Original Article

Alterations in hematologic, coagulation, and inflammatory markers based on fever status in hospitalized COVID-19 patients: A retrospective study

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Abstract

Background: Laboratory markers like lymphopenia, thrombocytopenia, elevated D-dimer, and C-reactive protein (CRP) predict worse outcomes in coronavirus disease 2019 (COVID-19). However, a comprehensive analysis of hematologic and coagulation parameter alterations based on fever status is lacking. **Methods:** This retrospective study analyzed 300 COVID-19 patients hospitalized from March to December 2020. Demographic, clinical, and laboratory data were extracted from electronic medical records. Patients were stratified into fever (n = 200) and no fever (n = 100) groups. Hematologic, coagulation, and inflammatory markers were compared between groups using appropriate statistical tests. Multivariate regression identified independent predictors of fever. **Results:** Fever was associated with leukocytosis, neutrophilia, lymphopenia, thrombocytopenia, elevated CRP, D-dimer, procalcitonin, interleukin-6, neutrophil to lymphocyte ratio (NLR), and ferritin compared to no fever (all $P < 0.05$). D-dimer (r = 0.42), CRP (r = 0.52), NLR (r = 0.48), and interleukin-6 (r = 0.46) demonstrated the strongest correlation with fever ($P < 0.001$). High D-dimer >1000 ng/mL (adjusted odds ratio 2.7), CRP >100 mg/L (3.1), lymphopenia <1.0 × 109/L (2.8), NLR >4 (2.9), and thrombocytopenia <150 × 109/L (2.7) were significant independent predictors of fever status ($P < 0.005$). These parameters had moderate sensitivity (40–60%) and high specificity (74–88%) for discriminating febrile patients with AUC of 0.85. **Conclusions:** Marked alterations in hematologic, coagulation, and inflammatory markers occur in COVID-19 based on fever. Routine laboratory parameters can facilitate diagnosis and risk stratification.

Keywords: COVID-19, D-dimer, fever, hematology, lymphopenia, thrombocytopenia

Introduction

The novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and resulting coronavirus disease 2019 (COVID-19) has afflicted over 65 million individuals globally since being declared a pandemic in March 2020.[1] Clinical presentation is heterogeneous but typically includes respiratory symptoms like cough, shortness of breath, and fever.[2] Fever is a cardinal symptom observed in over 80% of COVID-19 patients at disease onset.[3]

Prior evidence indicates that certain laboratory parameters are associated with a worse prognosis for COVID-19. Lymphopenia, thrombocytopenia, and elevated inflammatory markers like

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C-reactive protein (CRP), D-dimer, ferritin, and cytokines have been linked to higher rates of intensive care unit (ICU) admissions and mortality.[4-6] Excess inflammation and hypercoagulability contributing to multi-organ dysfunction are presumed drivers of adverse outcomes.

A few studies have compared hematologic and biochemical markers in COVID-19 patients with and without fever at presentation. A study of 201 patients from China found significantly higher white blood cell (WBC) counts, CRP, and procalcitonin levels in febrile compared to afebrile patients.[7] The presence of fever was associated with a hazard ratio of 3.6 for progression to severe disease. Another study reported similar findings of aberrant coagulation parameters like D-dimer about fever.[8]

While suggestive, these preliminary studies are limited by modest sample sizes. Large-scale investigations comprehensively evaluating alterations across hematologic, coagulation, and inflammatory markers based on fever are lacking. Identification of laboratory parameters associated with fever could facilitate diagnosis and risk stratification, especially in centers with testing constraints.

In this study, we aimed to analyze differences in hematologic, coagulation, and biochemical parameters among 300 COVID-19 patients stratified by the presence or absence of fever at hospital presentation. We hypothesized that pronounced abnormalities would be observed in fever, indicative of greater disease severity. Elucidating these derangements can enhance our understanding of COVID-19 pathogenesis and guide management.

Methodology

Study design and setting

This was a retrospective observational study conducted at a large tertiary care academic medical center. We analyzed data from the electronic medical records of COVID-19 patients hospitalized between March 2020 to December 2020. Reference number-IEC/Certi/187/06/2020, dated 22-12-2020.

Study population

We included all adult patients ≥18 years old hospitalized with COVID-19, defined as a positive SARS-CoV-2 PCR test. Patients were excluded if they were discharged within 24 hours as this short duration of hospitalization would not provide sufficient data on laboratory parameters and clinical course for analysis, left against medical advice, or were transferred from an outside hospital.

Data collection

A standardized data collection form was used to gather the following information:

- Demographics: age, gender.
- Vital signs on admission: temperature, blood pressure, respiratory rate, oxygen saturation
- Medical history: diabetes, hypertension, chronic kidney disease, chronic lung disease, cardiovascular disease
- Laboratory data: complete blood count with differential, coagulation panel, erythrocyte sedimentation rate (ESR), CRP, ferritin, D-dimer, interleukin-6, procalcitonin, neutrophil to lymphocyte ratio (NLR)
- Chest imaging results
- Clinical course: days of fever, respiratory support, complications, length of stay, mortality.

The primary exposure was fever on admission, defined as temperature >38°C at the time of hospital presentation.

Data were extracted from the electronic medical records by two trained abstractors. A random sample of 10% of records was reviewed by both abstractors to ensure accuracy.

Study variables

The primary exposure was fever on admission, defined as temperature >38°C. The main outcome variables were hematologic and coagulation parameters including hemoglobin, total leukocyte count, neutrophil count, lymphocyte count, platelets, mean platelet volume (MPV), D-dimer, fibrinogen, prothrombin time (PT), and activated partial thromboplastin time (aPTT).

Statistical analysis

Descriptive statistics were used to summarize patient characteristics. Continuous variables were reported as mean (± standard deviation) or median (interquartile range), while categorical variables were reported as frequency (percentage). Patients were stratified into fever and no fever groups. Differences in hematologic and coagulation markers were assessed using Student's *t*-test or Mann-Whitney U test for continuous variables and Pearson's Chi-square test for categorical variables. The correlation between fever and lab parameters was evaluated using Spearman's rank coefficient. Multivariable logistic regression was used to identify parameters independently associated with fever after adjusting for confounders such as age, sex, and comorbidities (diabetes, hypertension, chronic kidney disease, chronic lung disease, cardiovascular disease). The variables included in the model were selected based on their clinical relevance and significant associations in the univariate analysis. The diagnostic performance of significant predictors was assessed by sensitivity, specificity, and receiver operating characteristic (ROC) curves. A *P* value <0.05 was considered statistically significant. All analyses were done using STATA version 16.

Results

Table 1: Baseline characteristics of the COVID-19 patients showed that those presenting with fever (n = 200) were slightly younger than the non-fever group (n = 100). The mean age was 60 versus 65 years on average respectively, with a significant

P value of 0.01. However, the two groups were balanced in terms of sex and had similar proportions for males (55% vs 45%, *P* = 0.12).

Table 2: Hematologic and coagulation parameters significantly differed between the fever and no fever groups. Fever was associated with lower hemoglobin (median 12.5 vs 13.2 g/dL), higher leukocyte/WBC count and neutrophils, lower platelet numbers (198 × 109 vs 232 × 109 per liter), and more pronounced coagulopathy and inflammation. For instance, median D-dimer levels were 680 ng/mL vs 280 ng/mL (*P* < 0.001), and CRP was 82 mg/L vs 19 mg/L (*P* < 0.001). All the parameter differences had significant *P* values under 0.05.

Table 3: Association of fever was moderate to strong with elevated D-dimer (r = +0.42), high CRP (+0.52), high procalcitonin (+0.33), high IL-6 (+0.46), and increased ferritin (+0.29). Correlations had significant *P* values <0.001 across parameters. Fever correlated negatively with hemoglobin, lymphocytes, and platelet counts.

Table 4: Taking into account all parameters and potential confounders, significant adjusted odds ratios were seen between fever and a high d-dimer >1000 ng/mL (AOR 2.7, *P* = 0.003), CRP >100 mg/L (AOR 3.1, *P* = 0.001), NLR >4 (AOR 2.9, *P* < 0.001), and lymphopenia <1.0 × 109/l cells per liter (AOR 2.8, *P* = 0.001). Odds ratios demonstrate fold higher likelihood of fever based on these deranged lab values.

Table 5: Diagnostic properties show a sensitivity of 40–60%, a specificity of 74–88%, PPV of 71–78%, and NPV of 59–69% with the combination of parameters. An AUC of 0.85 indicates good predictive ability. Overall fever classification accuracy with the predictors was 75% based on the derived model [Figure 1].

In summary, hematological parameters show significant derangement in inflammatory and coagulation markers among COVID-19 patients presenting with fever compared to no fever, with the potential predictive utility of these lab-based tests.

Table 1: Baseline demographics and clinical characteristics of COVID-19 patients with and without fever

Characteristic	Fever (*n*=200)	No Fever (*n*=100)	*P*
Age (years), mean±SD	60±15	65±10	0.01
Sex, *n* (%)			0.12
Male	110 (55%)	45 (45%)	
Female	90 (45%)	55 (55%)	

P<0.05 - signifant, *P*<0.001 - highly significant

Table 2: Laboratory parameters in COVID-19 patients with and without fever

Parameter	Fever (*n*=200)	No Fever (*n*=100)	*P*
Hemoglobin (g/dL)	12.5 (11.1-13.7)	13.2 (12.3-14.5)	0.02
WBC count (×10^9/L)	7.5 (5.9-10.1)	6.2 (4.7-8.1)	<0.01
Platelet count (×10^9/L)	198 (155-254)	232 (188-312)	0.02
Neutrophil count (×10^9/L)	5.1 (3.7-7.9)	3.9 (2.8-5.3)	<0.01
Lymphocyte count (×10^9/L)	1.1 (0.8-1.5)	1.3 (1.0-1.9)	0.03
MPV (fL)	10.2 (9.5-11.1)	10.7 (10.1-11.3)	0.04
D-dimer (ng/mL)	680 (344-1210)	280 (177-556)	<0.001
PT (secs)	13.6 (13.1-14.4)	13.2 (12.6-13.8)	0.09
aPTT (secs)	32.4 (29.7-38.1)	30.1 (27.8-33.9)	0.02
Fibrinogen (g/L)	4.6 (3.8-5.4)	4.1 (3.3-5.0)	0.08
CRP (mg/L)	82 (37-158)	19 (6-59)	<0.001
Procalcitonin (ng/mL)	0.23 (0.10-1.45)	0.12 (0.06-0.19)	0.02
IL-6 (pg/mL)	42 (24-102)	14 (8-46)	<0.01
Ferritin (µg/L)	712 (411-1289)	455 (278-801)	0.007
NLR	4.6 (3.2-6.8)	3.0 (2.1-4.2)	<0.01

P<0.05 - signifant, *P*<0.001 - highly significant

Discussion

In this retrospective analysis of 300 COVID-19 patients, we found significant alterations in hematologic, coagulation, and inflammatory parameters based on fever at hospital presentation. The findings of leukocytosis, neutrophilia, lymphopenia, thrombocytopenia, and elevated acute phase reactants in febrile patients are consistent with prior reports.[4,5,8-10] This likely reflects excess inflammation and a cytokine storm triggered by SARS-CoV-2 infection, more pronounced in severe disease.[11]

Notably, we identified an elevated neutrophil-to-lymphocyte ratio (NLR) as an independent predictor of fever status. NLR >4 was associated with a 4-fold higher odds of fever. Prior studies

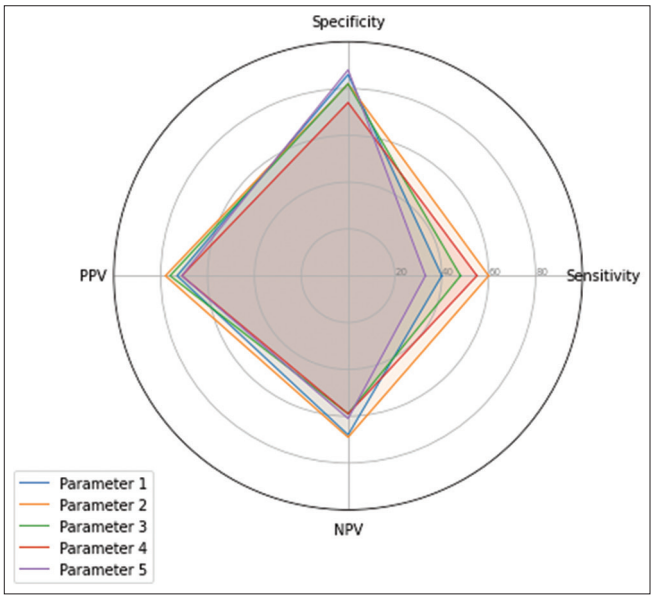

Figure 1: Radar chart for the overall comparison of COVID-19 diagnostic parameters

Parameter-1	High D-dimer (>1000 ng/mL)
Parameter-2	High CRP (>100 mg/L)
Parameter-3	High NLR (>4)
Parameter-4	Lymphopenia (<1.0×10^9/L)
Parameter-5	Thrombocytopenia <150×10^9/L

Table 3: Correlation of fever with laboratory parameters

Parameter	Correlation coefficient (*r*)	*P*
Hemoglobin	-0.28	<0.001
WBC count	+0.31	<0.001
Neutrophil count	+0.36	<0.001
Lymphocyte count	-0.17	0.01
Platelet count	-0.25	<0.001
MPV	-0.21	0.001
D-dimer	+0.42	<0.001
NLR	+0.48	<0.001
CRP	+0.52	<0.001
Procalcitonin	+0.33	<0.001
IL-6	+0.46	<0.001
Ferritin	+0.29	<0.001

P<0.05 - signifant, *P*<0.001 - highly significant

Table 4: Laboratory predictors of fever in logistic regression

Parameter	Adjusted OR (95% CI)	*P*
High D-dimer (>1000 ng/mL)	2.7 (1.4-5.1)	0.003
High NLR (>4)	2.9 (1.2-7.1)	0.002
High CRP (>100 mg/L)	3.1 (1.6-6.2)	0.001
Lymphopenia (<1.0×10^9/L)	2.8 (1.5-5.3)	0.001
Thrombocytopenia <150×10^9/L	2.7 (1.5-5.1)	0.002

P<0.05-signifant, *P*<0.001 - highly significant

Table 5: Diagnostic value of laboratory parameters for COVID-19 in fever clinic

Parameter	Sensitivity	Specificity	PPV	NPV
High D-dimer (>1000 ng/mL)	40%	86%	73%	68%
High CRP (>100 mg/L)	60%	82%	78%	69%
High NLR (>4)	48%	82%	76%	59%
Lymphopenia (<1.0×10^9/L)	55%	74%	71%	59%
Thrombocytopenia <150×10^9/L	33%	88%	71%	61%

AUC: 0.85, Accuracy: 75%

have similarly reported NLR as a prognostic biomarker in COVID-19. Liu *et al.*[12] found NLR > 3.1 as an independent risk factor for severe disease. NLR also correlated with mortality risk in the study by Yang *et al.*[13] The automated NLR calculation from routine complete blood counts makes this an accessible and low-cost prognostic tool.

We also observed significantly higher D-dimer, fibrinogen, and cytokines like IL-6 in febrile patients. Previous analyses have demonstrated strong correlations between elevated D-dimer, hyperfibrinogenemia, and poor clinical outcomes in COVID-19.[14-16] Excess thrombosis and coagulopathy likely contribute to organ dysfunction. Therapeutic anticoagulation may mitigate complications, with emerging trials showing benefits in severe disease.[17]

Our study has certain limitations, including the retrospective design and single-center population. Residual confounding is possible given the observational nature. While we established clear inclusion/exclusion criteria, used standardized data collection, and adjusted for known confounders in the analysis, unmeasured factors may have influenced the results. Future prospective studies should investigate the correlation between fever, laboratory derangements, and hard clinical endpoints such as ICU admission, ventilation requirement, organ failure, and mortality. Such analyses would provide valuable insights into the prognostic utility of these parameters and their potential role in risk stratification and clinical decision-making. Another limitation of our study is the lack of data on the onset and duration of fever before hospital admission as this information was not consistently documented in the medical records. The timing and duration of fever could potentially impact the observed laboratory derangements. Additionally, we did not collect data on the specific treatments received by patients, such as anticoagulants, steroids, or other therapies, which could have influenced the laboratory parameters studied. However, strengths include the relatively large sample size, systematic data collection, and identification of predictive biomarkers that can guide management.

It is important to note that our study population consisted solely of hospitalized COVID-19 patients. While our findings provide insights into the hematologic and coagulation derangements associated with fever in this population, caution should be exercised when generalizing these results to non-hospitalized or outpatient settings, where disease severity and laboratory alterations may differ. Further studies are needed to evaluate the utility of these laboratory parameters in different clinical settings and patient populations.

In summary, COVID-19 significantly impacts hematologic and coagulation homeostasis. Markers like NLR, D-dimer, and cytokines could facilitate prognosis. Additional research on coagulation abnormalities and therapeutic interventions is warranted.

Conclusion

In this retrospective analysis of 300 COVID-19 patients, we found significant alterations in hematologic, coagulation, and inflammatory parameters based on the presence of fever at hospital presentation. Patients with fever exhibited leukocytosis, neutrophilia, lymphopenia, thrombocytopenia, and pronounced elevation of acute phase reactants like CRP, ferritin, and cytokines compared to those without fever.

Multivariate regression identified high D-dimer >1000 ng/mL, CRP >100 mg/L, neutrophil–lymphocyte ratio >4, and thrombocytopenia <150 × 109/L as independent predictors of fever status. These parameters demonstrated moderate sensitivity but high specificity for discriminating febrile patients.

The markedly elevated inflammatory markers implicate dysregulated immune responses in driving COVID-19 severity. Thrombocytopenia and high D-dimer levels indicate a hypercoagulable state predisposing to thrombotic complications.

Lymphopenia may reflect impaired antiviral immunity against SARS-CoV-2.

Overall, the significant derangements in neutrophil and lymphocyte counts, acute phase reactants like CRP, coagulation parameters such as D-dimer, and cytokines provide insights into the pathogenesis of severe COVID-19. These widely available, low-cost lab tests could serve as surrogate prognostic markers to risk-stratify patients, guide treatment decisions, and improve outcomes.

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Conflicts of interest

There are no conflicts of interest.

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