



Title: The Prevalence of Hematological Manifestations and Their Association with Severity and Outcome of COVID-19

Authors:

1. Dr. Abrar J. Alwaheed. (First author): MBBS, MRCPI, RCPI CFP (Hem).¹
2. Dr. Reem J. Al Argan.: MBBS, SB-Med, SF-Endo, FACE, ECNU.¹
3. Dr. Dania M. Alkhafaji.: MBBS, SB-Med, SF-Endo, FACE.¹
4. Dr. Safi G. Alqatari.: MBBS, MRCPI, MMedSc, RCPI CFP (Rheum).¹
5. Dr. Alaa A. Alzaki: MBBS, FRCPC, ABIM.¹
6. Dr. Zainab A. AlElq: MBBS.¹
7. Dr. Fatimah I. Alabdrabalnabi: MBBS.²
8. Dr. Tariq S. Alsaif: MBBS.¹
9. Dr. Abdullah B. Almashouf: MBBS.¹
10. Dr. Zainab R. Albaggal: MBBS.¹

Affiliation

1. Department of Internal Medicine-College of Medicine-Imam Abdulrahman Bin Faisal University -King Fahd Hospital of the University-Khobar-Eastern Province-Saudi Arabia.
2. Department of Internal Medicine, Al Ahsaa General Directorate of Health Affairs, Al Ahsaa, Saudi Arabia.

Corresponding Author: Dr. Zainab Alelq, MBBS,SBIM.

Department of Internal Medicine- College of Medicine-Imam Abdulrahman Bin Faisal University-King Fahd Hospital of the University, Khobar, Eastern Province-Saudi Arabia.

Zip code: 34445

Email: zaelq@iau.edu.sa

ORCID ID: 0000-0002-1155-0951

Abstract: Background: The World Health Organization has declared Coronavirus Disease 2019 as pandemic on 2020. Initially, it was thought to be a respiratory tract illness. However, multi-systemic involvement has been observed, including hematopoietic system. Abnormal hematological parameters were associated with poor outcomes.

Objectives: Local studies are lacking so we aimed to study the prevalence and association of hematologic manifestations with the severity and outcome of COVID-19 disease. **Patients and Methods:** Retrospective observational study involving 357 patients with Coronavirus Disease 2019 who were admitted to King Fahad Hospital of the University from March to September 2020. After Institutional Review Board approval, the data was collected correlating demographics, comorbidities, abnormal hematologic results with Coronavirus Disease 2019 severity and outcome. The severity of the disease classified according to Saudi Arabian Ministry of Health. **Results:** The most prevalent Hematological abnormality was lymphopenia. Diabetes mellitus, thrombocytopenia, neutrophilia, high D-dimer and ferritin were found to be an independent risk factors for severe disease. While older age was an independent risk factor for worse outcome. Moreover, High Partial Thrombin Time, D-dimer and lactate dehydrogenase were associated with poor outcome. Critically ill patients were having higher risk for longer hospitalization, Intensive Care Unit admission, ventilation and death. **Conclusion:** Most of the hematologic and coagulation abnormalities in patients with COVID-19 are considered risk factors for disease severity and worse outcome. Accordingly, these patients should be identified and managed with close observation to prevent and minimize complications.

[Dr. Abrar J. Alwaheed. (First author): MBBS, MRCPI, RCPI CFP (Hem), Dr. Reem J. Al Argan.: MBBS, SB-Med, SF-Endo, FACE, ECNU. Dr. Dania M. Alkhafaji.: MBBS, SB-Med, SF-Endo, FACE. Dr. Safi G. Alqatari.: MBBS, MRCPI, MMedSc, RCPI CFP (Rheum). Dr. Alaa A. Alzaki: MBBS, FRCPC, ABIM. Dr. Zainab A. AlElq: MBBS. Dr. Fatimah I. Alabdrabalnabi: MBBS. Dr. Tariq S. Alsaif: MBBS. Dr. Abdullah B. Almashouf: MBBS. Dr. Zainab R. Albaggal: MBBS. **Title: The Prevalence of Hematological Manifestations and Their Association with Severity and Outcome of COVID-19.** *Researcher* 2023;15(1):54-64]. ISSN 1553-9865 (print); ISSN 2163-8950 (online). <http://www.sciencepub.net/researcher>. 07.doi: [10.7537/marsrsj150123.07](https://doi.org/10.7537/marsrsj150123.07).

Key Words: COVID-19, Hematology, Coagulation, Severity, Outcome.

What's new?

Global efforts were directed to understand the pathophysiological impact of COVID-19 on multiple organs and body systems including the hematological system. An extra interest toward exploring methods to identify those who are at risk of acquiring severe and critical disease. We aimed to study the prevalence of hematological manifestations and their association with severity and outcome of COVID-19 disease. We found that thrombocytopenia, neutrophilia, high D-dimer and ferritin were an independent risk factors for severe disease. While older age was an independent risk factor for worse outcome. This can help in future recognition of high risk individuals and enhance prompt management to minimize complications

Introduction

Coronavirus disease 2019 (COVID-19) has emerged first in Wuhan City, Hubei Province of China on 31 December 2019. It was declared by World Health Organization (WHO) to be pandemic on March 11, 2020.¹ It can present with multi-organ involvement including the respiratory, gastrointestinal, renal, neurologic and hematopoietic systems.² According to previous studies in China and Singapore, Patients usually present with fever, dry cough, shortness of breath, headache, sore throat and diarrhea.³ The most common comorbidities identified were hypertension, obesity and diabetes.⁴ The severity of COVID-19 infection varies from mild, moderate to severe with progression to Acute respiratory distress syndrome (ARDS) requiring Intensive Care Unit (ICU) admission, invasive mechanical ventilation and possible death. In a study by Guan et al, in China which included 1099 patients with COVID-19, abnormal hematologic results were observed in severe cases with leukopenia in 61.1%, lymphopenia 96.1% and thrombocytopenia in 57.7% patients.⁵ Another meta-analysis conducted by Henry et al, where they identified an association between abnormal hematologic parameters and poor clinical outcome.⁶ Moreover, Huang and Wang et al reported an increased risk for ICU admission and development of ARDS among patients with neutrophilia and lymphopenia.⁷ Thrombocytopenia in COVID-19 is multifactorial and it was found in severe cases and was directly linked to increased mortality in a meta-analysis of nine studies.⁸ Identifying patients with those abnormalities in their early presentation might halter disease progression. Limited number of publications addressed the hematological manifestation of COVID-19 disease in few areas of Saudi Arabia. However, Data among eastern province patients is lacking. We aimed to study the prevalence and association of hematologic manifestations with the severity and outcome of

COVID-19 disease at King Fahd Hospital of the University in the Eastern Province of Saudi Arabia.

Materials and Methods

Data Collection:

A retrospective observational study which was approved by institutional review board of Imam Abdulrahman Bin Faisal University, King Fahd Hospital of the University (KFHU), Eastern Province, Khobar, Saudi Arabia with the reference number IRB-2020-01-261. We included 357 patients with COVID-19 who were confirmed by positive SARS-COV2 PCR test and were hospitalized at KFHU during the period of March-September 2020. Patients less than 18 years of age or have less than 24 hours of hospital stay were excluded. The data were collected for patient's demographics (age, gender and nationality), comorbidities such as diabetes mellitus, hypertension, cardiac, renal, rheumatologic and hematological diseases. Baseline laboratory investigations including complete blood count (CBC), white blood cells (WBC) and differentials, hemoglobin level (Hgb) and platelet count were included. In addition, coagulation profile with prothrombin time (PT), activated partial thromboplastin time (aPTT), d-dimer and fibrinogen were included. Inflammatory markers such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), lactate dehydrogenase (LDH) and ferritin levels were also included. The severity of COVID-19 presentation was scored according to the Saudi Ministry of Health (MOH) criteria which categorizes the severity as following: A) Mild-moderate disease if there is no pneumonia on chest x-ray and no oxygen requirement B) Severe disease reflected by any one of the followings: Respiratory rate ≥ 30 /minute, Blood oxygen saturation $\leq 93\%$ on room air, PaO₂/FiO₂ < 300 or lung infiltrates $> 50\%$ of the lung field within 24-48 hours C) Critical disease reflected by any of the followings: adult respiratory distress syndrome (ARDS), sepsis, altered level of consciousness, multi-organ failure or with risk factors of cytokine storm syndrome if there is one or more of the followings: ferritin > 600 ug/L at presentation and LDH > 250 or elevated D-Dimer > 1 mcg/ml⁹. The outcome of the COVID-19 disease was determined by the length of hospitalization, ICU admission, mechanical ventilation and death.

Abnormal hematologic and inflammatory parameters such as lymphopenia, neutropenia, neutrophilia, thrombocytopenia, high ESR and CRP, high ferritin, high d-dimer, and deranged coagulation profile were correlated with the severity and outcome of COVID-19.

Data was analyzed by IBM SPSS.22. All categorical variables were presented as frequencies and percentages while all continuous data was presented as

Median and IQR. Chi-square test or Fisher exact test was used to check the association between variables, Kruskal Wallis test was used to compare the medians. Odds ratios (ORs) with their 95% confidence intervals (CI) were measured in multivariate analysis. Statistical significance was set at $P < 0.05$.

Results:

Demographics and prevalence of abnormal hematologic parameters, coagulation abnormality and inflammatory markers (n=357) (Table 1):

There were 243 (68.1%) males and 114 (31.9%) females. Majority (57.1%) were Saudis. The mean (\pm SD) age of patients was 52.7 (\pm 15.5) years (range 19–93). Majority (60.8%) of COVID-19 cases were in the age between 31 – 60 years. The most prevalent comorbidity was diabetes mellitus (DM) in (50.7%). Out of 181 diabetic patients, 173 (95.6%) had type-II diabetes. Critical cases accounted for 218 cases (61.1%), 38.9% were admitted in ICU (N=139), 27.5% required ventilation (N=98), with 17.1% mortality (N=61), whereas the median length of hospital stay was 10 days (6-17.5). Lymphopenia was found in 115 (32.2%) cases while neutrophilia in 74 (20.7%), thrombocytopenia in 63 (17.6%), neutropenia in 21 (5.9%), and thrombocytosis in 13 (3.6%) cases. In addition, high d-dimer was found in 204 (57.1%), and high PTT in 106 (29.7%) cases. On the other hand, elevated PT and fibrinogen were found in 25 cases (7%), and 19 cases (5.3%), respectively. While raised CRP was found in 329 (92.2%), high LDH in 291 (81.5%), high ESR in 274 (76.8%) and high ferritin in 180 (50.4%) cases.

Association of Gender and Comorbidities with Severity of COVID-19 (n=357) (Table 2):

Male gender, presence of comorbidities in particular DM, hypertension, CKD and cardiac disease were significantly associated with Critical COVID-19 (p-values < 0.0001). Half of the cases (50%) with GI and hematological disease had critical disease but this was not statistically significant (p-value 0.5).

Association between abnormal hematologic parameters, and Inflammatory Marker with severity of COVID-19 (n= 357) (Table 3):

In univariate analysis, patients with thrombocytopenia, lymphopenia and neutrophilia had significant association with critical COVID-19 (p-values < 0.05) except thrombocytosis and neutropenia. Moreover, all coagulation derangement including

elevated PT, aPTT, fibrinogen and d-dimer were significantly correlated with critical cases (p-value < 0.0001). In addition, raised ESR, CRP, ferritin and LDH were also correlated with severity of COVID-19 (p-values < 0.05).

Multivariate analysis for severity of Covid-19 in relation to age, gender, comorbidities, hematologic abnormalities, coagulation abnormalities and inflammatory markers (Table 4):

A multivariate analysis showed older age was significantly associated with severe disease as independent risk factor (ORs 2.8; $P = 0.009$). In addition, DM was the only comorbidity that was found to be independent factor for severe and critical disease (ORs 3.9, and 4.4, $P = 0.001, 0.0001$, respectively). Moreover, thrombocytopenia and neutrophilia were also found to be independent factors for critical COVID-19 (ORs 4.2, 5.8; $P = 0.008, 0.01$, respectively). In addition, high D-dimer and ferritin were also considered independent factors for critical disease (ORs 3.8, 3.7; $P = 0.0001, 0.007$, respectively).

Association between abnormal hematologic, deranged coagulation, inflammatory marker and outcomes of COVID-19 (n= 357) (Table 5):

Risk for ICU admission was significantly high in cases with lymphopenia, neutrophilia, high PTT, high D-dimer, high CRP and high LDH (p-values < 0.05), while mechanical ventilator was required in cases with neutrophilia, high PT, high PTT, high D-dimer and high LDH (p-values < 0.05). Moreover, the mortality rate was significantly high in cases with thrombocytopenia, high PTT, high D-dimer and high LDH (p-values < 0.05). In addition, longer hospital stay was found in cases with neutrophilia, high PTT, high D-dimer, high CRP, high ESR and high LHD (p-values < 0.05).

Multivariate analysis for outcome in relation to age, gender, comorbidities, hematologic abnormalities, coagulation abnormalities and inflammatory markers (Table 6):

In a multivariate analysis, the older age was found to be independent factor for worse outcome, in particular for ICU admission, ventilation and mortality (ORs 1.03, 1.03 & 1.05; $P_s < 0.001$). In addition, hematological disease was an independent factor for ICU admission while neutropenia and neutrophilia were independent factors for ICU admission and ventilation (p-value 0.001 and 0.01, respectively).

Tables:**Table-1 Demographics and prevalence of abnormal hematologic parameters, coagulation abnormality and inflammatory markers (n=357)**

		Frequency	Percent
Gender	Male	243	68.1
	Female	114	31.9
Age	≤ 30	31	8.7
	31 - 60	217	60.8
	>60	109	30.5
Nationality	Saudi	204	57.1
	Non-Saudi	153	42.9
Comorbidities	>1 Comorbidities	124	34.7
	DM	181	50.7
	HTN	131	36.7
	CKD	32	9.0
	Cardiac disease	52	14.6
	Hematologic	18	5.0
	GI disease	12	3.4
	Rheumatologic	6	1.7
Types of DM	Type-I	8	4.4
	Type-II	173	95.6
COVID-19 Severity	Mild-Moderate	62	17.4
	Severe	77	21.6
	Critical	218	61.1
Outcomes	ICU Admission	139	38.9
	Ventilation	98	27.5
	Hospital Stay Median (IQR)	10	(6 – 17.5)
	Death	61	17.1
Hematologic Abnormalities	Thrombocytopenia	63	17.6
	Thrombocytosis	13	3.6
	Lymphopenia	115	32.2
	Neutropenia	21	5.9
	Neutrophilia	74	20.7
Coagulation Abnormalities	High PT	25	7
	High PTT	106	29.7
	Abnormal fibrinogen	19	5.3
	High d-dimer	204	57.1
Inflammatory Markers	High CRP	329	92.2
	High ESR	274	76.8
	High ferritin	180	50.4
	High LDH	291	81.5

Table-2 Association of Gender and Comorbidities with Severity of COVID-19 (n= 357)

		Total	Severity			P-values
			Mild-Moderate	Severe	Critical	
Gender	Male	243	47 (19.3%)	38 (15.6%)	158 (65%)	<0.0001
	Female	114	15 (13.2%)	39 (34.2%)	60 (52.6%)	
Comorbidities	DM	181	13 (7.2%)	43 (23.8%)	125 (69.1%)	<0.0001
	HTN	131	19 (14.5%)	27 (20.6%)	85 (64.9%)	<0.0001
	CKD	32	2 (6.3%)	5 (15.6%)	25 (78.1%)	<0.0001
	Cardiac disease	52	9 (17.3%)	15 (28.8%)	28 (53.8%)	<0.0001
	Hematologic disease	18	3 (16.7%)	6 (33.3%)	9 (50%)	0.5
	GI disease	12	2 (16.7%)	4 (33.3%)	6 (50%)	0.5
	Rheumatologic disease	6	3 (50%)	1 (16.7%)	2 (33.3%)	0.5

Table-3 Association between abnormal hematologic parameters, and Inflammatory Marker with severity of COVID-19 (n= 357)

	Severity			P-values
	Mild-Moderate	Severe	critical	
Hematologic abnormalities				
Thrombocytopenia	4 (6.3%)	10 (15.9%)	49 (77.8%)	0.007
Thrombocytosis	3 (23.1%)	3 (23.1%)	7 (53.8%)	0.11
Lymphopenia	16 (13.9%)	22 (19.1%)	77 (67%)	<0.001
Neutropenia	8 (38.1%)	5 (23.8%)	8 (38.1%)	0.3
Neutrophilia	8 (10.8%)	16 (21.6%)	50 (67.6%)	0.008
Coagulation abnormalities				
aPTT	12 (11.3%)	20 (18.9%)	74 (69.8%)	<0.001
PT	4 (16%)	5 (20%)	16 (64%)	<0.001
Abnormal fibrinogen	0 (0%)	1 (5.3%)	18 (94.7%)	<0.0001
High d-dimer	21 (10.3%)	31 (15.2%)	152 (74.5%)	<0.0001
Inflammatory markers				
High CRP	49 (14.9%)	72 (21.9%)	208 (63.2%)	0.004
High ESR	41 (15%)	64 (23.4%)	169 (61.7%)	<0.001
High Ferritin	19 (10.6%)	26 (14.4%)	135 (75%)	<0.001
High LDH	39 (13.4%)	60 (20.6%)	192 (66%)	<0.001

Table-4: Multivariate analysis for severity of Covid-19 in relation to age, gender, comorbidities, hematologic abnormalities, coagulation abnormalities and inflammatory markers

	Severe OR (95% CI)	Critical OR (95% CI)
Age	2.8 (1.3 - 6), P=0.009	1 (0.5 - 2), P=0.952
Gender	1.6 (0.8 - 3.2), P=0.194	1.9 (1 - 3.6), P=0.035
Comorbidities		
DM	3.9 (1.8 - 8.7), P=0.001	4.4 (2.2 - 8.8), P=0.0001
HTN	0.7 (0.3 - 1.7), P=0.446	1 (0.5 - 2), P=0.907
CKD	1.8 (0.3 - 11.5), P=0.515	4.1 (0.8 - 20.7), P=0.09
Cardiac disease	0.9 (0.3 - 2.7), P=0.875	0.4 (0.2 - 1.1), P=0.084
Hematologic disease	2 (0.4 - 10.6), P=0.413	1.6 (0.3 - 7.6), P=0.547
GI disease	1.3 (0.2 - 8.4), P=0.793	0.6 (0.1 - 3.6), P=0.599
Rheumatologic disease	0.3 (0 - 3.5), P=0.329	0.3 (0 - 2.2), P=0.244
Hematologic abnormalities		
Thrombocytopenia	2.2 (0.6 - 7.3), P=0.212	4.2 (1.5 - 12.2), P=0.008
Thrombocytosis	2.7 (0.2 - 31.4), P=0.436	1.3 (0.1 - 14), P=0.839
Lymphopenia	0.5 (0.1 - 2.3), P=0.349	0.9 (0.2 - 3.3), P=0.863
Neutropenia	0.35 (0.08 - 1.5), P=0.156	0.17 (0.05 - 0.6), P=0.006
Neutrophilia	2.9 (0.7 - 12.4), P=0.156	5.8 (1.7 - 20.3), P=0.01
Coagulation abnormalities		
High PT	0.9 (0.2 - 3.7), P=0.891	1.2 (0.4 - 3.8), P=0.758
High PTT	1.2 (0.5 - 2.9), P=0.627	1.7 (0.8 - 3.4), P=0.167
Abnormal fibrinogen	NA	1 (0.9 - 1.1)0.86
High d-dimer	1.1 (0.5 - 2.2), P=0.878	3.8 (2 - 7), P=0.0001
Inflammatory markers		
High CRP	5.3 (0.4 - 74.9), P=0.219	5.9 (0.6 - 59.7), P=0.13
High ESR	2.4 (0.5 - 10.6), P=0.256	1.4 (0.5 - 4.3), P=0.543
High ferritin	2.8 (0.9 - 9.2), p=0.08	3.7 (1.4 - 9.6), P=0.007
High LDH	0.5 (0.1 - 1.9), P=0.307	1.7 (0.5 - 5.8), P=0.369

Table-5 Association between abnormal hematologic, deranged coagulation, inflammatory marker and outcomes of COVID-19

	Outcomes							
	ICU Admission	p-values	ventilation	p-values	Death	p-values	Hospital Stay	p-values
Thrombocytopenia	28 (44.4%)	0.32	22 (34.9%)	0.143	17 (27%)	0.021	11 (8 - 20)	0.08
Thrombocytosis	3 (23.1%)	0.23	2 (15.4%)	0.321	0 (0%)	0.095	7 (5 - 16.5)	0.3
Lymphopenia	56 (48.7%)	0.02	40 (34.8%)	0.05	26 (22.6%)	0.07	12 (8 - 20)	0.11
Neutropenia	2 (9.5%)	<0.0001	1 (4.8%)	0.003	1 (4.8%)	0.09	7 (5 - 11)	0.001
High PT	14 (56%)	0.07	12 (48%)	0.02	6 (24%)	0.34	10 (7.5 - 24)	0.5
High PTT	55 (51.9%)	0.006	42 (39.6%)	0.005	26 (24.5%)	0.04	13 (8 - 21.3)	0.004
Abnormal Fibrinogen	13 (68.4%)	0.331	12 (63.2%)	0.09	6 (31.6%)	0.51	21 (6 - 31)	0.75
High D-dimer	101 (49.5%)	<0.0001	77 (37.7%)	<0.0001	47 (23%)	0.001	12 (8 - 21)	<0.001
High CRP	132 (40.1%)	0.034	92 (28%)	0.25	56 (17%)	0.5	11 (7 - 18)	<0.001
High ESR	105 (38.3%)	0.263	72 (26.3%)	0.54	44 (16.1%)	0.06	11 (7 - 19)	0.007
High Ferritin	80 (44.4%)	0.252	62 (34.4%)	0.06	34 (18.9%)	0.5	12 (8 - 19)	0.07
High LDH	125 (43%)	0.001	90 (30.9%)	0.002	57 (19.6%)	0.008	11 (7 - 18)	<0.001

Table-6: Multivariate analysis for outcome in relation to age, gender, comorbidities, hematologic abnormalities, coagulation abnormalities and inflammatory markers.

	ICU OR (95% CI)	Ventilation OR (95% CI)	Death OR (95% CI)
Age	1.03 (1.02 - 1.05) P<0.001	1.03 (1.01 - 1.04) P<0.001	1.05 (1.03 - 1.07) P<0.001
Gender	0.95 (0.59 - 1.51) p=0.81	1.56 (0.92 - 2.65) p=0.1	0.68 (0.36 - 1.28) p=0.23
Comorbidities			
DM	1.4 (0.9 - 2.2) p=0.1	0.9 (0.56 - 1.45) p=0.66	0.7 (0.39 - 1.25) p=0.23
HTN	1.1(0.7 - 1.8) p=0.6	0.91 (0.53 - 1.55) p=0.72	0.75 (0.4 - 1.4) p=0.37
CKD	1.3(0.6 - 2.8) p=0.6	0.79 (0.35 - 1.8) p=0.57	0.99 (0.37 - 2.59) p=0.98
Cardiac disease	0.8 (0.4 - 1.5) p=0.5	1.12 (0.55 - 2.27) p=0.76	0.96 (0.43 - 2.18) p=0.93
Hematologic disease	0.1(0 - 0.6) P<0.001	7.18 (0.93 - 55.67) p=0.06	3.99 (0.5 - 31.87) p=0.19
GI disease	1.9 (0.5 - 6.8) p=0.3	0.45 (0.13 - 1.57) p=0.21	0.23 (0.07 - 0.82) p=0.02
Rheumatologic disease	0.3(0 - 3.6) p=0.4	1.63 (0.18 - 14.97) p=0.67	NA
Hematologic abnormalities			
Thrombocytopenia	3.4 (0.6 - 21) p=0.185	3.59 (0.6 - 21.43) p=0.16	1.85 (0.31 - 11.11) p=0.5
Thrombocytosis	0.7 (0.1 - 3.7) p=0.696	0.88 (0.15 - 5.15) p=0.89	NA
Lymphopenia	0.9 (0.3 - 2.2) p=0.744	1.5 (0.58 - 3.9) p=0.41	0.81 (0.25 - 2.59) p=0.72
Neutropenia	0.05 (0.01 - 0.3) p=0.001	0.06 (0.01 - 0.55) p=0.01	0.16 (0.02 - 1.43) p=0.1
Neutrophilia	18.5 (3 - 111) p=0.001	16.7 (2 - 100) p=0.01	5.09 (0.63 - 40.98) p=0.13
Coagulation abnormalities			
High PT	1.2 (0 - 39.2) p=0.9	1.18 (0.03 - 42.93) p=0.93	0.26 (0.02 - 4.34) p=0.35
High PTT	3.6 (0.2 - 59.7) p=0.4	5.52 (0.32 - 96.27) p=0.24	4.22 (0.61 - 29.07) p=0.14
Abnormal fibrinogen	3.6 (0.2 - 59.9) p=0.4	2.08 (0.14 - 31.06) p=0.6	2.32 (0.32 - 16.91) p=0.41
High d-dimer	0.5(0 - 12.7) p=0.6	0.95 (0.03 - 27.34) p=0.98	0.53 (0.06 - 4.42) p=0.56
Inflammatory markers			
High CRP	NA	NA	0.51 (0.05 - 5.47) p=0.58
High ESR	6.3 (0.3 - 151.3) p=0.3	5.23 (0.22 - 122.49) p=0.3	1.55 (0.42 - 5.76) p=0.51
High ferritin	0.4 (0 - 5.4) p=0.5	0.44 (0.03 - 5.85) p=0.53	0.87 (0.37 - 2.02) p=0.74
High LDH	0.2 (0 - 5.4) p=0.4	2.39 (0.11 - 53.1) p=0.58	2.89 (0.58 - 14.41) p=0.2

Discussion:

A handful of publications addressed the hematological manifestations of COVID-19 disease in few areas of the Kingdom. However, data among eastern province patients is scarce. To the best of our knowledge, this is the biggest article among Saudi publications. Herein, we studied the prevalence and the association of hematologic manifestations with the severity and outcome of COVID-19 disease at King Fahd Hospital of the University in the Eastern Province of Saudi Arabia.

We included 357 patients with COVID-19 infection and in congruous with other studies where majority of patients were adult males, 68.1% of our patients were males and 69.5% were between the age of 19 to 60 years.¹⁰⁻¹² This epidemiological difference was addressed in Alahdal et al study where he reported a significant difference in practice toward COVID-19 infection precautions between gender in Riyadh, Saudi Arabia, where females had better practice compared to males, hence well practice might rationalize the higher rate of COVID-19 infection among males.¹³

Throughout literature analysis we found that majority of patients infected by SARS-CoV-2 virus had comorbidities with diabetes mellitus accounting for the majority of cases followed by hypertension and cardiac diseases.^{10,14} This was also demonstrated in our study and might be related to the fact that more than 25% of our country populations have diabetes mellitus.¹⁵

Interestingly, although the expected severity pattern of COVID-19 infection is mild to moderate disease, most of our patients presented with severe to critical disease. This high prevalence of severe-critical disease could be attributed to the higher prevalence of comorbidities.¹⁶ Moreover, at the time of collecting our data, COVID-19 vaccine program was not yet established and the studies supports that the severity of COVID-19 can be reduced by vaccine specially for people >60 years old, and those with comorbidities.¹⁷

Variable risk factors for disease severity have been outlined in the literatures such as male gender, older age and comorbid diseases.¹⁷⁻¹⁹ A meta-analysis conducted in 59 studies comprising 36,470 patients reported that males and patients 70 years and above are more prone for ICU admission and high mortality rate.²⁰ Moreover, the presence of comorbidities such as diabetes mellitus was found to have a positive correlation with disease severity in a systematic review that included 22,359 patients.²¹ Hence, a multivariate analysis of our data demonstrated that older age is an independent risk factor for ICU admission, need for mechanical ventilation and mortality. While, DM was found to be an independent risk factor for critical COVID-19 disease. In consequence, identifying those patients in the early course of their disease is crucial in managing and halting further disease progression.

Another risk factor for disease severity is the coexistence of hematological disease. We found that patients with hematological disease were having an independent risk factor for ICU admission with a significant P-value. Those patients might be more vulnerable to COVID-19 infection and disease progression due to enhanced inflammatory response and affected immunity.

There are many postulated mechanisms for thrombocytopenia in COVID-19 patients. Potentially, SARS-CoV-2 virus can lead to activation of platelet aggregation and massive consumption of platelets.^{22,23} It was proclaimed to be associated with severe disease and worse outcome as denoted by Lippi et al and Yang et al.^{22,24} As Such, our data showed a strong association between thrombocytopenia and death (P-value 0.021) which was also supported by a meta-analysis of 17 studies.^{25,26}

In the other hand, thrombocytosis was related to disease progression, severity and mortality. It was observed in 13 cases of our cohort and nearly half of them had critical disease. This was in consonant with Terpos et al and Chen F et al, where they found that thrombocytosis was significantly associated with worse outcome and increased risk of COVID-19 complications and death.^{9,27}

Immense inter-individual differences in hematological abnormalities were observed between severe and non-severe patients. For instance, white blood cells particularly neutrophils and lymphocytes have unpredictable and variable response to COVID-19 infections. In many studies, lymphopenia was detected in critically ill patients, and was associated with increase rate of ICU admissions and mortality.^{9,20,28} According to our analysis, lymphopenia was reported in one-third of our critical patients and was significantly associated with COVID-19 disease severity, ICU admissions and ventilation.

While neutropenia was not commonly observed in patients with COVID-19 infection as supported by López Pereira et al and similarly noted in our study, neutrophilia was more evident in our patients and presented in 67.6% of our critical cases and was found to be an independent risk factor for critical disease.²⁹ Moreover, our data showed that both neutropenia and neutrophilia had significant association with ICU admission, mechanical ventilation, and longer hospital stay with significant P-value. A multivariate regression analysis of our data demonstrated the same correlation and these results were supported by other studies.^{30, 31}

Abnormal coagulation parameters such as elevated D-dimer, ferritin, and raised inflammatory markers were found to be associated with severe COVID-19.^{28,32} This was highlighted in our study where high ferritin was observed in 50.4%, where 75% of them had critical illness and this was similarly noted with high D-dimer.

Both elevated D-dimer and ferritin were independent risk factors for critical disease as demonstrated by multivariate analysis of our data.

A meta-analysis of 16 studies concluded that D-dimer > 0.5mg/dl are correlated with threefold risk of poor outcome in COVID-19 patients.²⁵ Furthermore, a total of 5394 patients in 18 Meta- analyses showed that patients with elevated LDH had five times risk for poor outcomes and it correlates with lung injury, disease severity and mortality.^{29,34} According to our analysis, abnormal coagulation profile in particular elevated PTT and D-dimer in addition to raised CRP, and LDH, were found to significantly correlate with ICU admissions. These laboratory findings in addition to high ESR value were associated with increased rate of mortality.³³

Finally, Fibrinogen level correlated with disease severity in our patients but not with poor outcomes and no association demonstrated on multivariate analysis.

This study highlights important findings that might enhance early recognition of high risk patient and promote instantaneous management. The limitations of our study include the conduction of our study in a single center hospital and the need for future studies that includes further number of cohorts. Moreover, our study was retrospective study; with lack of post discharge follow up.

Conclusion:

Most of the hematologic and coagulation abnormalities in patients with COVID-19 in addition to presence of comorbidities such as diabetes mellitus are considered risk factors for severe disease and worse outcome. However, older age, thrombocytopenia, neutropenia, neutrophilia, elevated d-dimer and ferritin are independent factors for severe and critical disease. Accordingly, these patients should be identified and managed with close observation to prevent and minimize the complications. In addition, COVID-19 vaccination would significantly affect the rate of infection, severity of the disease and prevent worse outcomes.

Running title: Hematological Manifestations of COVID-19

Authors Contribution:

All authors made a substantial contribution to the work reported. The authors confirm contribution to the paper as follows: the first author contributed in the design of the study concept, interpretation of the results, manuscript preparation and supervision of the work.

Argan R, Alkhafaji D, Alqatari S, and Alzaki A have contributed in the conception, study design, part in drafting, revising and critically reviewing the article.

Alabdrabalnabi F, AlElq Z, Albaggal Z, Alsaif Tariq and Almashouf A have contributed in the data

collection, Analysis and interpretation of the result and took part in drafting.

All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

All authors confirm that the manuscript is original research that has not been published and is not under consideration elsewhere.

Ethical Approval:

The study was approved by the Institutional Review Board (IRB) of Imam Abdulrahman Bin Faisal University with an approval number of (IRB -2020-01-261). Patients' consent to review their medical records was not required by the IRB of Imam Abdulrahman Bin Faisal University since it is a retrospective study. The data confidentiality and compliance with the Declaration of Helsinki were maintained.

Declarations:

Conflict of interest: The authors declare that they have no conflict of interest. .

Source of Funding: None declared.

Acknowledgments: None.

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