INTERNATIONAL JOURNAL OF CURRENT MEDICAL AND PHARMACEUTICAL RESEARCH
ISSN: 2395-6429, Impact Factor: 4.656
Available Online at www.journalcmpr.com
Volume 6; Issue 12(A); December 2020; Page No.5422-5427
DOI: http://dx.doi.org/10.24327/23956429.ijcmpr202012933

Research Article

DILEMMA OF THROMBOINFLAMATION IN THE PANDEMIC OF COVID-19

Imran Nazir[1]., Mansour Al Ghamedi [2]., Waleed AM Ahmed[3]., Hanan MM Abdullahi [4]., Mohammad A Farid[5] Yasser H Ahmed[6]., Khalid Khalil [7]., Anas M Al Hazmi[8]., Sayed S Rahman[9] and Amna Al Kalkami[10]

[1]FCPS-Med. Senior Registrar Internal Medicine, Security Forces Hospital Makkah, KSA
[2]Director Medical Affairs, Security Forces Hospital, Makkah
[3]SB-Med. SF-Med ID. Consultant ID Security Forces Hospital Makkah, KSA
[4]SB-Med. SB ID. Consultant ID, Security Forces Hospital Makkah, KSA
[5]MBBS. MD Nephrology Consultant Nephrologist & Head of nephrology. Khamis Mushyt General Hospital, KSA
[6]Consultant Hematologist, Security Forces Hospital, Makkah
[7]MSC-Medicine.Registrar internal medicine, Security Forces Hospital, Makkah. Dr. Anas
[8]SB-Trainee Resident, Security Forces Hospital, Makkah
[9]American Board of Nephrology Consultant nephrologist, Security Forces Hospital, Makkah
[10]Consultant Nephrologist, Security Forces Hospital, Makkah

ARTICLE INFO

Article History:
Received 4th September, 2020
Received in revised form 25th October, 2020
Accepted 23rd November, 2020
Published online 28th December, 2020

Key words:
COVID-19, Micro Thrombosis, D. dimer, Radiological Findings.

ABSTRACT

Background: COVID-19 is a current pandemic with its rapid alarming spread. COVID-19 is associated with an increased risk of thrombosis due to a transient heightened inflammatory state. Thromboinflamation can lead to severe manifestations and death in a proportion of patients. Recent literature document that micro thrombosis is one of primary lung pathophysiology in COVID-19. To determine the factors involved in micro thrombosis severity in COVID-19 will help to understand better about this disease.
Methods: This retrospective descriptive study was conducted in a single tertiary care center of Makkah, Saudi Arabia for four-month period (March 10, 2020, to July 10, 2020). Confirmed COVID-19 patients of either gender with age > 14 years were included in the study. The complete data was extracted from electronic medical records. Fischer exact test was applied to observe the correlation.
Results: A total of 226 patients were included in this study. The mean age of the patients was 58 years ± SD. = 2.836 ± 0.5289 and 95% CI. (2.767- 2.906).The predominant age group (76.6%) was older than 40 years of age. Fever was observed (77.4%), cough (77%), shortness of breath (53.5%), and myalgia (37.2%). Age, co-morbidity, smoking, Hypoxia, abnormal cellular elements, increased inflammatory markers, and specific radiological features have significant association with micro thrombosis severity.
Conclusion: Clinician could consider these factors as clinical predictors of micro thrombosis severity during hospitalization and be able to optimize the therapy.

INTRODUCTION

World Health Organization (WHO) declared COVID-19 as pandemic in March 2020. [1] COVID-19 infection is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[1].This pandemic besieged us with its rapid alarming spread worldwide and high mortality[2].SARS-Cov-2 targets the respiratory alveoli primarily that reaches target host cells through the angiotensin converting enzyme 2 (ACE2) receptor [3, 4]. COVID-19 infection is characterized by an exaggerated inflammatory response that can lead to severe manifestations such as adult respiratory syndrome, sepsis, coagulopathy, and death in a proportion of patients[5]. Although common presentation is with fever, cough, shortness of breath, malaise and gastrointestinal symptoms[6]. Pulmonary vasculature harbor a hypercoagulable state triggers by a severe dysfunctional inflammatory response leads to local thrombosis[7]. This phenomenon extends to local vasculature and then systemically to multi organs, results in macro- and micro-vascular thrombosis[8]. Thromboinflammation or immune-thrombosis is a term used when inflammation hyper activate the host defense systems that leads to activation of coagulation and thrombin generation as mutual critical components interactions [9, 10, 11]. The pathophysiological mechanisms

*Corresponding author: **Imran Nazir**
FCPS-Med. Senior Registrar Internal Medicine, Security Forces Hospital Makkah, KSA

included are cytokine storm, complement activation, and endothelitis that ends with hyper coagulation state in severe COVID-19 disease [12, 13, 14]. This virus itself directly activates the coagulation cascade too [15]. Recent literature document that COVID-19 unique pathophysiology is culprit for the high incidence of micro and macro-vasculature thrombosis despite prophylactic and therapeutic dose anticoagulation [10, 16.]

Recent knowledge document that different laboratory parameters changes are as in a pro thrombotic phase such as increased D-dimer, Fibrinogen, Factor VIII (FVIII), von Willebrand Factor (vWF) and decreased Anti thrombin III[3, 12, 17, 18]. While deranged cellular components (hemoglobin, neutrophils, lymphocytes & platelets), Prothrombin Time/Activated Partial Thromboplastin Time, Cytokines, interleukins (IL1- 6 and 7), acute phase reactants (C-Reactive Protein, ESR, Ferritin), Serum Lactate Dehydrogenase, Renal Function Test and Liver Function Tests highlight the type of pathophysiology and severity of thrombosis[19,20]. Indeed thrombosis and inflammation are two separate processes but mutually reinforce each other to some extent [21, 22]. Coagulation factors (pro- and anti-coagulants), [23, 24] and platelets[25, 26] has their important hemostatic effects, but they display their pro-inflammatory functions too.

A diagnosis of macrovascular & microvascular thrombosis may be underestimated because of limited imaging studies and non-encouraging behavior to performing autopsies. Limited imaging studies were performed because of concerns of non-availability of technology, corona epidemic SOP (standard operating procedure) for radiology departments and risk of transmission of infection. There is evidence of micro thrombosis in lung autopsies of COVID-19 patients [27, 28]. Recently it is seen the high tendency of macrovascular and microvascular thrombosis in mostly critical patients that lead to bad outcome [29, 30]. Surprisingly there is no data regarding the micro thrombosis in COVID-19 patients. This can be because of difficulties in assessment of micro thrombosis in live patients. As yet there is no test or assessment tool available to diagnose or assess its severity. More over the factors that are involved in progression and severity of micro thrombosis are still undercover.

Now this is need of time to evaluate the micro thrombosis in detail. Based on recent knowledge; D. dimer level, platelets count, fibrinogen level, and LDH can be considered as indicators of micro thrombosis severity. Literature documents the multiple factors along with older age group and people with co-morbidities might be at higher risk for severe illness and thrombosis. This pandemic gave us knowledge that thrombosis is one of the most severe sequela of this viral disease. The general rule for the management of thrombosis is the treatment of the underlying cause. American Society for Hematology recommends that VTE (venous thromboembolism) prophylaxis should be given for all hospitalized adults with COVID-19 per standard of care[31]. The National Institutes of Health (NIH) recommends anticoagulation according to weight and D. Dimer levels [32]. So, it is crucial to be able to appropriately manage the sequela of COVID-19-associated thrombosis and find the factors that involved in the severity of thrombosis. This will provide important prognostic and preventive insights which will likely guide alterations in management guidelines of COVID-19.

MATERIAL AND METHODS

The aim and objective of this study was to determine the factors that had dynamic role in the severity of micro thrombosis in COVID-19. It was a retrospective descriptive study that was carried out in single tertiary care center of Makkah, Saudi Arabiafrom March 10, 2020, to July 10, 2020. Study was conducted after institutional ethical committee approval. All confirmed COVID-19 positive patients (confirmed by real-time polymerase chain reaction testing via nasal and throat swabs) are included in study. Each patient's demographic data, laboratory parameters (Complete Blood Count, CRP, ferritin, LDH, D-dimer, and fibrinogen.) on 3rd day of admission were documented using a simple random sampling technique. Chest radiological findings, complications, and outcomes of infected patients were documented. Data were documented and analyzed using a Microsoft Excel spreadsheet and the Statistical Package for Social Sciences (SPSS) version 24. Platelets count, D. dimer, Fibrinogen, and LDH are used as indicators of severity of micro thrombosis. Fischer exact test was applied to assess association between independent variables and thrombosis severity. P -value was considered significant statistically when its value observed < .05.

RESULTS

There were a total of 266 admitted cases enrolled in the study. Males constituted 54% (n=122), and females accounted for 46.0% (n=104) of the patients. The mean age of the patients was 58 years ± SD. = 2.836 ± 0.5289 and 95% CI. (2.767-2.906).The patients with age more than 40 years were 76.6% and only 23.5% were in the 21–41-year-old age group. The following underlying chronic diseases were observed: hypertension 14.2% (n=32), diabetes 15.9% (n=36), chronic kidney diseases 3.1% (n=7), ischemic heart diseases 3.1% (n=7), chronic lung diseases 3.1% (n=7), and stroke 1.8% (n=4).

Mean with standard deviation of each indicator of severity of micro thrombosis is documented in Table-1 below.

Table 1 Statics of Micro Thrombosis Indicators.

Indicators.	Descriptive.		Statistic	Std. Error
Platelet count	Mean		3.013	.0463
	95% Confidence Interval for Mean	Lower Bound	2.922	
		Upper Bound	3.104	
	Median		3.000	
	Std. Deviation		.6959	
D-Dimer (mg/l)	Mean		1.770	.0588
	95% Confidence Interval for Mean	Lower Bound	1.654	
		Upper Bound	1.886	
	Median		1.000	
	Std. Deviation		.8845	
CRP (mg/l)	Mean		1.748	.0730
	95% Confidence Interval for Mean	Lower Bound	1.604	
		Upper Bound	1.892	
	Median		1.000	
	Std. Deviation		1.0967	
ESR	Mean		1.527	.0592
	95% Confidence Interval for Mean	Lower Bound	1.410	
		Upper Bound	1.643	

		Median	1.000	
		Std. Deviation	.8903	
		Mean	3.252	.0548
	95% Confidence Interval for Mean	Lower Bound	3.144	
Ferritin (ug/ml)		Upper Bound	3.360	
		Median	3.000	
		Std. Deviation	.8236	
		Mean	2.487	.0522
	95% Confidence Interval for Mean	Lower Bound	2.384	
LDH (U/liter)		Upper Bound	2.590	
		Median	2.000	
		Std. Deviation	.7845	
		Mean	4.451	.9490
	95% Confidence Interval for Mean	Lower Bound	2.581	
Fibrinogen (mg/dl)		Upper Bound	6.321	
		Median	2.000	
		Std. Deviation	14.2663	
		Mean	1.460	.0521
	95% Confidence Interval for Mean	Lower Bound	1.357	
Radiological features; (lung infiltration/Consolidation./ Ground glass		Upper Bound	1.563	
		Median	1.000	
		Std. Deviation	.7836	

Demographic and clinical covariates association with thrombosis severity shows significant results. Detail of each covariate and its association significance (P value) with thrombosis severity is documented separately in Tables 2 – 5 below.

Table 2 Platelets association with Independent Variables

variables	Platelet count (x10^3/cu mm)					
Age (years)	Total cases (N=266)	<100x	100-150x	151-400x	>400x	P-Value
21-40	53 (23.4%)	1 (0.4%)	1 (0.4%)	39 (17.2%)	12 (5.3%)	
41-65	157 (69.4%)	3 (1.3%)	4 (1.7%)	122 (53.9%)	28 (12.4%)	.000
> 65	16 (7.0%)	12 (5.3%)	0 (0.0%)	4 (1.7%)	0 (0.0%)	
SPO2 % by pulse oximeter						
93-96	210 (92.9%)	7 (3.0%)	5 (2.2%)	160 (70.8%)	38 (16.8%)	.000
<93	16 (7.0%)	9 (3.9%)	4 (1.7%)	5 (2.2%)	2 (0.9%)	
Radiological Features (in Chest x-ray)						
Infiltrat.	163 (72.1%)	1 (0.4%)	4 (1.7%)	125 (55.3%)	33 (14.6%)	
Consol.	22 (9.7%)	0 (0.0%)	1 (0.9%)	14 (6.2%)	7 (3.0%)	.000
Ground G	41 (18.1%)	15 (6.6%)	0 (0.0%)	26 (11.5%)	0 (0.0%)	
Hemoglobin (g/dl)						
10-12.5	12 (8.4%)	5 (2.2%)	0 (0.0%)	13 (5.7%)	1 (0.4%)	
12.6 -16	21 (83.6%)	11 (4.8%)	4 (0.9%)	141 (62.4%)	33 (14.6%)	.000
>16	174 (.9%)	0 (0.0%)	0 (0.0%)	2 (0.9%)	0 (0.0%)	
<10	19 (7.0%)	0 (0.0%)	1 (0.4%)	9 (3.9%)	6 (2.6%)	
Neutrophil count %						
<50	120 (53.0%)	0 (0.0%)	0 (0.0%)	12 (8.4%)	0 (0.0%)	
50-70	133 (58.8%)	2 (0.9%)	1 (0.4%)	17 (7.5%)	1 (0.4%)	.048
71-80	174 (76.9%)	14 (6.2%)	4 (1.7%)	117 (51.7%)	39 (17.2%)	
81-90	19 (8.4%)	0 (0.0%)	0 (0.0%)	19 (7.0%)	0 (0.0%)	
Lymphocyte count						
<5	15 (6.6%)	6 (2.6%)	0 (0.0%)	9 (3.9%)	0 (0.0%)	
5-10	74 (32.7%)	9 (3.9%)	3 (1.3%)	49 (21.7%)	13 (5.7%)	.000
11-20	34 (15.0%)	0 (0.4%)	2 (0.9%)	31 (13.7%)	1 (0.4%)	
21-40	103 (45.6%)	1 (0.4%)	0 (0.0%)	76 (33.6%)	26 (11.5%)	
Monocytes %						
0-5	102 (45.1%)	1 (0.4%)	4 (2.8%)	94 (39.4%)	3 (4.8%)	
6-12	114 (50.4%)	14 (6.2%)	1 (2.0%)	66 (32.6%)	33 (12.3%)	.039
13-20	10 (4.4%)	1 (0.4%)	0 (.2%)	5 (2.7%)	4 (.8%)	
Eosinophils %						
0.0-0.1	68 (30.0%)	13 (5.7%)	2 (0.9%)	53 (23.4%)	0 (0.0%)	.000
.11-0.5%	67 (29.6%)	3 (1.3%)	3 (1.3%)	47 (20.8%)	14 (6.2%)	
0.51-0.7	85 (37.6%)	0 (0.0%)	0 (0.0%)	61 (26.9%)	24 (10.6%)	
>0.7	6 (2.6%)	0 (0.0%)	0 (0.0%)	4 (1.7%)	2 (0.9%)	
ESR						
<15	153 (67.7%)	0 (0.0%)	0 (0.0%)	117 (51.7%)	36 (15.9%)	.000
15-30	42 (18.6%)	8 (3.5%)	2 (0.9%)	28 (12.4%)	4 (1.7%)	
>30	16 (7.0%)	7 (3.0%)	1 (0.4%)	8 (3.5%)	0 (0.0%)	
4.0	15 (6.6%)	1 (0.4%)	2 (0.9%)	12 (5.3%)	0 (0.0%)	
C-Reactive Protein (CRP). mg/dl						
<0.9	144 (63.7%)	8 (3.5%)	0 (0.0%)	101 (22.7%)	35 (44.7%)	
1-3	22 (9.7%)	0 (0.0%)	0 (0.0%)	22 (13.3%)	0 (0.0%)	.000
3.1-5	33 (14.6%)	6 (2.6%)	3 (1.3%)	21 (24.1%)	3 (1.3%)	
5.1-7	27 (11.9%)	2 (0.9%)	2 (0.9%)	21 (14.6%)	2 (0.9%)	
Ferritin (ug/ml)						
205-300	29 (12.8%)	0 (0.0%)	1 (0.4%)	20 (8.8%)	8 (3.5%)	
301-500	137 (60.6%)	14 (6.2%)	1 (0.4%)	94 (41.6%)	28 (12.4%)	.015
501-700	34 (15.0%)	1 (0.4%)	1 (0.4%)	30 (13.3%)	2 (0.9%)	
701-900	26 (11.5%)	1 (0.4%)	2 (0.9%)	21 (9.3%)	2 (0.9 %)	

Abbreviations used in table are Infiltrat: Infiltrations Consol: Consolidation Ground G: Ground Glass appearance

Table 3 D. Dimer association with patient's Independent Variables

Variables	D. Dimer ug/ml					
Age Years	Total N=226	<0.5	0.6-1	1.1-5	> 5.1	P-Value
14-40	53 (23.4%)	24 (10.6%)	14 (6.2%)	12 (5.3%)	3 (1.3%)	
41-65	157 (69.4%)	90 (39.8%)	36 (15.9%)	29 (12.8%)	2 (0.9%)	.028
> 65	16 (7.0%)	1 (0.4%)	3 (1.3%)	12 (5.3%)	0 (0.0%)	
SPO2 % by pulse oximeter						
93-96	210 (92.9%)	113 (50.0%)	49 (21.7%)	44 (19.4%)	4 (1.7%)	.000
<93	16 (7.0%)	2 (0.9%)	4 (1.7%)	9 (3.9%)	1 (0.4%)	
ESR						
<15	153 (67.7%)	107 (47.3%)	30 (13.3%)	15 (6.6%)	1 (0.4%)	
15-30	42 (18.6%)	8 (3.5%)	10 (4.4%)	23 (10.2%)	1 (0.4%)	
>30	16 (7.0%)	0 (0.0%)	4 (1.7%)	11 (4.8%)	1 (0.4%)	.000
40	15 (6.6%)	0 (0.0%)	9 (3.9%)	4 (1.7%)	2 (0.9%)	
C- Reactive Protein (CRP) mg/dl						
<0.9	144 (63.7%)	103 (45.6%)	25 (11.0%)	16 (7.0%)	0 (0.0%)	
1-3	22 (9.7%)	8 (3.5%)	5 (2.2%)	9 (3.9%)	0 (0.0%)	
3.1-5	33 (14.6%)	4 (1.7%)	7 (3.0%)	21 (9.3%)	1 (0.4%)	.000
5.1-7	27 (11.9%)	0 (0.0%)	16 (7.0%)	7 (3.0%)	4 (1.7%)	
Hemoglobin (g/dl)						
10-12.5	19 (8.4%)	4 (1.7%)	5 (2.2%)	8 (3.5%)	2 (0.9%)	
12.6 -16	189 (83.6%)	97 (42.9%)	45 (19.9%)	44 (19.5%)	3 (1.3%)	.001
>16	2 (0.9%)	0 (0.0%)	2 (0.9%)	0 (0.0%)	0 (0.0%)	
<10	16 (7.0%)	14 (6.2%)	1 (0.4%)	1 (0.4%)	0 (0.0%)	
Neutrophil count %						
<50	12 (5.3%)	3 (1.3%)	4 (1.7%)	5 (2.2%)	0 (0.0%)	
50-70	21 (9.3%)	7 (3.0%)	9 (3.9%)	4 (1.7%)	1 (0.4%)	
71-80	174 (76.9%)	91 (40.3%)	38 (16.8%)	42 (18.6%)	3 (1.3%)	.045
81-90	19 (8.4%)	14 (6.2%)	2 (0.9%)	2 (0.9%)	1 (0.4%)	
Lymphocyte count %						
<5	15 (6.6%)	3 (1.3%)	5 (2.2%)	6 (2.6%)	1 (0.4%)	
5-10	74 (32.7%)	29 (12.8%)	22 (9.7%)	22 (9.7%)	1 (0.4%)	
11-20	34 (15.0%)	17 (7.5%)	7 (3.0%)	8 (3.5%)	2 (0.9%)	.013
21-40	103 (45.6%)	66 (29.2%)	19 (8.4%)	17 (7.5%)	1 (0.4%)	
Monocyte count %						
0-5	102 (45.1%)	48 (21.2%)	31 (13.7%)	22 (9.7%)	1 (0.4%)	
6-12	114 (50.4%)	60 (26.5%)	22 (9.7%)	29 (12.8%)	3 (1.3%)	.095
13-20	10 (4.4%)	7 (3.0%)	0 (0.0%)	2 (0.9%)	1 (0.4%)	
Eosinophil count %						
0.0-0.1	68 (30.0%)	19 (8.4%)	15 (6.6%)	30 (13.3%)	4 (1.7%)	
0.11-0.5	67 (29.6%)	45 (19.9%)	15 (6.6%)	6 (2.6%)	1 (0.4%)	.000
0.51-0.7	85 (37.6%)	49 (21.7%)	19 (8.4%)	17 (7.5%)	0 (0.0%)	
>0.7	6 (2.6%)	2 (0.9%)	4 (1.7%)	0 (0.0%)	0 (0.0%)	
Ferritin (ug/ml)						
205-300	29 (12.8%)	17 (7.5%)	5 (2.2%)	7 (3.0%)	0 (0.0%)	
301-500	137 (60.6%)	75 (33.1%)	24 (10.6%)	37 (16.4%)	1 (0.4%)	
501-700	34 (15.0%)	17 (7.5%)	10 (4.4%)	6 (2.6%)	1 (0.4%)	.000
701-900	26 (11.5%)	6 (2.6%)	14 (6.2%)	3 (1.3%)	3 (1.3%)	

Table 4 LDH association with independent variables

Variables	Lactate Dehydrogenase (LDH) u/l				P-Value
AGE Years	Total Cases (N=226)	140-280u/l	281-400u/l	401-500u/l	
21-40	53 (23.4%)	41(18.1%)	5 (2.2%)	7 (3.0%)	.000
41-65	157 (69.5%)	116 (51.3%)	19 (8.4%)	22 (9.7%)	
> 65	16 (7.0%)	0 (0.0%)	4 (1.7%)	12 (5.3%)	
SPO2 (by Pulse oximeter)					
93-96%	210 (92.9%)	153 (67.7%)	25 (11.0%)	32 (14.2%)	.000
<93%	16 (7.0%)	4 (1.7%)	3 (1.3%)	9 (3.9%)	
Neutrophil %					
<50	12 (5.3%)	6 (2.6%)	0 (0.0%)	6 (2.6%)	.005
50-70	21 (9.3%)	9 (3.9%)	7 (3.0%)	5 (2.2%)	
71-80	174 (76.9%)	128 (56.6%)	19 (8.4%)	27 (11.9%)	
81-90	19 (8.4%)	14 (6.2%)	2 (0.9%)	3 (1.3%)	
Lymphocyte %					
<5	15 (6.6%)	0 (0.0%)	7 (3.0%)	8 (3.5%)	.000
5-10	74 (32.7%)	42 (18.6%)	5 (2.2%)	27 (11.9%)	
11-20	34 (15.0%)	22 (9.7%)	9 (3.9%)	3 (1.3%)	
21-40	103 (45.6%)	93 (41.2%)	7 (3.0%)	3 (1.3%)	
Eosinophils %					
0.0-0.1	68 (30.0%)	28 (12.4%)	14 (6.2%)	26 (11.5%)	.000
0.11-0.5	67 (29.6%)	46 (20.3%)	11 (4.8%)	10 (4.4%)	
0.51-0.7	85 (37.6%)	79 (34.9%)	1 (0.4%)	5 (2.2%)	
>0.7	6 (2.6%)	4 (1.7%)	2 (0.9%)	0 (0.0%)	
ESR					
<15	153 (67.7%)	139 (61.5%)	10 (4.4%)	4 (1.7%)	.000
15-30	42 (18.6%)	18 (7.9%)	16 (7.0%)	8 (3.5%)	
>30	16 (7.0%)	0 (0.0%)	2 (0.9%)	14 (6.2%)	
C- Reactive Protein (CRP) mg/dl					
<0.9	144 (63.7%)	127 (56.2%)	5 (2.2%)	12 (5.3%)	.000
1-3	22 (9.7%)	16 (7.0%)	6 (2.6%)	0 (0.0%)	
3.1-5	33 (14.6%)	12 (5.3%)	14 (6.2%)	7 (3.0%)	
5.1-7	27 (11.9%)	2 (0.9%)	3 (1.3%)	22 (9.7%)	
Ferritin (ug/ml)					
205-300	29 (12.8%)	22 (9.7%)	4 (1.7%)	3 (1.3%)	.000
301-500	137 (60.6%)	101 (44.7%)	19 (8.4%)	17 (7.5%)	
501-700	34 (15.0%)	27 (11.9%)	1 (0.0%)	6 (2.6%)	
701-900	26 (11.5%)	7 (3.0%)	4 (1.7%)	15 (6.6%)	
Radiological Features in chest x-ray					
Infiltration	163 (72.1%)	128 (56.6%)	23 (10.2%)	12 (5.3%)	.000
Consolidat.	22 (9.7%)	21 (9.3%)	1 (0.4%)	0 (0.0%)	
Ground G.	41 (18.1%)	8 (3.5%)	4 (1.7%)	29 (12.8%)	
Mechanical Ventilation					
YES	22 (9.7%)	0 (0.0%)	9 (3.9%)	13 (5.7%)	.000
NO	204 (90.3%)	157 (69.5%)	19 (8.4%)	28 (12.4%)	

Abbreviations used in table are Consolidat: Consolidation Ground G: Ground Glass appearance LDH: Lactate dehydrogenase.

Table 5 Fibrinogen association with Patient's Independent Variables

Variables	Total cases	Fibrinogen (mg/dl)			P-value
Age Years	**N=226**	**200-400 mg/dl**	**401-450 mg/dl**	**451-500 mg/dl**	
21-40	53 (23.4%)	43 (19.0%)	9 (3.9%)	0 (0.0%)	.000
41-65	157 (69.4%)	127 (56.2%)	21 (9.3%)	5 (2.2%)	
> 65	16 (7.0%)	1 (0.4%)	1 (0.4%)	14 (6.2%)	
SPO2 % by Pulse oximeter					
93-96	210 (92.9%)	166 (73.4%)	29 (12.8%)	10 (4.4%)	.000
<93	16 (7.0%)	5 (2.2%)	2 (0.9%)	9 (3.9%)	
Hemoglobin (g/dl)					
10-12.5	19 (8.4%)	10 (4.4%)	2 (0.9%)	7 (3.0%)	.017
12.6 -16	189 (83.6%)	147 (65.0%)	26 (11.5%)	12 (5.3%)	
>16	2 (0.9%)	2 (0.9%)	0 (0.0%)	0 (0.0%)	
<10	16 (7.0%)	12 (5.3%)	3 (1.3%)	0 (0.0%)	
Neutrophil %					
<50	12 (5.3%)	6 (2.6%)	6 (2.6%)	0 (0.0%)	.000
50-70	21 (9.2%)	11 (4.8%)	2 (0.9%)	8 (3.5%)	
71-80	174 (77.8%)	140 (61.9%)	21 (9.3%)	11 (4.8%)	
81-90	19 (8.4%)	14 (6.2%)	2 (0.9%)	0 (0.0%)	
Lymphocyte %					
<5	15 (6.6%)	3 (1.3%)	2 (0.9%)	10 (4.4%)	.000
5-10	74 (32.7%)	46 (20.3%)	18 (7.9%)	8 (3.5%)	
11-20	34 (15.0%)	27 (11.9%)	3 (1.3%)	1 (0.4%)	
21-40	103(45.6%)	95 (42.0%)	8 (3.5%)	0 (0.0%)	
Eosinophil %					
0.0-0.1	68 (30.0%)	38 (16.8%)	14 (6.1%)	14 (6.2%)	.000
0.11-0.5	67 (29.6%)	49 (21.7%)	12 (5.3%)	4 (1.7%)	
0.51-0.7	85 (37.6%)	79 (34.9%)	4 (1.7%)	1 (0.4%)	
>0.7	6 (2.6%)	5 (2.2%)	1 (0.4%)	0 (0.0%)	
Monocytes %					
0-5	102 (45.1%)	81 (35.8%)	18 (7.9%)	1 (0.4%)	.002
6-12	114 (50.4%)	84 (37.1%)	11 (4.8%)	16 (7.0%)	
13-20	10 (4.4%)	6 (2.6%)	2 (0.9%)	2 (0.9%)	
ESR					
<15	153 (67.7%)	134 (59.3%)	10 (4.4%)	4 (1.7%)	.000
15-30	42 (18.6%)	26 (11.5%)	6 (2.6%)	10 (4.4%)	
>30	16 (7.0%)	5 (2.2%)	6 (2.6%)	5 (2.2%)	
4.0	15 (6.6%)	6 (2.6%)	9 (3.9%)	0 (0.0%)	
C-Reactive Protein (mg/dl)					
<0.9	144 (63.7%)	120 (53.0%)	11 (4.8%)	8 (3.5%)	.000
1-3	22 (9.7%)	18 (7.9%)	3 (1.3%)	1 (0.4%)	
3.1-5	33 (14.6%)	19 (8.4%)	4 (1.7%)	10 (4.4%)	
5.1-7	27 (11.9%)	14 (6.1%)	13 (5.7%)	0 (0.0%)	
Ferritin (ug/ml)					
205-300	29 (12.8%)	23 (10.2%)	4 (1.7%)	1 (0.4%)	.005
301-500	137 (60.6%)	105 (46.4%)	11 (4.8%)	18 (7.9%)	
501-700	34 (15.0%)	26 (11.5%)	7 (3.0%)	0 (0.0%)	
701-900	26 (11.5%)	17 (7.5%)	9 (3.9%)	0 (0.0%)	
Radiological Features in Chest X-ray.					
Lung Infil.	163 (72.1%)	138 (61.0%)	15 (6.6%)	7 (3.0%)	.000
Consolid.	22 (9.7%)	18 (7.9%)	2 (0.9%)	0 (0.0%)	
Ground G.	41 (18.1%)	15 (6.6%)	14 (6.2%)	12 (5.3%)	
Mechanical Ventilation.					
Yes	22 (9.7%)	2 (0.9%)	4 (1.7%)	16 (7.0%)	.000
No	204 (90.3%)	169 (74.8%)	27 (11.9%)	3 (1.3%)	

Abbreviations used in table are Infiltrat: Infiltrations consoled: consolidation Ground G: Ground Glass appearance

Infection with COVID-19 is associated with significant mortality, and 13.3% (n= 30) of cases required intensive care unit admission. Almost 84.5% (n=191) of patients needed supplementary oxygen, and 9.7% (n=22) required invasive ventilation. The mortality rate during this four month period was 4.8% (n=19).

So, there was a significant association (P value) of thrombosis severity indicators (platelets count, LDH, D. dimer, and fibrinogen level) with age, co-morbidities, smoking, Spo2, anemia, neutrophilia, lymphopenia, monocytopenia, eosinopenia, thrombocytopenia, ESR, CRP, Ferritin, and ground glass appearance on chest radiographs.

DISCUSSION

COVID-19 causes a hypercoagulable state through mechanisms unique to it and centers across the thrombosis and inflammation [33, 34] Thrombosis (micro & macro-vasculature) is a well-established cause of mortality in COVID-19 [20]. Detail data of micro thrombosis is not well established because of lack of autopsies and difficulties in arrangement of radiological investigations.

So, it can be precluded from above literature that there is well established direct relationship between inflammation and thrombosis, [19] and mortality is predominantly caused by thrombosis in the lungs, started at focal microvascular level. We observed that advance age, co-morbidities, smoking, shortness of breath (SOB), some clinical signs, blood cellular components, elevated inflammatory markers, organ dysfunction markers, radiological ground glass appearance are the factors that has association with the severity of thrombosis (detail in Table 2 - 5).

Zhou *et al*. [31] confirmed that increased age of patients with COVID-19 was associated with death. Petrilli *et al*. [35] described characteristics of COVID-19 patients in New York City. They found that older age was one of the most important predictors of severe outcome. The decrease in Lymphocyte (T-cell and B-cell) function depending on age and production of type 2 cytokines, could lead to a lack in control of viral replication and more pro inflammatory responses that may lead to increase in the severity of the disease and poor outcome [36]. Same observation is consistent in our study. Recent literature from Italy documents the high mortality rate (60%) in COVID-19 patients [37]. Mortality was seen patients with three or more comorbidities [37, 38]. Smoking is another potential risk factor reported. Firstly, smoking is detrimental to the immune system and its responsiveness to infections and, up regulates the ACE-2 receptors in the airways [35].The higher prevalence of male smokers especially among the Italian elderly population, and more co-morbidities may explain their higher mortality as compared to our study.

Recent literature documented that deranged cellular components, Cytokines, interleukins, acute phase reactants, biochemical tests of liver, renal and heart have been consistent with a pro thrombotic state and highlight the severity of thrombosis. Neutrophil count, lymphocyte count, and platelet count correlate with disease severity and thrombosis[37, 39, 40]. Consequently, monocytes and macrophages are theorized to play a crucial role in the inflammation and thrombosis seen in COVID-19. Thrombocytopenia is a common phenomenon in critically ill patients.

Actually all hematological and serological data is almost consistent with above literature except mortality rate. Mortality rate is high in almost all above studies as compared to our study (4.8%). This can be explained by more age group, more co-morbidities and population effect. Now we learned a lot from the evolving experience of these pandemic and dramatically updated management guidelines. So, less mortality in our study can be justified by the above factors.

So, considering the knowledge of above literature, it is justified to say that more age group, hypoxia, co-morbidities, smoking, lymphopenia, monocytopenia, eosinopenia, thrombocytopenia, ESR, CRP, Ferritin, and radiological ground glass appearance associate with severity of thrombosis.

CONCLUSION

COVID-19 posed a significant health threat globally in 2020. COVID-19 is associated with significant mortality preceded by thrombosis. Documented important distinguishing factors in our study have significant association with microthrombosis severity. Clinician's early clinical assessment, hematological, serological and radiological distinguishing features can guide for early optimal management of thrombosis that help to decrease the mortality. Limitation of our study was that there was no instrument used to direct measurement of microthrombosis. Further research is needed to elucidate the diagnostic tool of micro thrombosis and multicenter research is required to see the risk factors association with severity of thrombosis.

Ethical considerations

Ethical approval was obtained from the Medical Research Ethics Committee of the hospital. Confidentiality and anonymity of the subjects were maintained as rules/poly of hospital and no names were mentioned in the questionnaires.

Conflict of interest

All the authors declared the absence of any commercial or financial relationships that could be construed as a potential conflict of interest in the conduction of this research.

Acknowledgments

The author would like to thank Dr. Ahmad Farooq and Dr. Abdul Hamid Infection Prevention control department to facilitate to availability of data.

References

1. WHO. World experts and funders set priorities for COVID-19 research [internet]. 2020 March 30; [cited 2020 August 12].available from: https://www.who.int/news-room/detail/30-03-2020-world-experts-and-funders-set-priorities-for-covid-19-research.
2. Bonilla-Aldana DK, Dhama K, Rodriguez-Morales AJ. Revisiting the one health approach in the context of COVID-19: a look into the ecology of this emerging disease. AdvAnim Vet Sci. 2020; 8:234-37.
3. Emami A, Javanmardi F, Pirbonyeh N, Akbari A. Prevalence of Underlying Diseases in Hospitalized Patients with COVID-19: a Systematic Review and Meta-Analysis. Arch AcadEmerg Med. 2020; 8 (1):e35.
4. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L *et al*. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020 Feb 15; 395 (10223):497-506.
5. Miesbach W, Makris M. COVID-19: Coagulopathy, Risk of Thrombosis, and the Rationale for Anticoagulation. ClinApplThrombHemost. 2020 Jan-Dec; 26: 1076029620938149
6. Yi Y, Lagniton PNP, Ye S, Li E, Xu RH. COVID-19: what has been learned and to be learned about the novel coronavirus disease. Int J Biol Sci. 2020; 16 (10):1753-1766.
7. Rotzingera DC, Beigelman-Aubrya C, von Garnierb C, Qanadli SD. Pulmonary embolism in patients with COVID-19: Time to change the paradigm of computed tomography. Thromb Research.2020 Apr 11;190:58–59.
8. Abou-Ismail MY, Diamond A, Kapoor S, Arafah Y, Nayak L. The hypercoagulable state in COVID-19: Incidence, pathophysiology, and management. Thromb Res. 2020 Jun 20;194:101-115.
9. D. Giannis, I.A. Ziogas, P. Gianni. Coagulation disorders in coronavirus infected patients: COVID-19, SARS-CoV-1, MERS-CoV and lessons from the past. J Clin Virol.2020; 127:104362
10. Klok FA, Kruip MJHA, van der Meer NJM, *et al*. Incidence of thrombotic complications in critically ill

ICU patients with COVID-19. Thromb Res. 2020; 191:145-47.
11. Middeldorp S, Coppens M, van Haaps TF, *et al*. Incidence of venous thromboembolism in hospitalized patients with COVID-19. J ThrombHaemost. 2020; 18(8):1995-2002.
12. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX *et al*. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med.2020; 382: (18).1708-20.
13. Campbell CM, Kahwash R. Will Complement Inhibition Be the New Target in Treating COVID-19-Related Systemic Thrombosis? Circulation. 2020; 141(22):1739-1741.
14. Varga Z, Flammer AJ, Steiger P, *et al*. Endothelial cell infection and endotheliitis in COVID-19. Lancet. 2020; 395(10234):1417-18. doi:10.1016/S0140-6736(20)30937-5
15. Oudkerk M, Büller HR, Kuijpers D, *et al*. Diagnosis, Prevention, and Treatment of Thromboembolic Complications in COVID-19: Report of the National Institute for Public Health of the Netherlands. Radiology. 2020; 201629.
16. Llitjos JF, Leclerc M, Chochois C, *et al*. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. *J ThrombHaemost*. 2020;18 (7):1743-46.
17. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J ThrombHaemost*. 2020;18 (4):844-47.
18. Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. *J ThrombHaemost*. 2020 Jun; 18 (6):1421-24.
19. Fogarty H, Townsend L, Ni Cheallaigh C, *et al*. COVID19 coagulopathy in Caucasian patients. Br J Haematol. 2020;189 (6):1044-49.
20. Zhang L, Yan X, Fan Q, *et al*. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. *J ThrombHaemost*. 2020;18 (6):1324-29.
21. Jackson SP, Darbousset R, Schoenwaelder SM, *et al*. Thromboinflammation: challenges of therapeutically targeting coagulation and other host defense mechanisms. Blood 2019; 133: 906-18.
22. Iba T, Levy JH. Inflammation and thrombosis: roles of neutrophils, platelets and endothelial cells and their interactions in thrombus formation during sepsis. J ThrombHaemost 2018; 16: 231-41.
23. Claushuis TAM, de Stoppelaar SF, Stroo I, *et al*. Thrombin contributes to protective immunity in pneumonia-derived sepsis via fibrin polymerization and platelet-neutrophil interactions. *J ThrombHaemost* 2017; 15: 744-57.
24. Burzynski LC, Humphry M, Pyrillou K, *et al*. the coagulation and immune systems are directly linked through the activation of interleukin-1α by thrombin. Immunity 2019; 50:1033-42.e6.
25. Vardon-Bounes F, Ruiz S, Gratacap MP, *et al*. Platelets are critical key players in sepsis. Int J MolSci 2019; 20: 3494
26. Assinger A. Platelets and Infection – An Emerging Role of Platelets in Viral Infection. Front Immunol 2014; 5: 649.
27. Borczuk, A.C., Salvatore, S.P., Seshan, S.V. *et al.* COVID-19 pulmonary pathology: a multi-institutional autopsy cohort from Italy and New York City. *Mod Pathol* 2020.
28. EketundeA O, Mellacheruvu S, Oreoluwa P. A Review of Postmortem Findings in Patients with COVID-19. Cureus 2020 July; 12(7): e9438.
29. Danzi GB, Loffi M, Galeazzi G, Gherbesi E. Acute pulmonary embolism and COVID-19 pneumonia: a random association? *Eur Heart J*. 2020 May 14;41(19):1858.
30. Cellina M, Oliva G. Acute pulmonary embolism in a patient with COVID-19 pneumonia. DiagnInterv Imaging. 2020 May;101(5):325-326.
31. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, *et al*. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study Lancet 2020;395(10229):1038.
32. American Society of Hematology. ASH guidelines on use of anticoagulation in COVID-19 [internet]. 2020 [cited 2020 August 12]. Available from: https://www. Hematology .org/education/clinicians/guidelines-and-quality-care/clinical-practice-guidelines/venous-thromboembolism-guidelines/anticoagulation -and-covid-19
33. National Institutes of Health. Coronavirus Disease 2019 treatment guidelines [internet]. 2020 [cited 2020 August 12]. Available from: https:// www.covid19 treatment guidelines .nih.gov
34. Ministry of Health Saudi Arabia. Coronavirus Disease COVID-19 Guidelines (v1.3) [internet]. 2020 May [cited 2020 august 12]. Available from: https:// www. moh.gov.sa/Ministry/ MediaCenter/Publications/Documents Coronavirus-Disease-2019-Guidelines-v1.3.pdf
35. Petrilli CM, Jones SA, Yang J, *et al*. Factors associated with hospitalization and critical illness among 4103 patients with COVID-19 disease in New York City. Med Rxiv. 2020.
36. Wang T, Chen R, Liu C, Liang W, Guan W, Tang R, *et al*. Attention should be paid to venous thromboembolism prophylaxis in the management of COVID-19. The Lancet. Haematology.2020; 7(5):362–63.
37. Michelozzi P, de'Donato F, Scortichini M, De Sario M,Noccioli F, Rossi P, *et al*.
38. Mortality impacts of the coronavirus disease (COVID-19) outbreak by sex and age: rapid mortality surveillance system, Italy. Euro Surveill. 2020 May 14; 25(19): 2000620.
39. Ranucci M, Ballotta A, Di Dedda U, Bayshnikova E, Dei Poli M, Resta M, *et al*. The procoagulant pattern of patients with COVID-19 acute respiratory distress syndrome. J ThrombHaemost. 2020 Jul; 18(7):1747-51.
40. National Health Institute. Characteristics of SARS-CoV-2 patients dying in Italy[internet]. Report based on available data on 2020 April 29. [Cited 2020 August 12]. Available from: https://www.epicentro.iss.it/en/coronavirus/bollettino/Report-COVID-2019_29 april_2020.pdf
41. Fan BE, Chong VCL, Chan SSW, Lim GH, Lim KGE, Tan GB, *et al*. Hematologic parameters in patients with COVID-19 infection. *Am J Hematol*. 2020 Jun; 95(6):E131-E134.