive value for pulmonary involvement than in females. Conversely, WBC (AUC = 0.466, $p = 0.435$) and PLT (AUC = 0.477, $p = 0.596$) failed to achieve statistical significance, and therefore exhibited no meaningful discriminatory capacity.

Overall, CRP, NLR, and D-dimer showed significant but moderate diagnostic performance for predicting CT positivity in both sexes, whereas WBC and platelet count were not useful discriminators. These findings indicate that inflammatory biomarkers, particularly CRP and NLR, may provide clinically relevant information regarding pulmonary involvement in COVID-19 patients, while the diagnostic contribution of WBC and PLT appears limited.

Gender-stratified ROC-derived cut-off values, sensitivity, specificity, AUC values, and corresponding p-values are presented in Table 5 and Figure 1.

DISCUSSION

This study comprehensively investigated the relationship between hemogram parameters and thoracic CT findings in COVID-19 patients. Our findings indicate that some parameters obtained from simple blood tests may be clinically valuable biomarkers for predicting the presence and severity of COVID-19 pneumonia. CT-positive cases had significantly higher NLR, CRP, NEU, D-dimer, and MPV values than CT-negative cases; conversely, LYM, MONO, EOS, and BASO levels were lower. The synergistic relationship between these hematological parameters comprehensively reflects the systemic inflammation and immune response pattern of COVID-19.

Table 3. Gender-specific hematological parameters associated with CT positivity.

Parameter	Female, (n = 218)			Male, (n = 219)		
	CT negative (n = 65)	CT positive (n = 153)	p-value	CT negative (n = 59)	CT positive (n = 160)	p-value
WBC ($\times 10^3$/µL)	5.37 ± 1.31	6.04 ± 2.27	0.028	6.94 ± 2.53	6.65 ± 2.71	0.478
RBC ($\times 10^6$/µL)	4.71 ± 0.49	4.68 ± 0.51	0.686	5.12 ± 0.64	5.02 ± 0.61	0.310
HGB (g/dL)	13.26 ± 1.33	12.99 ± 1.54	0.235	14.84 ± 1.84	14.33 ± 1.63	0.051
HCT (%)	40.39 ± 3.71	40.05 ± 4.42	0.584	44.31 ± 4.78	43.16 ± 4.53	0.104
MCV (fL)	85.84 ± 4.51	85.4 ± 5.95	0.662	86.75 ± 4.66	86.02 ± 5.46	0.361
RDW (%)	13.58 ± 1.19	13.78 ± 1.56	0.343	13.38 ± 1.10	13.41 ± 1.33	0.871
PLT (×103/µL)	233.78 ± 51.08	235.87 ± 90.61	0.862	212.91 ± 62.47	213.35 ± 88.30	0.972
MPV (fL)	10.17 ± 0.97	10.48 ± 0.88	0.024	10.28 ± 0.84	10.33 ± 0.89	0.726
PCT (%)	0.23 ± 0.04	0.24 ± 0.08	0.391	0.21 ± 0.06	0.32 ± 1.32	0.532
PDW (%)	11.62 ± 2.20	12.10 ± 2.09	0.128	11.87 ± 1.72	11.96 ± 2.05	0.761
NEU ($\times 10^{3/}$µL)	3.19 ± 1.07	4.14 ± 2.05	0.001	4.24 ± 2.22	4.89 ± 2.61	0.095
LYM ($\times 10^3$/µL)	1.53 ± 0.66	1.39 ± 0.63	0.156	1.85 ± 0.97	1.23 ± 0.51	0.001
MONO ($\times 10^3$/µL)	0.57 ± 0.15	0.44 ± 0.18	0.001	0.70 ± 0.31	0.48 ± 0.21	0.001
EOS ($\times 10^3$/µL)	0.05 ± 0.07	0.03 ± 0.06	0.009	0.07 ± 0.09	0.03 ± 0.06	0.001
BASO ($\times 10^3$/µL)	0.02 ± 0.01	0.01 ± 0.01	0.001	0.03 ± 0.02	0.01 ± 0.02	0.001
NLR	2.53 ± 1.58	3.64 ± 2.52	0.001	3.13 ± 2.89	4.76 ± 3.53	0.002
Procalcitonin (ng/mL)	0.20 ± 0.18	0.17 ± 0.28	0.537	0.29 ± 0.52	0.22 ± 0.28	0.165
D-dimer (µg/mL)	0.63 ± 0.55	0.88 ± 0.96	0.048	0.89 ± 1.37	0.80 ± 0.89	0.570
CRP (mg/L)	33.41 ± 29.52	51.90 ± 48.39	0.005	42.71 ± 29.00	73.45 ± 59.19	0.001

BASO: Basophil count, CRP: C-reactive protein, CT: Computed tomography, EOS: Eosinophil count, HCT: Hematocrit, HGB: Hemoglobin, LYM: Lymphocyte count, MCV: Mean corpuscular volume, MONO: Monocyte count, MPV: Mean platelet volume, NEU: Neutrophil count, NLR: Neutrophil-to-lymphocyte ratio, PCT: Plateletcrit, PDW: Platelet distribution width, PLT: Platelet count, RBC: Red blood cell, RDW: Red cell distribution width, WBC: White blood cell.

Table 4. Gender-stratified point-biserial correlation coefficients (r, r^2) between hematological parameters and CT positivity.

Parameter	Female			Male		
	r	r^2	p-value	r	r^2	p-value
WBC ($\times 10^3$/µL)	0.149	0.022	0.028	0.048	0.002	0.478
RBC ($\times 10^6$/µL)	0.028	0.001	0.686	0.069	0.005	0.310
HGB (g/dL)	0.081	0.007	0.235	0.132	0.017	0.051
HCT (%)	0.037	0.001	0.584	0.110	0.012	0.104
MCV (fL)	0.030	0.001	0.662	0.062	0.004	0.361
RDW (%)	0.065	0.004	0.343	0.011	0.001	0.871
PLT ($\times 10^3$/µL)	0.012	0.001	0.862	0.002	0.001	0.972
MPV (fL)	0.152	0.023	0.024	0.024	0.001	0.726
PCT (%)	0.058	0.003	0.391	0.042	0.002	0.532
PDW (%)	0.103	0.011	0.128	0.021	0.001	0.761
NEU ($\times 10^3$/µL)	0.234	0.055	0.001	0.113	0.013	0.095
LYM ($\times 10^3$/µL)	0.097	0.009	0.156	0.380	0.144	0.001
MONO ($\times 10^3$/µL)	0.307	0.094	0.001	0.419	0.176	0.001
EOS ($\times 10^3$/µL)	0.176	0.031	0.009	0.232	0.054	0.001
BASO ($\times 10^3$/µL)	0.264	0.070	0.001	0.253	0.064	0.001
NLR	0.218	0.047	0.001	0.211	0.044	0.002
Procalcitonin (ng/mL)	0.042	0.002	0.537	0.094	0.009	0.165
D-dimer (µg/mL)	0.134	0.018	0.048	0.039	0.001	0.570
CRP (mg/L)	0.191	0.036	0.005	0.251	0.063	0.001

r: Correlation coefficient; r^2: Variance explained (%). BASO: Basophil count, CRP: C-reactive protein, CT: Computed tomography, EOS: Eosinophil count, HCT: Hematocrit, HGB: Hemoglobin, LYM: Lymphocyte count, MCV: Mean corpuscular volume, MONO: Monocyte count, MPV: Mean platelet volume, NEU: Neutrophil count, NLR: Neutrophil-to-lymphocyte ratio, PCT: Plateletcrit, PDW: Platelet distribution width, PLT: Platelet count, RBC: Red blood cell, RDW: Red cell distribution width, WBC: White blood cell.

Table 5. ROC-derived cut-off values and diagnostic performance of hematological parameters stratified by gender.

Gender	Parameter	AUC (95% CI)	p-value	Cut-off	Sensitivity	Specificity
Female	NLR	0.641	<0.001	3.292	0.440	0.797
Female	CRP	0.698	<0.001	28	0.500	0.899
Female	D-dimer	0.624	0.001	0.62	0.512	0.725
Female	WBC	0.573	0.070	6.29	0.422	0.768
Female	PLT	0.484	0.699	287	0.235	0.942
Male	NLR	0.680	<0.001	2.587	0.727	0.656
Male	CRP	0.654	<0.001	55	0.442	0.902
Male	D-dimer	0.635	<0.001	0.50	0.535	0.738
Male	WBC	0.466	0.435	3.66	0.965	0.082
Male	PLT	0.477	0.596	330	0.110	0.951

AUC: Area under the curve, CI: Confidence interval, CRP: C-reactive protein, NLR: Neutrophil-to-lymphocyte ratio, PLT: Platelet count, ROC: Receiver operating characteristic, WBC: White blood cell.

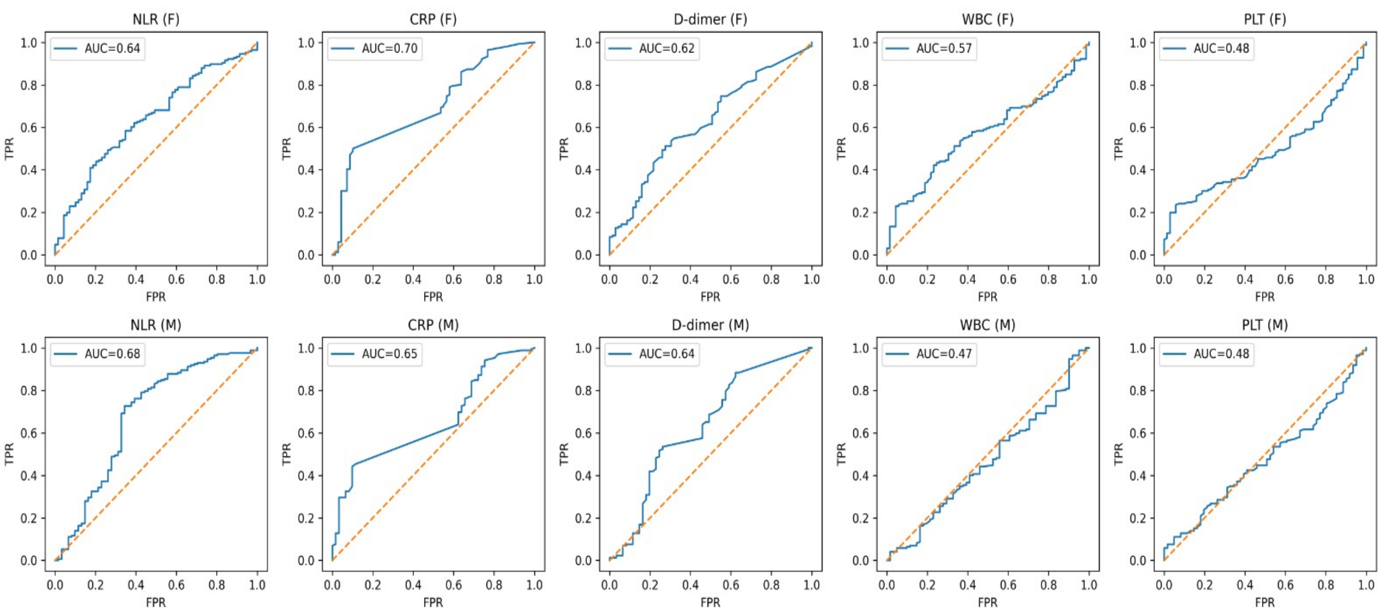

Figure 1. Receiver operating characteristic (ROC) curve analysis of hematological parameters for predicting computed tomography positivity stratified by gender. The upper panel represents females and the lower panel represents males. Each subplot shows the ROC curve and corresponding AUC for the respective parameter. CRP: C-reactive protein, NLR: Neutrophil-to-lymphocyte ratio, PLT: Platelet count, WBC: White blood cell, FPR: False positive rate, AUC: Area under the curve.

Providing a stronger diagnostic value than the parameters evaluated alone. Indeed, it is well known in the literature that NEU count increases, LYM count decreases significantly (lymphopenia) and NLR ratio increases in severe COVID-19 cases (7,8).

Lymphopenia in COVID-19 infection is accepted in the literature as a parameter of critical importance in determining the severity and prognosis of the disease (6). Man et al. (9) reported that lymphopenia and high NLR values showed a strong correlation with the CT severity score in COVID-19 patients. The strong correlation between the LYM level (CT-positive: 1.12 ± 0.58. CT-negative: 1.58 ± 0.71, $p < 0.001$) and NLR values (CT-positive: 4.89 ± 4.12. CT-negative: 2.87 ± 2.43. $p < 0.001$) determined in our study suggests that evaluating these parameters together may increase the diagnostic power. In our study, the significantly lower LYM count in CT-positive patients supports the direct effect of the virus on LYMs or its indirect effect through cytokine storm (10).

The mechanism of lymphocytopenia can be explained by angiotensin-converting enzyme 2 (ACE-2) receptors expressed on LYMs, which facilitate the direct invasion of SARS-CoV-2 into these cells and subsequent cell lysis. In addition, in the study conducted by Huang et al. (16) mediators such as proinflammatory cytokines [especially interleukin (IL)-6, IL-2, IL-7] and tumor necrosis factor-alpha, which are elevated during the fulminant cytokine storm process, can induce LYM apoptosis. These findings explain the molecular basis of the decrease in LYM count that we detected in CT-positive patients.

NLR stands out as a valuable biomarker in predicting COVID-19 severity as a sensitive indicator of inflammatory response and immune system dysregulation (11). Liu et al. (17) found the AUC value of NLR to be 0.841. while El Hussini et al. (18) reported that NLR >2.5 could predict significant lesions that would require thoracic CT. The mean NLR values detected in our study (4.89 ± 4.12 in the CT positive group) are above the threshold values in the literature, confirming that NLR shows a significant increase in patients with COVID-19 pneumonia.

NLR provides a "bidirectional" inflammatory index by simultaneously reflecting increased NEU and decreased LYM counts, which explains why it is a stronger marker than NEU or LYM counts alone in diseases in which complex immunopathological mechanisms play a role, such as COVID-19. Similarly, Erdogan et al. (12) confirmed this prognostic value in their patient cohort.

One of the most important findings of our study is that the MPV value is significantly correlated with CT positivity, especially in female patients ($p < 0.05$). This gender-specific finding suggests that platelet dynamics in COVID-19 are affected by hormonal factors (13). High MPV is considered a reflection of increased platelet production and megakaryocyte activation. Platelet activation in COVID-19 is a multidimensional process. The direct effect of the virus on endothelial cells, inflammatory mediators released during the cytokine storm, and ACE-2 receptor dysregulation lead to both numerical and functional changes in platelets. The fact that MPV values >10.2 fL in women detected in our study are a significant marker for pulmonary involvement emphasizes the clinical importance of gender-specific platelet reactivity. Current meta-analyses confirm that the prognostic value of MPV in COVID-19 is preserved regardless of gender and age (19). Platelet-endothelium interactions underlie the immunothrombotic complications of COVID-19. Activated platelets promote the formation of neutrophil extracellular traps (NETs), thereby contributing to microthrombus formation. Recent studies suggest that NET activity triggers organ damage and contributes to the development of microthrombosis by increasing endothelial inflammation (20). This mechanism increases the severity of COVID-19 pneumonia, particularly by damaging the pulmonary microvasculature. Although the role of other platelet indices such as PDW and PCT in COVID-19 has not yet been fully elucidated, the evaluation of MPV together with other hematological parameters in our study provides a comprehensive picture of platelet dysfunction.

Our findings regarding MONO and BASO levels are also consistent with the literature. In our gender-stratified correlation analysis, MONO levels explained 17.6% of the variance in CT positivity in males and 9.4% in females (r^2), indicating that monocytopenia is a strong, practical marker for the evaluation of COVID-19 pneumonia. It was concluded that thoracic CT should be considered a priority, especially in patients with MONO counts <0.4×10^3/µL, regardless of gender. Zhou et al. (14) reported that monocytopenia may be an indicator of severe immune response in severe COVID-19 patients, and Pehlivan et al. (15) reported that monocytopenia may be a determinant of COVID-19 survival.

Schulte-Schrepping et al. (21) examined in detail the decrease and dysfunction of MONO subpopulations in severe COVID-19 cases and observed a phenotypic change from classical CD14++CD16- MONOs to inflammatory CD14++CD16+ MONOs in COVID-19 patients. This finding supports the association between monocytopenia and severe COVID-19 in our study. Similarly, the decrease in BASO count may be related to the reduction of allergic/immunomodulation capacity in the setting of intense inflammation

In our gender-stratified analyses, significant differences between female and male patients were observed in hemogram parameters that predict CT positivity. These findings indicate that standard approaches are inadequate for COVID-19, and that gender-specific personalized medicine approaches should be developed. MPV and WBC parameters have stronger predictive value in females, whereas LYM and MONO parameters have stronger predictive value in males; this suggests the need to develop gender-specific algorithms in clinical evaluation. Takahashi et al. (22), showed that gender modulates the immune response to COVID-19. T-cell activation was more pronounced in females, whereas inflammatory cytokines were more pronounced in males. The significant difference in MPV among females suggests gender-specific pathophysiological mechanisms in the thrombotic sequelae of COVID-19. Scully et al. (8), showed the modulatory effects of gonadal steroids such as estrogen and progesterone on the coagulation cascade and platelet functions. These hormones are thought to influence endothelial cells and platelets, which may alter platelet dynamics and, therefore, MPV in females. In a meta-analysis conducted by Wang et al. (23), it was emphasized that the endothelial protective and anti-inflammatory effects of estrogen in female patients may positively affect the course of COVID-19. Gender-specific differences in prothrombotic mechanisms may be observed. Klein et al. (7) showed that gender has distinct effects on virus clearance, immune response quality, and inflammatory cytokine production. These findings explain the pathophysiological basis of the gender-specific hematological parameters we detected in our study.

Our findings support the hypothesis that hemogram parameters, particularly MPV, NLR, and MONO values, correlate with thoracic CT findings in COVID-19 patients. These markers may serve as accessible biomarkers for predicting pulmonary involvement when CT imaging is unavailable, offering a cost-effective approach for resource-limited settings. Unlike previous studies, our gender-stratified analysis provides novel insights into how blood parameters can predict CT-confirmed lung involvement, particularly valuable when RT-PCR results are inconclusive. This approach could enhance patient management in centers with limited diagnostic resources during pandemic conditions.

Another important finding in our study was the relationship between PCR results and CT findings, as revealed by the data we obtained in COVID-19 patients. WBC and NEU levels were significantly higher in the PCR (-)/CT (+) group than in the PCR (+)/CT (+) group. These findings indicate the diagnostic value of hematological parameters is further increased in patients who are PCR-negative but radiologically positive. The high NEU levels detected in the PCR (-)/CT (+) group suggest that these patients should be followed more carefully in terms of the risk of bacterial co-infection. Ai et al. (6) reported that the sensitivity of the RT-PCR test was 71% and that 75% of PCR-negative patients had positive CT findings. Wang et al. (24) showed that PCR sensitivity varies significantly depending on the sample type. In this context, the high NEU and leukocyte levels observed in the PCR (-)/CT (+) group in our study emphasize the diagnostic and prognostic value of inflammatory hemogram parameters, especially in patients with suspected infection but with negative PCR results. These findings emphasize the importance of a holistic evaluation of clinical, laboratory, and imaging modalities, rather than relying on a single diagnostic method in the diagnosis of COVID-19.

An important contribution of our study is determining the role of hematological parameters in differentiating COVID-19 from other pulmonary pathologies. Although similar hemogram changes can be observed in bacterial pneumonia, viral pneumonia, and other lung infections, the co-occurrence of monocytopenia and high MPV in females, especially in COVID-19. is thought to create a pattern specific to this disease.

COVID-19 infection primarily affects the respiratory system, but it can also involve multiple organ systems. The abnormalities in hemogram parameters detected in our study may indicate not only pulmonary involvement but also a systemic inflammatory response. Teuwen et al. (25) showed that COVID-19 can cause multiple organ involvement by causing endothelial cell damage and thrombotic complications. Beceren et al. (26) reported that MPV may be an indicator of cardiac myocyte damage together with troponin elevation in predicting mortality in COVID-19 patients. These findings suggest that the hemogram parameters detected in our study reflect a systemic inflammatory response and may predict extrapulmonary organ involvement.

An important contribution of our study to clinical practice is demonstrating that hematological parameters are cost-effective in the diagnosis and follow-up of COVID-19. A hemogram test is approximately 20-30 times less expensive than thorax CT, and results are available within 15-30 minutes. Especially during pandemics, when healthcare resources are limited, study-specific cut-off values derived from our ROC analysis, such as NLR >3.292 (females) and >2.587 (males), and CRP >28 mg/L (females) and >55 mg/L (males), may support triage decisions and reduce unnecessary CT scans, thus reducing costs and preventing radiation exposure.

Study Limitations

Our study has some methodological limitations. Due to the retrospective design, longitudinal clinical follow-up data for the patients were, and serial changes in hemogram parameters could not be evaluated. In addition, the differential diagnosis of diseases with similar clinical presentations based on hemogram parameters, such as bacterial pneumonia, influenza pneumonia, and other viral pneumonias, could not be evaluated. This situation limits the ability to determine whether the suggested threshold values are specific to COVID-19. The potential effects of confounding variables, such as comorbid diseases, pharmacological treatments, and genetic factors, on hematological parameters could not be fully controlled. However, our number of patients is relatively high and the inclusion of patients without PCR positivity but with radiological findings provides a population suitable for real-world data.

The higher AUC value of NLR observed in males (0.680) than in females (0.641) may indicate stronger discriminatory performance. However, formal comparisons between AUC values were not performed, and this observation should be interpreted cautiously. This is consistent with the existing literature showing that male patients tend to exhibit stronger innate immune and inflammatory responses in COVID-19, which may translate into a higher discriminatory power of NLR for predicting pulmonary involvement in this group. The observed gender differences in optimal cut-off values and AUC levels further suggest that inflammatory biomarkers may behave differently between males and females, highlighting the importance of gender-stratified clinical interpretation. Applying uniform thresholds across both sexes may lead to suboptimal sensitivity or specificity in one group, underscoring the need for sex-specific reference values in clinical triage protocols.

CONCLUSION

This study found between thoracic CT findings and hemogram parameters in COVID-19 patients. In CT-positive patients, NLR, NEU, CRP and D-dimer values were found to be statistically significantly higher; LYM, MONO, EOS and BASO values were found to be significantly lower ($p < 0.01$). In female patients, the MPV value was significantly associated with CT positivity ($p < 0.05$). Point-biserial correlation analysis (r^2) revealed that MONO levels explained 9.4% of the variance in CT positivity in women and 17.6% in men. Leukocyte and NEU levels were significantly higher in the PCR (-)/CT (+) group than in the PCR (+)/CT (+) group ($p < 0.001$). Hemogram parameters, particularly NLR, MPV, and monocytopenia, may aid the evaluation of COVID-19 pneumonia and guide treatment strategies when CT cannot be performed. The fact that MONO levels have twice the predictive value in men compared with women (17.6% in men and 9.4% in women) underscores the need to develop gender-specific triage algorithms. These findings emphasize the inadequacy of standard approaches to COVID-19 and the importance of personalized medicine.

These findings suggest that platelet activation may exhibit sex-specific characteristics in COVID-19 and that MPV may be a useful biomarker, particularly in female patients. Gender-stratified analysis of platelet parameters may offer a new paradigm in thrombotic risk assessment in COVID-19.

Ethics

Ethics Committee Approval: This retrospective, single-center study was conducted between October and December 2020 after obtaining ethical approval from the University of Health Sciences Türkiye, Dışkapı YıldırıM Beyazıt Training and Research Hospital Ethics Committee (approval no: 104-14, date: 08.02.2021).

Informed Consent: Informed consent was not required as this was a retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: T.Y.A., C.A., Concept: T.Y.A., C.A., Design: T.Y.A., C.A., Data Collection or Processing: T.Y.A., C.A., Analysis or Interpretation: T.Y.A., C.A., Literature Search: T.Y.A., C.A., Writing: T.Y.A., C.A.

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