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HAEMATOLOGICAL PARAMETERS AND OUTCOME IN HOSPITALIZED PATIENTS WITH COVID-19: A DEVELOPING COUNTRY EXPERIENCE

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Background: Coronavirus disease 2019 (COVID-19) is a multisystem disorder and haematological abnormalities are frequently documented in affected patients. **Methods:** This retrospective study included 549 patients hospitalized with COVID-19 from 1st June to 15th July 2020 at Pak Emirates hospital, Rawalpindi Pakistan. $p<0.05$ was considered statistically significant. **Results:** Median age was 60 years (range 12–94 years), males 442 (80.5%) and females 107 (19.5%). There was no patient with mild illness, 181 (32.9%) had moderate, 158 (28.7%) severe and 210 (38.2%) patients had critical disease. Patients with severe and critical disease had lower absolute lymphocyte count (ALC) and platelets ($p<0.001$ for both) while higher white blood cell count (WBC), neutrophil lymphocyte ratio (NLR), C-reactive protein (CRP), interleukin-6 (IL-6) and lactate dehydrogenase levels (LDH) levels (all $p<0.001$). Overall survival of study cohort was 83.2% (n=457). Median haemoglobin and platelet count were significantly lower ($p<0.001$) while WBC, ANC, NLR, prothrombin time (PT), activated partial thromboplastin time (APTT), ferritin, IL-6, LDH were significantly higher ($p<0.001$) for patients who died. On multivariate logistic regression analysis WBC count>$10x10^9$/l (odds ratio [OR] 2.19 [95% CI 1.3–4.2] $p=0.01$), NLR>9 (OR 3.4 [95% CI 0.87–6.8], $p<0.001$), platelets<$150x10^9$/l (OR 3.9 [95% CI 1.4–9.8] $p<0.001$), CRP >100; (OR 4.1[95% CI 0.78–10.9] $p<0.001$) and ferritin >1000 (OR 5.3 [95% CI 1.9–13.5], $p<0.001$) were associated with increased risk of death in patients with COVID-19. **Conclusion:** Monitoring of haematological, coagulation and inflammatory parameters provide reliable, convenient, rapid and cost-effective method for predicting disease severity, complications and prognosis of COVID-19 patients.

Keywords: Coronavirus; Haematology; Cytokine Release Syndrome; Death

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INTRODUCTION

Initial reports of Coronavirus disease 2019 (COVID-19) came from Wuhan[1] China in December 2019 and has affected more than 21 million people with more than 0.7 million deaths by August 14, 2020. Host cells are invaded by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) by binding to angiotensin converting enzyme 2 (ACE-2) receptor.[2] As COVID-19 pandemic continues to devastate humanity socially, monetarily and specially medically; there is a need to identify simple, reliable and economical predictors of disease progression and outcome. Haematological and immune abnormalities are commonly seen in advanced COVID-19 patients.[3] Different studies across the globe have documented several clinical and laboratory parameters in patients with severe and critical COVID-19 including lymphopenia, neutrophil lymphocyte ratio (NLR), d-dimers, platelet count, interleukin-6 (IL-6) levels and ferritin levels.[4–9] Coagulation disorders are frequently seen in severe and critical COVID-19 patients ranging from dissemination intravascular coagulation (DIC) to COVID associated coagulopathy (CAC).[10] Only limited data on haematological parameters of COVID-19 is published from South Asia, this study highlights haematological abnormalities in Pakistani COVID-19 patients.

MATERIAL AND METHODS

This retrospective cohort study was carried out at Department of Internal Medicine and Critical care, Pakistan Emirates Hospital (PEMH) Rawalpindi Pakistan. The study was approved by institutional review board and hospital ethical committee. Medical records of all hospitalized COVID-19 patients from 1st June to 15th July 2020 were reviewed retrospectively. Study inclusion criteria included (1) SARS-CoV2 RNA detection by PCR (2) Age more than 12 years (3) Hospitalized patients (4) Both

genders. Exclusion criteria were as follows (1) Those with incomplete haematological and coagulation profile (2) Unknown outcomes (left against medical advice, transferred to other hospital). Classification of disease severity was taken as the worst classification during hospital admission. For purpose of study and data analysis, haematological parameters at the time of the worst disease severity were extracted and analysed.

Disease severity was classified as per National Health Services of Pakistan guidelines.[11] Mild cases were defined as symptoms consistent with COVID without any hemodynamic compromise, need for oxygen or chest x-ray findings and oxygen saturation ≥94%. Moderate cases included patients with Hypoxia (Oxygen saturation 90%) or chest X-ray with infiltrates involving <50% of lung fields and no complications or manifestations associated with severe disease. Severe cases were patients with clinical signs of pneumonia plus any of the following; Respiratory rate >30, severe respiratory distress; SpO2 ≤90% on room air, chest X-ray involving >50% of lung fields. Critical disease was defined as presence of one or more of following in a patient with SARS-CoV2 infection; Acute respiratory distress syndrome (ARDS), multi organ dysfunction syndrome (MODS), septic shock. ARDS was defined as per Berlin definition[12] and septic shock as per The Third International Consensus Definitions for Sepsis and Septic Shock[13]. Scoring for disseminated intravascular coagulation (DIC) was done using International Society on Thrombosis and Haemostasis (ISTH) scoring system.[14]

Lymphopenia was defined as lymphocyte count $<1x10^9$/l, thrombocytopenia as platelet $<150x10^9$/l. Data was extracted from hospital records regarding demographic, clinical, laboratory and survival information. As per PEMH COVID-19 management protocol; Demographic data, clinical presentation and disease severity assessment was recorded for all patients at admission. Disease severity assessment was done daily for all hospitalized patients at time of admission and daily during duration of hospitalization. Following tests were performed for all the patients at admission and then serially during duration of hospitalization; Complete blood counts (CBC), prothrombin time (PT), activated partial thromboplastin time (APTT), ferritin, lactate dehydrogenase (LDH), D-dimers, liver and renal function tests, X-ray chest. Interleukin-6 (IL-6) testing was done for patients with severe and critical COVID-19. Treatment was given as per disease severity according to hospital guidelines for COVID-19 management. Patients with mild disease were observed. Those with moderate disease were treated with protocol-B (tablet aspirin 75 mg daily, enoxaparin 1 mg/kg once daily, methylprednisolone (MP) 0.5 mg/kg). Patients with severe disease were given protocol C (aspirin 150 mg, enoxaparin 1.5–2 mg/kg, methylprednisolone 1 mg/kg, awake proning). For critical disease protocol D was given which was similar to protocol C except use of CPAP 8-10cmH2O. For patients with documented cytokine release syndrome (CRS) methylprednisolone 2 mg/kg was used. Novel therapies used included tocilizumab, remdesivir, hydroxychloroquine, therapeutic plasma exchange, mesenchymal stem cells.

Continuous variables were expressed as median and range, categorical as number and percentages. Chi square test was used for comparing categorical variables, independent student t test and Mann-Whitney U test were used to analyze normally distributed and non-normally distributed continuous variables respectively. $p<0.05$ was considered statistically significant. Kaplan Meier test was used for survival analysis. Data was analysed using SPSS version 23 unless otherwise indicated.

RESULTS

We analysed data from 549 SARS-CoV2 PCR positive patients admitted to PEMH with diagnosis of COVID-19. Median age of study population was 60 years (range 12–94 years), 302 patients (52.7%) were younger than 60 years while 247 (43.1%) were older. Males were 442 (80.5%) and females 107 (19.5%). One or more comorbid were present in 415 (75.5%) patients. Contact history was positive in 151 (26.4%) patients. Common symptoms at admission were cough (414; 72.3%), fever (398; 69.5%), shortness of breath (380; 66.3%), myalgia (89; 15.5%), diarrhoea (39: 6.8%), fatigue (38; 6%) and vomiting (23; 4%). There was no patient with mild illness, 181 (32.9%) with moderate disease, 158 (28.7%) with severe and 210 (38.2%) with critical disease. More than 50% lung involvement was documented on high resolution computed tomography (HRCT) during course of illness in 288 (52.4%) patients. Cytokine release syndrome (CRS) was the most common complication in 290 (52.8%) patients followed by acute respiratory distress syndrome (ARDS) in 194 (35.3%), multi-organ dysfunction syndrome (MODS) in 78 (14.2%), acute kidney injury (AKI) in 48 (8.7%), acute hepatitis 41 (7.4%), disseminated intravascular coagulation (DIC) 39 (7.1%) and thrombotic complications in 85 (15.5%) patients. DIC was diagnosed as per International society on thrombosis and haematology (ISTH) scoring system and correlated with disease severity (56.4% in critical disease versus 17.9% in moderate disease, $p=0.03$) and outcome, 86.1% survival without DIC versus 46.2% with DIC ($p<0.001$; OR 3.86 and 95% CI

2.69–5.55). Demographic and clinical characteristics of study population as per disease severity are summarized in table-1. Patients with severe and critical disease were older, had more comorbidities at time of presentation, higher complication rate and inferior overall survival (Table-1).

Median haemoglobin (Hb) of study cohort was 12.8 g/dl (range 5.5–17), White blood cell (WBC) $10.8x10^9$/l (range 0.2–68.8), absolute neutrophil count (ANC) $8.3x10^9$/l (range 0.08–67), neutrophil lymphocyte ratio (NLR) 8.3 (range 0.6–58.7), C-reactive protein (CRP) 85 mg/l (range 0.2–499), ferritin 1200 ug/ml (range 55–18982), lactate dehydrogenase (LDH) 594 IU/l (111-2798) and interleukin-6 levels 41 (1–5000). Haematological characteristics of study population as per disease severity are summarized in table-2.

Patients with severe and critical disease had lower absolute lymphocyte count (ALC) and platelets (p<0.001 for both) while higher WBC, ANC, NLR, d-dimers, CRP, IL-6 and LDH levels (all p<0.001). Patients with blood group AYE had more critical disease as compared to other blood groups (p=0.03). Overall survival of study cohort was 83.2% (n=457). Patients who died were significantly older than those alive (median 68 versus 59 years), p=0.01. Effect of haematological parameters on patient's survival outcome is documented in table-3. Median haemoglobin and platelet count were significantly lower (p<0.001) while WBC, ANC, NLR, PT, APTT, ferritin, IL-6, LDH were significantly higher (p<0.001) in dead patients. Although ALC and blood group AYE were associated with more severe disease (p<0.001 and 0.03 respectively), this did not have impact on survival outcomes (Table-3).

Table 1: Demographic and clinical characteristics of study population

	Moderate (n=181)	Severe (n=158)	Critical (n=210)	*p*-value
Age (years) Median(range)	56 (13–94)	61 (24–92)	63 (12–80)	<0.001
Gender, n (%)				
Male	139 (76.8)	136 (86.1)	167 (79.5)	0.08
Female	42 (23.2)	22 (13.9)	43 (20.5)	
Contact history	62 (34.3)	33 (21.9)	56 (37.1)	0.07
Comorbidity type, n (%)				0.002
DM	35 (19.3)	54 (34.1)	76 (36.1)	
HTN	36 (19.8)	33 (20.8)	52 (24.7)	
IHD	15 (8.2)	12 (7.5)	29 (13.8)	
OAD	8 (4.4)	11 (6.9)	15 (7.1)	
Renal disorder	13 (7.1)	4 (2.5)	3 (1.4)	
Malignancy	7 (3.8)	4 (2.5)	3 (1.4)	
Others	15 (8.2)	34 (21.5)	44 (20.9)	
Symptoms; n (%)				
Fever	107 (59.1)	108 (68.4)	183 (87.1)	<0.001
Cough	115 (63.5)	120 (75.9)	179 (85.2)	<0.001
SOB	66 (36.5)	122 (77.2)	192 (91.4)	<0.001
Myalgias	42 (23.2)	24 (15.1)	27 (12.8)	0.01
Duration of fever in days; median(range)	3 (1–7)	4 (1–9)	5.2 (1–17)	
Lung involvement on HRCT				
Normal	6 (3.3)	-	-	<0.001
<50%	162 (89.5)	57 (36.1)	38 (18.1)	
>50%	13 (7.2)	101 (63.9)	172 (81.9)	
Complications				
CRS; n (%)	43 (23.8)	84 (53.2)	163 (77.6)	0.03
Thromboembolism; n (%)	-	8 (5.1)	10 (4.8)	0.03
ARDS; n (%)	2 (1.1)	14 (8.9)	178 (84.8)	<0.001
AKI; n (%)	-	13 (8.7)	35 (16.6)	<0.001
Acute Hepatitis; n (%)	8 (4.4)	12 (7.56)	21 (10)	.11
MODS; n (%)	9 (5)	5 (3.2)	64 (30)	<0.001
Septic shock; n (%)	-	2 (1.3)	12 (5.7)	-
ACS; n (%)	7 (3.9)	6 (3.8)	9 (4.3)	0.96
Treatment				
Steroids; n (%)	151 (83.4)	158 (100)	210 (100)	-
TPE; n (%)	18 (9.9)	58 (36.7)	85 (40.5)	<0.001
Tocilizumab; n (%)	-	-	3 (1.4)	-
MSCs; n (%)	-	1 (0.6)	5 (2.3	-
Remdesivir; n (%)	-	1 (0.6)	7 (3.3)	-
CP; n (%)	-	4 (2.5)	13 (6.1)	0.09
Day 7 PCR negativity; n (%)	70 (38.7)	63 (39.9)	47 (22.4)	<0.001
Days of hospitalization; median(range)	8 (1–45)	13 (4–51)	14 (6–45)	0.02

Table-2: Haematological characteristics of study population

Characteristics (n=549)	Disease severity; n (%)			*p* value
	Moderate (n=181)	Severe (n=158)	Critical (n=210)	
Haemoglobin, g/dl				.280
<12 (n=136)	44 (24.3)	33 (20.9)	59 (28.1)	
>12 (n=413)	137 (75.7)	125 (79.1)	151 (71.9)	
WBC x10^9/l				<0.001
<4 (n=28)	14 (7.7)	8 (5.1)	6 (2.9)	
4-10 (n=263)	117 (64.6)	65 (41.1)	81 (38.6)	
>10 (n=258)	50 (27.6)	85 (53.8)	123 (58.6)	
ANC x10^9/l				<0.001
<1.5 (n=3)	1 (0.6)	2 (1.3)	-	
1.5-6 (n=194)	96 (53)	44 (27.8)	54 (25.7)	
>6 (n=352)	84 (46.4)	112 (70.9)	156 (74.3)	
ALC x10^9/l				<0.001
<1 (n=300)	62 (34.3)	92 (58.2)	146 (69.5)	
>1 (n=249)	119 (65.7)	66 (41.8)	64 (30.5)	
NLR				<0.001
1-3 (n=86)	51 (28.2)	17 (10.8)	18 (8.6)	
>3-9 (n=244)	97 (53.6)	68 (43)	79 (37.6)	
>9 (n=219)	22 (18.2)	73 (46.2)	113 (53.8)	
Platelet x10^9/l				<0.001
<150 (n=143)	31 (17.1)	40 (25.3)	72 (34.3)	
150-400 (n=376)	140 (77.3)	108 (68.4)	128 (61)	
>400 (n=30)	10 (5.5)	10 (6.3)	10 (4.8)	
PT above normal, seconds				<0.001
<3 (n=458)	168 (92.8)	136 (86.1)	153 (72.9)	
≥ 3 (n=43)	13 (7.2)	15 (13.9)	57 (27.1)	
APTT above normal, seconds				0.01
<3 (n=442)	163 (90.1)	130 (82.3)	149 (71)	
≥ 3 (n=64)	18 (9.9)	28 (17.7)	61 (29)	
D-dimers, mg/l				<0.001
<400 (n=438)	165 (91.2)	128 (81)	145 (69)	
>400 (n=111)	16 (8.8)	30 (19)	65 (31)	
C-reactive protein, mg/l				<0.001
<50 (n=177)	105 (58)	46 (29.1)	26 (12.4)	
50-100 (n=140)	50 (27.6)	42 (26.6)	48 (22.9)	
>100 (n=232)	26 (14.4)	70 (44.3)	136 (64.8)	
IL-6, pg/ml				<0.001
<16 (n=103)	52 (55.3)	28 (27.5)	23 (13.7)	
≥16 (n=261)	42 (44.7)	74 (72.5)	145 (86.3)	
Serum ferritin, ug/l				<0.001
<300 (n=111)	70 (38.7)	20 (12.7)	21 (10)	
300-1000 (n=223)	77 (42.5)	67 (42.4)	79 (37.6)	
>1000 (n=215)	34 (18.8)	71 (44.9)	110 (52.4)	
LDH, IU/l				<0.001
<280 (n=98)	75 (41.4)	9 (5.7)	14 (6.7)	
≥280 (n=451)	106 (58.6)	149 (94.3)	196 (93.3)	
Blood group (n=216) n(%)	n= (45)	n= (62)	n= (109)	
AYE	12 (6.6)	11 (7)	39 (18.6)	0.03
BEE	15 (5.7)	20 (12.7)	35 (16.7)	0.98
AB	4 (2.2)	9 (5.7)	5 (2.4)	0.07
O	14 (7.7)	22 (13.9)	30 (14.3)	0.55

Table-3: Effect of haematological parameters on survival outcome

Characteristics (n=549)	Alive (n=457)	Dead (n=92)	*p*-value
Haemoglobin, g/dl	13.13 (2.01)	12.35 (2.39)	0.001
WBC x10^9/l	10.19 (6.8)	14.48 (5.78)	<0.001
ANC x10^9/l	8.28 (6.27)	12.47 (5.41)	<0.001
ALC x10^9/l	1.16 (0.763)	0.82 (1.2)	0.02
NLR	8.9 (7.45)	17.44 (13.32)	<0.001
Platelet count x10^9/l	231 (107)	171 (100)	<0.001
Prothrombin time, seconds	14.43 (1.4)	16.56 (3.6)	<0.001
Activated partial thromboplastin time, seconds	33.63 (7.32)	41.01 (12.59)	<0.001
d-dimers, mg/l	283 (203)	553 (423)	<0.001
Plasma fibrinogen, g/l	274 (23.68)	292 (34.66)	<0.001
C-reactive protein, mg/l	94.4 (80)	168 (107.6)	<0.001
IL-6, pg/ml	98.8 (456)	453 (751)	0.001
Serum ferritin, ug/l	1065 (1246)	1851 (2891)	<0.001
LDH, IU/l	528.76 (334)	846.87 (527)	<0.001
Blood group (n=216) n (%)			0.537
AYE	49 (79)	13 (21)	
BEE	56 (80)	14 (20)	
AB	17 (95)	1 (5)	
O	56 (85)	10 (15)	

Values express mean (SD) for continuous variables and number (%) for categorical variables

Table-4: Haematological parameters and complications in hospitalized patients with COVID-19

Characteristics n=549	Complication									
	CRS		Thrombosis		ARDS		MODS		Acute Hepatitis	
	n (%)	*p*-value	n (%)	*p*-value	n (%)	*p*-value	n (%)	*p*-value	n (%)	*p*-value
Haemoglobin, g/dl				0.01		0.179		0.03		0.346
<12 (n=136)	75 (55.1)	0.53	9 (6.6)		55 (40.9)		27 (19.9)		13 (9.6)	
>12 (n=413)	215 (52.1)		9 (2.2)		139 (33.7)		51 (12.3)		28 (6.8)	
WBC x10^9/l		<0.010		0.735		0.001		0.05		0.165
<4 (n=28)	13 (46.4)		1 (3.6)		6 (21.4)		1 (3.6)		2 (7.1)	
4-10 (n=263)	117 (44.5)		7 (2.7)		76 (28.9)		32 (12.2)		14 (5.3)	
>10 (n=258)	160 (62)		10 (3.9)		112 (43.4)		45 (17.4)		25 (9.7)	
ANC x10^9/l		<0.001		0.07		0.014		0.02		0.424
<1.5 (n=3)	2 (66.7)		-		1 (33.3)		-		-	
1.5-6 (n=194)	77 (39.7)		3 (1.5)		53 (27.3)		19 (9.8)		11 (5.7)	
>6 (n=352)	211 (59.9)		15 (4.3)		140 (39.8)		59 (16.8)		30 (8.5)	
ALC x10^9/l		<0.001		0.29		<0.001		0.002		0.629
<1 (n=300)	210 (70)		12 (4)		136 (45.3)		55 (18.3)		24 (8)	
>1 (n=249)	80 (32.1)		6 (2.4)		58 (23.3)		23 (9.2)		17 (6.8)	
NLR		<0.001		0.12		<0.001		0.01		0.258
1-3 (n=86)	16 (18.6)		3 (3.5)		19 (22.1)		8 (9.3)		4 (4.7)	
>3-9 (n=244)	120 (49.3)		4 (1.6)		70 (28.7)		27 (11.1)		16 (6.6)	
>9 (n=219)	154 (70.3)		11 (5)		105 (47.9)		43 (19.6)		21 (9.6)	
Platelet x10^9/l		0.01		0.544		<0.001		0.001		0.691
<150 (n=143)	91 (63.6)		7 (4.9)		70 (49)		34 (23.8)		13 (9.1)	
150-400 (n=376)	184 (48.9)		10 (2.7)		114 (30.3)		41 (10.9)		26 (6.9)	
>400 (n=30)	15 (50)		1 (3.3)		10 (33.3)		3 (10)		2 (6.7)	
PT above normal,		0.884		0.17		0.04		0.001		0.226
<3 (n=458)	229 (50)		14 (3.7)		145 (31.7)		53 (11.6)		30 (6.6)	
≥ 3 (n=43)	21 (48.8)		4 (7)		20 (46.5)		13 (30.2)		4 (9.3)	
APTT above normal, seconds		0.365		0.528		0.25		0.006		0.012
<3 (n=442)	215 (48.6)		14 (3.2)		141 (31.9)		53 (12)		26 (5.9)	
≥ 3 (n=64)	35 (54.7)		4 (4.7)		25 (39.1)		13 (20)		8 (12.5)	
D-dimers, mg/l		0.001		0.416		<0.001		0.005		0.156
<400 (n=438)	216 (49.3)		13 (3)		130 (29.7)		53 (12.1)		29 (6.6)	
>400 (n=111)	74 (66.7)		5 (4.5)		64 (57.7)		25 (22.5)		12 (10.8)	
Plasma fibrinogen, g/l		0.004		0.235		0.001		<0.001		0.62
Mean (SD)	280 (25)		284 (24)		274 (28.6)		287 (20.9)		274 (24.82)	
C-reactive protein, mg/l		<0.001		0.25		<0.001		<0.001		0.647
<50 (n=177)	55 (31.1)		4 (2.3)		28 (15.8)		12 (6.8)		11 (6.2)	
50-100 (n=140)	60 (42.0)		3 (2.1)		43 (30.7)		16 (11.4)		10 (7.1)	
>100 (n=232)	175 (75.4)		11 (4.7)		123 (53)		50 (21.6)		20 (8.6)	
IL-6, pg/ml		<0.001		0.69		<0.001		0.006		0.838
<16 (n=103)	34 (33)		4 (3.9)		20 (19.4)		9 (8.7)		8 (7.8)	
≥16 (n=261)	225 (86.2)		8 (3.1)		140 (53.6)		55 (21.1)		24 (9.2)	
Serum ferritin, ug/l		<0.001		0.62		<0.001		<0.001		<0.001
<300 (n=111)	15 (13.5)		3 (2.7)		20 (18)		8 (7.2)		3 (2.7)	
300-1000 (n=223)	86 (38.6)		6 (2.7)		73 (32.7)		22 (9.9)		9 (4)	
>1000 (n=215)	189 (87.9)		9 (4.2)		101 (47)		48 (22.3)		29 (13.5)	
LDH, IU/l		<0.001		0.89		<0.001		0.11		0.02
<280 (n=98)	23 (23.5		3 (3.1)		14 (14.3)		9 (9.2)		2 (2)	
≥280 (n=451)	267(59.2)		15 (3.3)		180 (39.9)		69 (15.3)		39 (8.6)	

Effect of haematological parameters on COVID-19 complications is tabulated (Table-4). Patients with CRS had lower ALC (p<0.001) and platelet count (p=0.01) while higher WBC, ANC, NLR, PT, APTT, ferritin, d-dimers, IL-6, LDH and CRP (all p<0.05). Those with thrombosis had a lower haemoglobin (p=0.01) while other haematological and coagulation parameters were not significantly different from patients without thrombosis. Patients with ARDS had lower platelets and higher WBC, ANC, NLR, PT, CRP, ferritin, LDH (all p<0.05) while no difference with respect to haemoglobin and APTT was documented. OS of study cohort was 83.2% (n=457). OS for patients with moderate disease (n=181) was 97.2%; severe disease (n=158) 91.1% and for critical disease(n=210) OS was 65.2%, log rank <0.001 (Figure-1). Effect of haematological parameters on survival outcomes is shown in figure-2. On multivariate logistic regression analysis WBC count >1010^9/l; odds ratio [OR] 2.19 [95% confidence interval (CI) 1.3–4.2], p=0.01, NLR>9; OR 3.4 [95% CI 0.87–6.8], p<0.001, platelets <150 x10^9/l; OR 3.9 [95% CI 1.4–9.8] p<0.001, CRP >100; OR 4.1[95% CI 0.78–10.9] p<0.001, ferritin>1000; odds ratio 5.3 [95% CI 1.9–13.5], p<0.001 were associated with increased risk of death in patients with COVID-19.

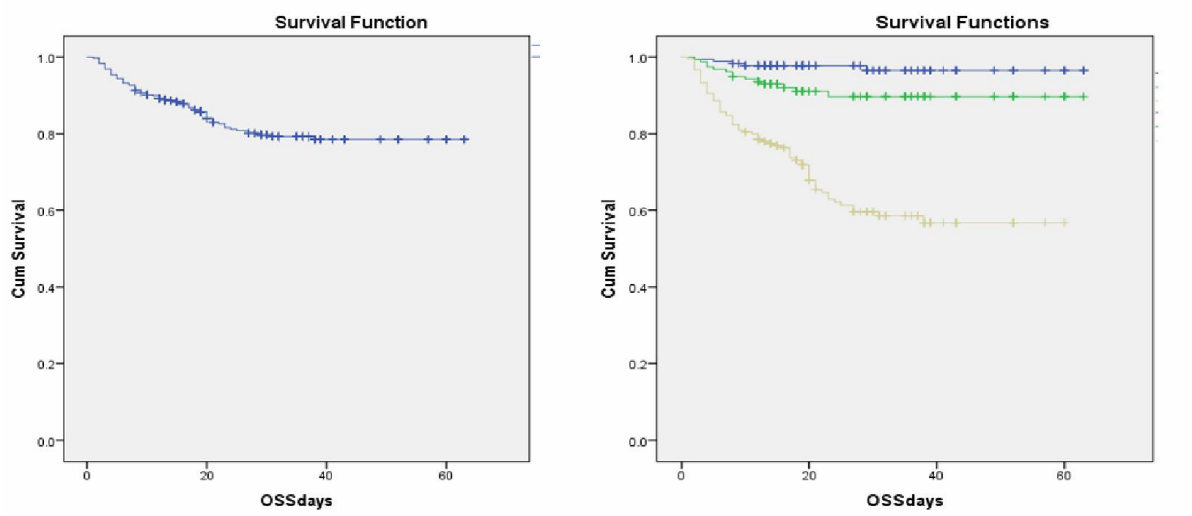

Figure-1: Overall survival and survival as per disease severity (a) OS of study cohort 83.2%. (b) OS as per disease severity. Moderate (n=181) blue line OS 97.2%; severe (n=158) green line OS 91.1%; critical (n=210) brown line OS 65.2%: log rank <0.001

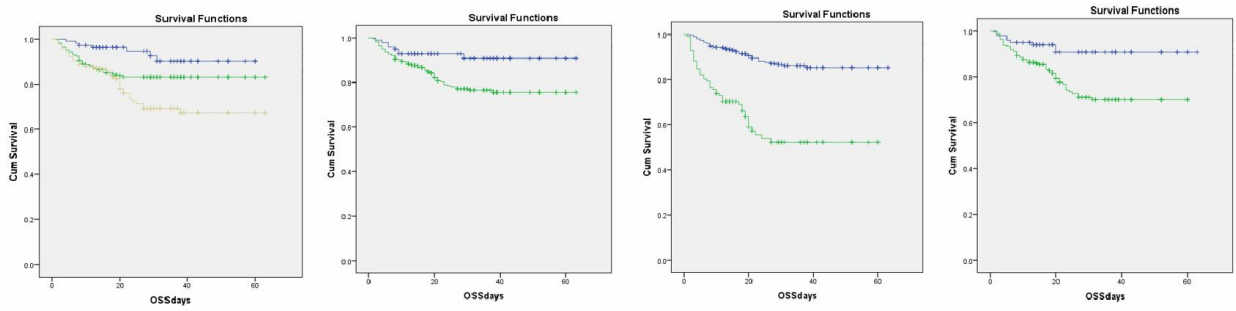

Figure 2: Effect of haematological parameters on overall survival (OS)

(a) OS 72.8% for Hb<12 g/dl (blue line) and 86.7% for Hb>12g/dl (green line); log rank<0.001 **(b)** OS 96.4% for WBC <4 x10^9/l (blue line) ,90.5% for WBC 4-10 x10^9/l (green line)and 74.4% for WBC >10 x10^9/l (brown line); log rank<0.001**(c)** OS 93% for NLR 1-3 (blue line) ,89.3% for NLR >3-9 (green line)and 72.6 % for NLR >9 (brown line); log rank<0.001 **(d)** OS 93.2 % for CRP <50 (blue line) ,90.7% for CRP 50-100 (green line)and 71.1 % for CRP>100(brown line); log rank<0.001 **(e)** OS 93.7 % for ferritin <300 (blue line) ,84.3% for ferritin 300-1000 (green line)and 76.7 % for ferritin>1000(brown line); log rank 0.001 **(f)** OS 91.8% for LDH<280 IU/l (blue line) and 81.4% for LDH>280 IU/l (green line); log rank<0.011 **(g)** OS 89.3% for d-dimers<400 (blue line) and 59.5% for d-dimers>400 (green line); log rank<0.001**(h)** OS 92.2 % for IL-6 <16 (blue line) and 77.8% for IL-6 > 16 (green line); log rank 0.001

DISCUSSION

Coronavirus disease 2019 (COVID-19) is a multisystem disorder involving pulmonary, cardiovascular, renal, gastrointestinal and hematopoietic system.[15] Haematological abnormalities are frequently documented in COVID-19 patients and has prognostic and therapeutic significance.[16] Monitoring lymphocyte count dynamics and inflammatory markers (CRP, ferritin, IL-6, LDH) my help to identify cases with worse prognosis and need for prompt intervention to improve outcome. Elevated d-dimers are reported in patients with moderate to severe disease and their rise during disease course are indicator of worsening of disease.[17,18] Moreover, hyperferritinemia, prolongation of PT, APTT, hypofibrinogenemia, thrombocytopenia are markers of severity, progression to critical disease and poor prognosis. Studies have shown that patients admitted to ICU had more marked leucocytosis, lymphopenia, prolonged PT and d-dimers as compared to non-ICU patients[1,16], 96.1% versus 80.4% for lymphocytopenia, 57.7% versus 31.6% for thrombocytopenia and 61.1% versus 28.1% for leukopenia.

Lymphopenia is most frequently encountered abnormality in 35–83% patients[18,19] and is reported to be associated with severity of disease[18]. In our study lymphopenia (defined as ALC<1x10^9/l) was present in 300 (52.4%) patients. Frequency of lymphopenia was higher in patients with critical disease (69.5%) as compared to moderate disease (34.3%), p<0.001 and was associated with inferior survival outcomes (78.7% versus 88.8%), p<0.001. These results are similar to those of Guan *et al*[19] and

Fan *et al*[18]. Different studies have documented that anaemia is not a significant feature of COVID-19.[1,19] In our study, no significant difference in haemoglobin level was observed as per disease severity (p=0.28). Similar observation was published by Guan *et al.*[19] Similar to studies from Singapore and Wuhan[20], critically ill patients had significantly lower median ALC, neutrophilia and high NLR (all p<0.001). Thrombocytopenia was present in 143(26%) patients in our study, 17.1% in moderate and 34.3% in critically ill patients (p<0.001) and was associated with increased COVID-19 related mortality. These findings are similar to other published studies.[6,19] In a meta-analysis of nine studies, thrombocytopenia was found to be significantly more pronounced in severe COVID-19 cases and independently associated with increased mortality.[21] In our study NLR was higher among critically ill patients (p<0.001) and was associated with inferior survival outcomes (p<0.001). Different studies have documented utility of NLR in predicting disease severity, progression and planning further treatment. Ciccullo *et al* documented that NLR<4 was associated with early clinical improvement and better survival outcomes.[22] In our study high CRP, d-dimers, IL-6 levels correlated with disease severity and outcome. These findings are in line with international published literature. Tang *et al* showed that COVID non-survivors had significantly higher levels of d-dimer, fibrin degradation products, PT and APTT when compared to survivors.[23] In our study, patients with severe and critical disease had higher CRP, serum ferritin, IL-6 and LDH levels. Overall survival was inferior in patients with higher inflammatory markers. Guan *et al* reported that higher CRP was associated with more severe disease, higher ICU admission rate and need for mechanical ventilation.[19] Higher CRP, ferritin, IL-6, d-dimers in our study correlated with development of CRS, ARDS and MODS. Similar to our results, Wu *et al* reported that higher CRP, ferritin and d-dimers were associated with ARDS development.[24] Elevation of these inflammatory markers point to exaggerated immune response leading to acute lung injury, ARDS and MODS. DIC was present in 39 patients (7.1%) and correlated with disease severity and inferior survival. Diagnosis of DIC was made as per ISTH scoring system. This study highlights the importance of haematological and inflammatory parameters in predicting severity, complications of disease, survival outcomes and monitoring response to therapy. Limitations of our study included lack of dynamic monitoring of haematological parameters, which can give a better understanding of disease evolution. Lymphocyte subset analysis was not done due to lack of resources; this could have helped in predicting disease progression.

CONCLUSION

Monitoring haematological, coagulation and inflammatory parameters provide reliable, convenient, rapid and cost-effective method for predicting disease severity, complications of COVID-19 and monitoring response to therapy.

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AUTHORS' CONTRIBUTION

RI, SKM, ZM contributed to study design, data analysis. AN, AS, SR, IF, WA, FS collected the data. SS, RS, QN wrote the manuscript and critically reviewed the study.

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