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COVID-19 and its Effect on Coagulation Profile: A Systematic Review

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Abstract: ***Introduction: Corona Virus Disease (COVID-19) is a global pandemic and has become a major threat to health care system across the world. Majority of the cases present with mild symptoms but in some cases there is progression to Acute Respiratory Distress Syndrome (ARDS) leading to death. The major concern associated with COVID-19 is the fatality associated with infection.To prevent such an adverse incident there is an urgent need to identify biomarkers that effectively and timely determine the likelihood of progression to critical form of disease. Coagulopathy is common in COVID-19 patients with severe/critical form of disease. This review article aims to explore coagulation profile in COVID-19 patients and to correlate the same with the severity of illness. Material & Methods: A systematic search of published articles from January 1 to July 1, 2020 on COVID-19 was performed for identifying abnormalities in coagulation parameters in COVID-19 patients. Individual articles were screened and thereafter data was collected as perPreferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Results: A total of 163 articles on COVID-19 were screened from which only 60 articles with various laboratory parameters including coagulation profile were finally included in the review. Conclusion: Coagulopathy in COVID-19 patients has been found to be associated with an increased risk of death. Various evidences such as elevated levels of D-dimers, Fibrinogen, prolonged Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT) and thrombocytopenia can help clinicians in risk stratification and early prediction of progression to severe/fatal form of COVID-19.***

Keywords: COVID-19, D-dimers, Thrombocytopenia, Fibrinogen, Prothrombin Time,Activated Partial Thromboplastin Time

1. Introduction

First pneumonia case of unknown origin came in December 2019 in Wuhan, China which was later determined to be because of a novel corona virus named SARS-CoV-2. WHO in February 2020 changed its name to COVID-19 as the disease spread worldwide.[1] WHO declared COVID-19 as global pandemic on 11th March, 2020. As of 26thJuly, according to the WHO data (situation report-188) there were 1,57,85,641 total global cases with 6,40,016 deaths across the globe. In India there were 13,85,522 cases and 32,063 deaths due to COVID-19 till 26th of July 2020.[2]

COVID-19 has been found to be associated with deranged coagulation and venous thromboembolism. The extensive thrombosis seen in COVID patients can be attributed to Cytokine storm induced by SARS CoV -2, expression of tissue factor on immune cells and activation of extrinsic coagulation cascade. Further pro-inflammatory cytokines cause injury in the microcirculation and lead to thrombus formation. Further the diminished activity of urokinase-type plasminogen activator and the release of plasminogen activator inhibitor-1 suppresses fibrinolysis. Moreover, accelerated inflammation damages endothelium to which activated platelets readily bind thereby leading to thrombus formation.[3]

The thrombi so formed eventually involve micro-vasculature of lungs and thereby impair blood supply and gas exchange across the alveolileading to respiratory deterioration seen in severe/ critically ill COVID patients. Autopsy findings in such patients further supports this fact as it revealed damaged alveoli with fibrin exudates along with hyaline thrombi in small blood vessels and immune cell infiltration in the walls.[4] The need of the hour is early recognition of coagulation disorder by regular monitoring of various coagulation variables like PT, APTT, TT, INR, Fibrinogen Degradation Products, Fibrinogen, D-Dimer and Platelets count so that subsequent intervention in the form of antithrombotic interventions can be initiated for curbing the mortality associated with COVID-19.

Till date, several meta-analyses have been conducted on the relationship between severity and mortality of COVID-19 with various laboratory parameters.[5-11] However research articles on detailed assessment of coagulation parameters in COVID-19 patients is lacking. In the present study we aimed to identify all the available research data on abnormalities in various parameters of coagulation profile in COVID-19 patients and to gather information on how their levels vary and to study their relationship with seriousness/ fatality of the disease.

2. Material and methods

2.1 Search Strategy

A comprehensive literature search was performed on Pubmed, Dynamed, Google scholar, Cochrane databases for identification of articles on derangement of coagulation profile in COVID-19 patients as per Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA)

guidelines. We used the following keywords for the search: COVID-19, Corona-virus, Coagulation profile, Fibrinogen, D-dimers, PT, APTT, Thrombocytopenia, FDP, Laboratory biomarkers, Laboratory parameters without date. A total of 163 studies were identified of which 14 were from Dynamed, 53 from google scholar, 25 on Pubmed and 71 were from various references. Our review included studies published between January 1- July 1, 2020. We then screened various articles on the basis of title, abstract and full text as per the search criteria:

2.2 Inclusion criteria for studies was:

- Lab parameters Y/N
- Comparison groups Y/N
- English Language Y/N
- Case series > 10 cases

Case reports, review articles, letters, meta-analysis articles were excluded.

Table 1: Studies on assessment of various Coagulation parameters in Covid-19 patients

S.No	Marker	Study	Country	Cases	Interpretation
1	Fibrinogen, D-Dimer	Celal Satici[12]	Turkey	Alive 625, deceased 55	No significant changes
2.	PT,APTT, D-Dimer, platelets	Chaomin Wu[14]	China	With ARDS Alive(40) Dead (44) without ARDS (17)	PT, D-Dimer raised significantly Platelet number increased in patients with ARDS but difference statistically not significant
3.	PT,APTT, D-Dimer, platelets	Dawai Wang[15]	China	Survivor (88), Non-Survivor (19)	D-Dimer raised significantly, platelet count statistically decreased in Non- survivors as compared to survivors
4.	D-Dimer, platelets	Dong Ji[17]	China	Stable(168) Progressive (40)	D-Dimer raised significantly
5.	PT, APTT, D-Dimer, platelets	Feng Pan[18]	China	Discharge(35), Death (89)	No significant findings
6.	Fibrinogen, D-Dimer	Jianhong Fu[13]	China	Severe(16), non severe(59)	D-Dimer and Fibrinogen levels were significantly raised
7.	APTT, D-Dimer	Jiao Gong[19]	China	Severe(28), Non-Severe (161)	No significant change
8.	D-Dimer, Fibrinogen	Maurizio Cecconi[66]	Italy	Survivor ICU/Death Total(239)	D-Dimer and Fibrinogen are significantly raised
9.	PT, APTT, Fibrinogen,D-Dimer, FDP	Ning Tang[58]	China	Survivor(162) Non-Survivor(21)	PT, D-Dimer and FDP are significantly raised
10.	PT,APTT, D-Dimer, Fibrinogen, platelets	Shangrong Wu[20]	China	Moderate(203) Severe(67)	D-Dimer significantly raised Platelet count decreased in severe group
11.	D-Dimer, platelets	Tielong Chen[21]	China	<65years(148) >65 years(55) Died(19) Survived(36)	D-Dimer levels raised significantly Platelet count significantly decreased in dead patients than survivors.
12.	PT, APTT, D-Dimer, platelets	Chaolin Huang[22]	China	ICU(13), Non-ICU(28)	PT, D-Dimer raised significantly Platelet count increased in ICU patients but difference not statistically significant
13.	PT, APTT, D-Dimer, platelets	Dawai Wang[24]	China	ICU(36) Non ICU (102)	D-Dimer raised significantly Platelet count decreased in ICU patients but difference not statistically significant
14.	PT, D-Dimer, platelets	Fei Zhou[25]	China	Survivor(137) Non-Survivor(54)	D-Dimer level raised significantly in Non-survivor, platelet count significantly higher in survivor.
15.	D-Dimer, platelets	Guan W[26]	China	Severe(173) Non-Severe(926)	Raised D-Dimer levels in severe and Decreased platelet count observed in 36.2% of cases
16.	PT, APTT, D-Dimer, Fibrinogen	Yi Han[70]	China	Severe(48), Non-severe(59)	PT, D-Dimer, Fibrinogen levels raised significantly
17.	PT, APTT, D-Dimer, platelets	Lang Wang[27]	China	Survival(274), Dead(65)	PT, D-Dimer levels raised significantly in dead, platelet count significantly higher in survival group.
18.	D-Dimer, platelets	Michael Dreher[28]	Germany	With ARDS(24), WithoutARDS(26)	D-Dimer levels raised significantly in ARDS group
19.	D-Dimer, platelets	Pingzheng Mo[29]	China	General(70) Refractory(85)	Platelet count significantly decreased in Refractory group; No significant change in other parameters
20.	D-Dimer	Qing Deng[30]	China	Severe(67) Non-Severe(45)	D-Dimer raised significantly
21.	PT, APTT, D-Dimer	Rong-Hui Du[31]	China	Deceased (21) Survivors (158)	D-Dimer raised significantly
22.	PT, APTT, D-Dimer, platelets	Ruchong Chen[32]	China	Survivors (445) Non-Survivors 103 Mild(346), Severe(155), Critical(48)	PT, D-Dimer raised significantly and Platelet count significantly decreased in Non-survivor group

23.	PT, APTT, D-Dimer, platelets	Shaoqing Lei[33]	China	ICU(15) Non-ICU (19)	No significant changes
24.	PT, APTT, D-Dimer, platelets	Suxin Wan[34]	China	Mild(95), Severe(40)	APTT and D-DImer raised significantly and Platelet count significantly decreased in Severe cases
25.	D-Dimer, platelets	Wen Luo[35]	China	ICU(07), Non ICU(28)	D-Dimer raised significantly, Platelet count decreased in ICU patients but not statistically significant
26.	D-Dimer, platelets	XiaochenLi[36]	China	Non severe(279) Severe(269)	D-Dimer raised significantly and Platelet count significantly lower in severe group.
27.	PT, TT, APTT, D-Dimer, Fibrinogen	Yong Gao[72]	China	Severe(15) Mild(28)	TT, Fibrinogen and D-Dimer were raised significantly
28.	PT, FDP,D-Dimer	Yongli Zheng[71]	China	Critical(32), Non-Critical(67)	PT, FDP, D-Dimer raised significantly
29.	PT ratio, D-Dimer, Fibrinogen, Fibrin monomers, platelets	David M. Smadja[68]	France	ICU(20), Non ICU(20)	Fibrinogen and D-Dimer raised significantly and Platelet count decreased in in ICU patients but not statistically significant
30.	D-Dimer, PT, APTT, Fibrinogen, TT	Hui Long[63]	China	Mild (39) Severe(48) Critical(28)	D-Dimer, PT, APTT raised significantly and fibrinogen decreased significantly
31.	D-Dimer, PT, platelets	Kaiyan Li[37]	China	Survivor(87) Non-Survivor(15)	PT, D-Dimer raised significantly and platelet were significantly lower in Non-survivors
32.	PT, APTT, D-Dimer, platelets	Nanshan Chen[38]	China	Case series(99)	No significant changes
33.	Median D-Dimer levels, platelets	Tobias Herold[39]	Germany	Mechanical ventilation Required(57) Not required(32)	D-Dimer raised significantly and platelet count Increased in mechanical ventilator requiring patients but difference not statistically significant
34.	PT, APTT, D-Dimer, Fibrinogen, platelets	Xiaojie Bi[65]	China	Severe(22) Non-Severe(91)	Fibrinogen and D- Dimer raised and Platelet count were much lower in severe group
35.	D-Dimer	Christopher M Petrilli[40]	USA	Not admitted (2538), Admitted(2741)	D-Dimer levels raised
36.	Fibrinogen, D-dimer	G Q Qian[41]	China	Mild(82) Severe(9)	No significant changes
37.	D-Dimer, platelets	Matthew J Cummings[42]	USA	Observational Cohort(257)	D-Dimer levels raised
38.	PT, APTT, D-Dimer, platelets	Ruchong Chen[43]	China	Retrospective Cohort(1590)	D-Dimer levels raised significantly in fatal cases
39.	APTT, PT, TT, D-Dimer	Kun Wang[73]	China	Survivor(296) Non-Survivor(19)	D-Dimer and TT raised and APTT lower in Non-Survivor group
40.	PT,APTT, D-Dimer, Fibrinogen, platelets	Pier Paolo Di Micco[59]	Italy	Covid-19(67) Control (67)	Fibrinogen levels raised significantly in Covid-19 patients and Platelet count was decreased in Covid-19 patients with SARS but difference statistically not significant and was found to be increased in Covid-19 group than control group with no statistically significant difference
41.	D-Dimer, platelets	Francesco Violi[44]	Italy	Survivor(255) Non-Survivor(64)	D-Dimer raised significantly and Platelet count decreased in Non-survivors but difference not statistically significant
42.	D-Dimer, APTT,PT, FDP, INR, Fibrinogen	Tao Li[64]	China	Covid-19 (40) Control (57)	D-Dimer, APTT, PT, Fibrinogen, FDP levels were raised
43.	PT, APTT, PT, TT, D-Dimer, Antithrombin, FDP, INR	Yanghong Zhang[60]	China	Aggravated(17) Non-Aggravated (54)	PT, INR, FDP, D-DImer levels were significantly raised while AT levels lower
44.	INR, PT, APTT, Fibrinogen, FDP,D-Dimer	Ying Zou[45]	China62	Mild(277) Severe(26)	INR, PT, APTT, Fibrinogen, FDP, D-Dimer raised significantly
45.	D-Dimer	Jin-JIn Zhang[46]	China	Severe (58) Non-Severe(82)	D-Dimer levels raised significantly
46.	D-Dimer	Tao Liu[47]	China	Severe(69) Non-Severe(11)	D-dimer levels raised significantly
47.	PT, platelets	Xiabao Yang[48]	China	Survivor(20) Non Survivor(32)	PT levels raised significantly and platelet count increased in Non- survivor group but not significantly
48.	D-Dimer, PT, APTT, Fibrinogen	Litao Zhang[61]	China	D-Dmer< 2 ụg/ml(276) D-Dimer > 2ụg/ml(67)	PT and D-Dimer raised significantly in serious cases
49.	Platelets	Shaobo Shi[49]	China	Death (62) Survivor (609)	Platelet count is significantly lower in non-survivors.
50.	Platelets	Davide	Italy	Covid +ve (105)	Platelet count increased in Covid +ve patients but

		Ferrari[50]		Covid -ve (102)	difference not statistically significant
51.	Platelets	Heshui Shi[51]	China	Based ontimeinterval between S/S and CTscanfour groups group 1 subclinical group 2 CT ≤1wkgroup 3 (CT >1 to 2 weeks S/S) ; group 4 (CT scans >2 to 3weeks)	No significant difference between platelet count in different groups
52.	Platelets	Yuwei Liu[67]	China	Tertiles of NLR Tertile 1 (82)0.54-2.21 Tertile 2 (81) 2.21-4.82 Tertile 3 (82) >4.82	No significant differences in groups
53.	Platelets	Rong Qu[52]	China	Severe (3) non severe (27)	Platelet count decreased in severe patients but not statistically significant
54.	Platelets	Yue-Ping Liu[53]	China	Event group (23) Free of event group (61	Platelet countsignificantly increased in event group than those in the Free Of Event group
55.	Platelets	Quilin Li[54]	China	Control (531) Covid (458)	Platelet count was found to be decreased in Covid group with no statistical significant differenve
56.	Platelets	Xiurong Ding[55]	China	Severe (15) Non-severe (57)	Platelet count decreased in severe group but difference not statistically significant
57.	Platelets	Huan Li[56]	China	Moderate (60) Severe (56) Criticallysevere(16)	Platelet count had no significant changes.
58.	Platelets	Wei Liu[57]	China	Improvement (67) Progression (11)	Platelet count decreased in progression group but not statistically significant differences were found between 2 groups
59.	Platelets	Zhongliang Wang[16]	China	SpO2 > 90 (55) SpO2 <90 (14)	Platelet count decreased in <90 Spo2 group but not statistically significant
60.	Platelets	BE Fan[23]	Singapore	ICU (9) Non-ICU (58)	Platelet count increased in ICU patients but difference not statistically significant

Table 2: Studies that compare D-dimers levels in Covid-19 patients

S.No	Study	Country	Cases	Interpretation
1	CelalSatici	Turkey	Alive625, deceased 55	No significant changes
2.	Chaomin Wu	China	With ARDS Alive(40) Dead (44) without ARDS (17)	D-Dimer raised significantly in patients with ARDS
3.	Dawai Wang	China	Survivor (88), Non-Survivor (19)	D-Dimer raised significantly in non-survivor group
4.	Dong Li	China	Stable(168) Progressive (40)	D-Dimer raised significantly in progressive group
5.	Feng Pan	China	Discharge(35), Death (89)	No significant difference observed
6.	Jianhong Fu	China	Severe(16), non severe(59)	D-Dimer significantly raised in severe group
7.	Jiao Gong	China	Severe(28), Non-Severe(161)	No significant difference observed
8.	Maurizio Cecconi	Italy	Survivor ICU/Death Total(239)	D-Dimer significantly raised in ICU/dead group
9.	Ning Tang	China	Survivor(162) Non-Survivor(21)	D-Dimer significantly raised in Non-survivor
10.	Shangrong Wu	China	Moderate(203) Severe(67)	D-Dimer significantly raised in severe group
11.	Tielong Chen	China	<65years(148) >65 years(55) Died(19) Survived(36)	D-Dimer levels raised significantly in >65 group
12.	Chaolin Huang	China	ICU(13), Non-ICU(28)	D-Dimer raised significantly in ICU group
13.	Dawai Wang	China	ICU(36). Non ICU (102)	D-Dimer raised significantly in ICU group
14.	Fei Zhou	China	Survivor(137) Non-Survivor(54)	D-Dimer level raised significantly in Non-Survivor group
15.	Guan W	China	Severe(173) Non-Severe(926)	Raised D-Dimer levels in severe cases
16.	Yi Han	China	Severe(48), Non-severe(59)	D-Dimer levels raised significantly in Severe group
17.	Lang Wang	China	Survival(274), Dead(65)	D-Dimer levels raised significantly in Dead
18.	Michael Dreher	Germany	With ARDS(24), Without ARDS(26)	D-Dimer levels raised significantly in ARDS group
19.	Pingzheng Mo	China	General(70) Refractory(85)	No significant difference observed

20.	Qing Deng	China	Severe(67) Non-Severe(45)	D-Dimer raised significantly
21.	Rong-Hui Du	China	Deceased(21) Survivors(158)	D-Dimer raised significantly in Deceased
22.	Ruchong Chen	China	Survivors(445) Non-Survivors(103) Mild(346), Severe(155), Critical(48)	D-Dimer raised significantly in severe/critical
23.	Shaoqing Lei	China	ICU(15) Non-ICU (19)	No significant changes
24.	Suxin Wang	China	Mild(95), Severe(40)	D-DImer raised significantly in severe cases
25.	Wen Luo	China	ICU(07), Non ICU(28)	D-Dimer raised significantly in ICU cases
26.	Xiaochen Li	China	Non severe(279) Severe(269)	D-Dimer raised significantly in severe cases
27.	Yong Gao	China	Severe(15) Mild(28)	D-Dimer raised significantly in severe cases
28.	Yongli Zhang	China	Critical(32), Non-Critical(67)	D-Dimer raised significantly in critical cases
29.	DavidM. Smadja	France	ICU(20), Non ICU(20)	D-Dimer raised significantly in ICU patients
30.	Hui Long	China	Mild (39) Severe(48) Critical(28)	D-Dimer raised significantly in severe cases
31.	Kaiyan Li	China	Survivor(87) Non-Survivor(15)	D-Dimer raised significantly in non-survivors
32.	Nanshan Chen	China	Case series(99)	No significant changes
33.	Tobias Herold	Germany	Mechanical ventilation Required(57) Not required(32)	D-Dimer raised significantly in patients required mechanical ventilation
34.	Xiaojie Bi	China	Severe(22) Non-Severe(91)	D- Dimer raised in severe cases
35.	Christopher M Petrilli	USA	Notadmitted (2538), Admitted(2741)	D-Dimer levels raised in severe and fatal cases
36.	G Q Qian	China	Mild(82) Severe(9)	No significant changes
37.	Matthew J Cummings	USA	Observational Cohort(257)	D-Dimer levels raised in fatal cases
38.	Ruchong Chen	China	Retrospective Cohort(1590)	D-Dimer levels raised significantly in fatal cases
39.	Kun Wang	China	Survivor(296) Non-Survivor(19)	D-Dimer raised in Non-Survivor group
40.	Pier Paolo Di Micco	Italy	Covid-19(67) Control (67)	No significant change in Covid-19 patients in covid group
41.	Francesco Violi	Italy	Survivor(255) Non-Survivor(64)	D-Dimer raised significantly in non survivor
42.	Tao Li	China	Covid-19 (40) Control (57)	D-Dimer levels raised in covid group
43.	Yanghong Zhang	China	Aggravated(17) Non-Aggravated(54)	D-DImer levels were significantly raised in aggravated cases
44.	Ying Zhou	China	Mild(277) Severe(26)	D-Dimer raised significantly in severe cases
45.	Jin-JInJhang	China	Severe (58) Non-Severe(82)	D-Dimer levels raised significantly in severe cases
46.	Tao Liu	China	Severe(69) Non-Severe(11)	D-dimer levels raised significantly in severe cases
47.	Litao Zhang	China	D-Dmer<2ụg/ml(276) D-Dimer > 2ụg/ml(67)	D-Dimer raised significantly in serious cases

Table 3: Studies that compare Fibrinogen levels in Covid-19 patients

	Study	Country	Cases	Interpretation
1	CelalSatici	Turkey	Alive (625) deceased(55)	Increased fibrinogen levels were seen in deceased patients but difference was not statistically significant.
2	Jianhong Fu	China	Severe(16), non severe(59)	Compared to mild/moderate Covid-19 group, fibrinogen levels were significantly raised in severe cases

3.	Maurizio Cecconi	Italy	Survivor ICU/Death Total(239)	Fibrinogen are significantly raised in ICU/death group
4.	Ning Tang	China	Survivor(162) Non-Survivor(21	Increased fibrinogen levels were seen in non-survivors but difference was not statistically significant.
5.	Shangrong Wu	China	Moderate(203) Severe(67)	Increased fibrinogen levels were seen in severe group but difference was not statistically significant.
6	Yi Han	China	Severe(48), Non-severe(59)	Fibrinogen levels raised significantly in severe cases
7	Yong Gao	China	Severe(15) Mild(28)	Fibrinogen raised significantly in severe cases
8	David M. Smadja	France	ICU(20), Non ICU(20)	Fibrinogen raised significantly in ICU patients.
9	Hui Long	China	Mild (39) Severe(48) Critical(28)	Fibrinogen increased significantly in severe cases while lower levels were seen in deceased cases
10	Xiaojie Bi	China	Severe(22) Non-Severe(91)	Fibrinogen raised in severe cases. Fibrinogen Albumin Ratio and PLT count were independent risk factors for severe illness and the severity of COVID-19 might be excluded when FAR<0.0883 and PLT count>135*109 /L.
11	G Q Qian	China	Mild(82) Severe(9)	Increased fibrinogen levels were seen in severe group but difference was not statistically significant.
12	Pierpaolo Di Micco	Italy	Covid-19(67) Control (67)	Fibrinogen levels raised significantly in Covid-19 patients
13	Tao Li	China	Covid-19 (40) Control (57)	Fibrinogen levels were significantly raised in Covid cases as compared to controls.
14	Ying Zhou	China	Mild(277) Severe(26)	Fibrinogen raised significantly in severe cases
15	Litao Zhang	China	D-Dimer <2ụg/ml(276) d-Dimer > 2ụg/ml(67)	Increased fibrinogen levels were seen in group with d-dimer > 2 ug/ml but difference was not statistically significant.

Table 4: Studies that compare Platelet counts levels in Covid-19 patients

S. No.	Author	Country	Groups	Interpretation
1.	Chaomin Wu	China	With ARDS (84) -alive(40) -dead (44) Without ARDS (17)	Platelet number increased in patients with ARDS but difference statistically not significant
2	DawaI Wang	China	Survivor (88) Non-survivor (19)	Platelet count statistically decreased in Non- survivors as compared to survivors
3	Feng Pan	China	Discharge (35) Death (89)	Platelet count decreased in death group but difference statistically not significant
4	Jiao Gong	China	Non-severe (161) Severe (28)	Platelets decreased in severe group but difference statistically not significant
5	Shangrong Wu	China	Moderate (203) Severe (67)	Platelet count decreased in severe group
6	Shaobo Shi	China	Death (62) Survivor (609)	Platelet count is significantly lower in non-survivors.
7	Tielong Chen	China	<65yrs (148) > 65 yrs (55) Died (19) Survived (36)	Platelet count significantly decreased in dead patients than survivors.
8	Chaolin Huang	China	ICU (13) Non-ICU (28)	Platelet count increased in ICU patients but difference not statistically significant
9	Davide Ferrari	Italy	Covid +ve (105) Covid -ve (102)	Platelet count increased in Covid +ve patients but difference not statistically significant
10	Dawei Wang	China	ICU (36) Non-ICU (102)	Platelet count decreased in ICU patients but difference not statistically significant
11	Fei Zhou	China	Survivor (137) Non-survivor (54)	Platelet count significantly higher in survivor group.
12	Guan W	China	Non-severe (926) Severe (173)	Decreased platelet count observed in 36.2% of cases
13	Heshui Shi	China	Based ontimeinterval between S/S and CTscanfour groups group 1subclinical group 2 CT ≤1wk	No significant difference between platelet count in different groups

			group 3 (CT >1 to 2 weeks S/S) ; group 4 (CT scans >2 - 3wks)	
14	Lang Wang	China	Survival (274) Dead (65)	Platelet count significantly higher in survival group.
15	Pingzheng Mo	China	General (70) Refractory (85)	Platelet count significantly decreased in Refractory group
16	Ruchong Chen	China	Survivor (445) Non-survivor (103) Mild (345) Severe (155) critical (48)	Platelet count significantly decreased in Non-survivor group
17	Shaoqing Lei	China	ICU (15) Non-ICU (19)	Platelet count increased in ICU group but statistically not significant
18	Suxin Wang	China	Mild (95) Severe (40)	Platelet count significantly decreased in Severe cases
19	Wen Luo	China	Generalward (28) ICU (07)	Platelet count decreased in ICU patients but not statistically significant
20	Xiaochen LI	China	Nonsevere (279) Severe (269)	Platelet count significantly lower in severe group.
21	Yuwei Liu	China	Tertiles of NLR Tertile 1 (82) 0.54-2.21 Tertile 2 (81) 2.21-4.82 Tertile 3 (82) >4.82	No significant differences in groups
22	David M. Smadja	France	Medicine ward(20)ICU (20)	Platelet count decreased in in ICU patients but not statistically significant
23	Kaiyan LI	China	Survivor (87) non-survivor (15)	platelet were significantly lower in Non-survivors
24	Nanshan Chen	China	Nogroupsdescriptive study	Decreased In 12% and increased in 4% of cases
25	Rong Qu	China	Severe (3) non severe (27)	Platelet count decreased in severe patients but not statistically significant
26	Tobias Herold	Germany	Mechanical ventilation Not required (57) Required (32)	Increased in mechanical ventilator requiring patients but difference not statistically significant
27	Xiaojie Bi	China	Severe (22) Non-severe (91)	PLT count were much lower in severe group
28	Yue-Ping Liu	China	Event group (23) Free of event group (61)	Platelet count Significantly increased in event group than those in the Free Of Event group
29	GQ Qian	China	Mild (82) Severe (9)	Platelet count decreased in severe patients but not statistically significant
30	Matthew J. Cummings	USA	--	No significant finding
31	Ruchong Chen	China	1590 patients Cohort	No significant findings
32	Pierpaolo di Micco	Italy	Covid -19 (67) Control (67) Covid-19 with SARS Covid-19 without SARS	Platelet count was decreased in Covid-19 patients with SARS but difference statistically not significant and was found to be increased in Covid-19 group than control group with no statistically significant difference
33	Quilin Li	China	Control (531) Covid (458)	Platelet count was found to be decreased in Covid group with no statistical significant difference
34	Francesco Violi	Italy	Survivor (255) Non-survivor (64)	Platelet count decreased in Non-survivors but difference not statistically significant
35	Xiurong Ding	China	Severe (15) Non-severe (57)	Platelet count decreased in severe group but difference not statistically significant
36	Huan Li	China	Moderate (60) Severe (56) Critically severe (16)	PLThad no significant changes.
34. 37	Tao Liu	China	Severe (69) Non severe (11)	Decreased in severe patients but not statistically significant
38	Wei Lou	China	Improvement (67) Progression (11)	Platelet count decreased in progression group but not statistically significant differences were found between 2 groups

39	Xiabao Yang	China	Survivor (20) non-survivor (32)	Increased in Non-Survivor group
40	Zhongliang Wang	China	SpO2 > 90 (55) SpO2 <90 (14)	Platelet count decreased in <90 Spo2 group but not statistically significant
41	Litao Zhang	China	D-dimer <2µg/ml (276) D-dimer > 2µg/ml (67)	Platelet count significantly decreased in D-Dimer>2µg/ml group
42	Xiaobo Yang	China	Non-survivor (238) Survivors (1238)	Thromocytopenia was more likely to occur in non-survivors than survivor.
43	BE Fan	Singapore	ICU (9) Non-ICU (58)	Platelet count increased in ICU patients but difference not statistically significant

Table 5: Studies that compare PT in Covid-19 patients

S.No	Study	Country	Cases	Interpretation
1.	Chaomin Wu	China	With ARDS Alive(40) Dead (44) without ARDS (17)	PT raised significantly in ARDS patients
2.	Dawai Wang	China	Survivor (88), Non-Survivor(19)	PT decreased but No statistically significant change
3.	Feng Pan	China	Discharge(35), Death (89)	PT increased but No statistically significant findings
4.	Ning Tang	China	Survivor(162) Non-Survivor(21)	PT significantly raised in non survivors
5.	Shangrong Wu	China	Moderate(203) Severe(67)	PT raised but No statistically significant change
6.	Chaolin Huang	China	ICU(13), Non-ICU(28)	PT raised significantly in ICU patients
7.	Dawai Wang	China	ICU(36). Non ICU (102)	No statistically significant change
8.	Fei Zhou	China	Survivor(137) Non-Survivor(54)	No statistically significant change
9.	Yi Han	China	Severe(48), Non-severe(59)	PT raised significantly in severe patients
10.	Lang Wang	China	Survival(274), Dead(65)	PT raised significantly in dead group
11.	Rong-Hui Du	China	Deceased(21) Survivors(158)	PT raised in deceased but No statistically significant change
12.	Ruchong Chen	China	Survivors(445) Non-Survivors(103) Mild(346), Severe(155), Critical(48)	PT raised significantly in severe/critical cases
13.	Shaoqing Lei	China	ICU(15) Non-ICU (19)	Increased in ICU group but No statistically significant change
14.	Suxin Wang	China	Mild(95), Severe(40)	No statistically significant change
15.	Yong Gao	China	Severe(15) Mild(28)	Decreased in severe but No statistically significant change
16.	Yongli Zhang	China	Critical(32), Non-Critical(67)	PT raised significantly in critical cases
17.	David M. Smadja	France	ICU(20), Non ICU(20)	No statistically significant change
18.	Hui Long	China	Mild (39) Severe(48) Critical(28)	PT raised significantly in severe/critical cases
19.	Kaiyan Li	China	Survivor(87) Non-Survivor(15)	PT raised significantly in non-survivor cases
20.	Nanshan Chen	China	Case series(99)	Decreased in more no of patients
21.	Xiaojie Bi	China	Severe(22) Non-Severe(91)	Raised significantly in severe group
22.	Ruchong Chen	China	Retrospective Cohort(1590)	No statistically significant change
23.	Kun Wang	China	Survivor(296) Non-Survivor(19)	PT raised in non-survivors but No statistically significant change
24.	Pier Paolo Di Micco	Italy	Covid-19(67) Control (67)	Raised in more number of covid 19 cases than control but No statistically significant change
42.	Tao Li	China	Covid-19 (40) Control (57)	PT levels were raised in covid cases
25.	Yanghong Zhang	China	Aggravated(17) Non-Aggravated(54)	PT levels were significantly raised in aggravated group

26.	Ying Zhou	China	Mild(277) Severe(26)	PT raised significantly in severe cases
27.	Xiabao Yang	China	Survivor(20) Non Survivor(32)	PT levels raised significantly in non-survivor cases
28.	Litao Zhang	China	D-Dimer <2µg/ml(276) D-Dimer > 2µg/ml(67)	PT raised significantly in serious cases

Table 6: Studies that compare APTT in Covid-19 patients

S.No.	Study	Country	Cases	Interpretation
1.	Chaomin Wu	China	With ARDS Alive(40);Dead (44) without ARDS (17)	APTT decreased in ARDS group but No statistically significant change
2.	Dawai Wang	China	Survivor (88), Non-Survivor(19)	APTT increased but No statistically significant change
3.	Feng Pan	China	Discharge(35), Death (89)	APTT decreased in non-survivors but No statistically significant change
4.	Jiao Gong	China	Severe(28), Non-Severe(161)	APTT raised but No statistically significant change
5.	Ning Tang	China	Survivor(162) Non-Survivor(21)	Raised in non-survivors but No statistically significant change
6.	Shangrong Wu	China	Moderate(203) Severe(67)	APTT raised but No statistically significant change
7.	Chaolin Huang	China	ICU(13), Non-ICU(28)	APTT decreased in ICU patients but No statistically significant change
8.	Dawai Wang	China	ICU(36). Non ICU (102)	APTT decreased in ICU group but No statistically significant change
9.	Yi Han	China	Severe(48), Non-severe(59)	APTT significantly increased in Severe group
10.	Lang Wang	China	Survival(274), Dead(65)	APTT raised in dead group but No statistically significant change
11.	Rong-Hui Du	China	Deceased(21) Survivors(158)	Raised in deceased group but No statistically significant change
12.	Ruchong Chen	China	Survivors(445) Non-Survivors(103) Mild(346), Severe (155) Critical(48)	APTT raised in non-survivors and severe cases but No statistically significant change
13.	Shaoqing Lei	China	ICU(15) Non-ICU (19)	Increased in ICU group but No statistically significant change
14.	Suxin Wang	China	Mild(95), Severe(40)	APTT levels raised significantly in severe cases
15.	Yong Gao	China	Severe(15) Mild(28)	Decreased in severe group but No statistically significant change
16.	Hui Long	China	Mild (39) Severe(48) Critical(28)	APTT raised significantly in severe and critical group as compared to mild.
17.	Nanshan Chen	China	Case series(99)	Decreased in more number of patients
18.	Xiaojie Bi	China	Severe(22) Non-Severe(91)	No statistically significant change
19.	Ruchong Chen	China	Retrospective Cohort(1590)	No statistically significant change
20.	Kun Wang	China	Survivor(296) Non-Survivor(19)	APTT lower in Non-Survivor group
21.	Pier Paolo Di Micco	Italy	Covid-19(67) Control (67)	Found raised in more no of patients than control group but No statistically significant change
22.	Tao Li	China	Covid-19 (40) Control (57)	APTT levels were raised in cases than controls
23.	Yanghong Zhang	China	Aggravated(17) Non-Aggravated(54)	Raised in aggravated group but No statistically significant change
24.	Ying Zhou	China	Mild(277) Severe(26)	APTT raised significantly
25.	Litao Zhang	China	D-Dimer <2µg/ml(276) D-Dimer > 2µg/ml(67)	Raised in group D-Dimer >2 but No statistically significant change

Table 7: Studies that compare levels of INR in Covid-19 patients

S.No	Author	Country	Groups	Interpretation
1.	Jiao Gong	China	Non-severe (161) Severe (28)	Increased in severe group but differences were not statistically significant
2.	Kaiyan LI	China	Survivor (87) non-survivor (15)	INRwas significantly raised in non-survivor group.
3.	Tao Li	China	Covid-19 (40) Control (57)	INR was significantly increased in covid-19 patients.
4.	Yanghong Zhang	China	Aggravated (17) Non-aggravated (54)	INR was significantly raised while AT was lower in aggravated group .
5.	Ying Zou	China	Mild (277) Severe (26)	Themedian coagulation parameters in severe group were higher than those in the mild group: INR, the differences were statistically significant ($p < 0.05$).

Table 8: Studies that compare levels of Fibrin Degradation Products (FDP) in Covid-19 patients

S.No	Author	Country	Groups	Interpretation
1.	Ning Tang	China	Survivor(162) Non-Survivor(21)	FDP levels are significantly raised in non survivors
2.	Yongli Zhang	China	Critical(32), Non-Critical(67)	FDP raised significantly in critical group
3.	Tao Li	China	Covid-19 (40) Control (57)	FDP levels were raised in covid 19 group
4.	Yanghong Zhang	China	Aggravated(17) Non-Aggravated (54)	FDP levels were significantly raised in aggravated group
5.	Ying Zhou	China	Mild(277) Severe(26)	FDP levels raised significantly in severe group

Table 9: Studies that compare Thrombin Time (TT) in Covid-19 patients

S.No	Author	Country	Groups	Interpretation
1.	Yong Gao	China	Severe(15) Mild(28)	TT was raised significantly in severe group
2.	Hui Long	China	Mild (39) Severe(48) Critical(28)	No significant changes observed in the three groups.
3.	Kun Wang	China	Survivor(296) Non-Survivor(19)	TT significantly raised in non survivors in the training cohort.
4.	Yanghong Zhang	China	Aggravated(17) Non-Aggravated(54)	No difference in the TT value between patients in aggravated and non-aggravated group ($P > .05$)

Table 10: Studies that compare Anti-Thrombin (AT) in Covid-19 patients

S.No	Author	Country	Groups	Interpretation
1.	Yanghong Zhang	China	Aggravated(17) Non-Aggravated(54)	Anti-thrombin levels lower in nonaggravated group

Table 11: Summary of changes in Coagulation parameters in Severe Covid-19 infection

S.No.	Biomarker	Changes seen in severe COVID patients
1.	D-dimer	Increase
2.	Fibrinogen	Raised
3.	Platelet count	Decrease
4.	PT	Prolonged
5.	APTT	Prolonged
6.	INR	Raised
7.	FDP	Raised
8.	TT	Raised
9.	AT	Decrease

PT= Prothrombin Time; APTT= Activated Partial Thromboplastin Time; INR=International Normalised ratio; FDP=Fibrin Degradation Product; TT=Thrombin Time; AT= Anti-Thrombin

3. Results

Further, after extensive screening; 73 studies describing laboratory parameters in COVID-19 patients were finally included in the study. After going through the full text of the articles, we were able to identify 60articles on analysis of coagulation parameters in COVID-19 patients. (Table 1). Evidence from all studies available in literature indicate that COVID-19 patients exhibit specificderangement in coagulation parameters i.e. high levels of D-Dimers, prolonged PT and low Plateletcount suggesting a hypercoagulable state leading to microthrombosis in COVID-19.[12-57] We analysed all the available articles for derangements in Various coagulation parameters including D-dimers, Fibrinogen, platelet count, PT, APTT, FDP, TT, AT and D-dimers among COVID-19 patients with varying levels of severity.

3.1 D-dimers

D-dimer is the degradation product of crosslinked fibrin resulting from plasmin cleavage. Rising levels indicate simultaneous activation of coagulation and fibrinolysis. D-dimer is a sensitive biomarker to rule out venous thromboembolism. Various studies have assessed the levels of D-dimers in COVID-19 patients. (Table 2). Several

studies from Wuhan have shown association of elevated D-dimers with high mortality in COVID-19 patients. Ning Tang studied coagulation parameters of Novel Coronavirus Pneumonia (NCP) patients and compared the same between survivors and non-survivors and observed significantly higher D-dimer and FDP levels in non-survivors and concluded that elevated D-dimer and FDP are significantly associated with poor prognosis and have the potential to guide therapy.[58] In an Italian cohort study by Pierpaolo Di Micco et al, D-dimer levels showed a non significant but increasing trend between COVID-19 patients with and without SARS.[59]

Yanghong Zhang et at compared blood coagulation data in aggravated group and the non aggravated group of COVID-19 and in healthy controls and noted that patients with COVID-19 had significantly elevated values of various coagulation parameters including D-Dimers.Similar findings were obtained on comparison of coagulation parameters between patients with aggravated and non-aggravated COVID-19 disease. Correlation analysis of parameters of coagulation function with those of liver function revealed that D-Dimers were positively correlated with AST, TBiL, DBiL, LDH, and CRP and concluded that coagulation derangement in COVID-19 patients may be influenced by liver function and inflammation.[60] Litao Zhang et al stated that elevated D-dimer indicate a hypercoagulable state in COVID-19 patients and based on the finding of C-index of 0.883, the authors concluded that D-dimer > 2.0 µg/mL predicted increased in-hospital mortality in COVID patients.[61]

Similarly, Ying Zou et al from Shanghai China compared coagulation function in patients with severe and mild COVID-19 and noted statistically significant difference in the D-dimer values in the two groups (1.04 vs. 0.43µg/mL).[62] In an another study from Wuhan; Hui Long et al investigated the dynamic changes in various coagulation indicators and observed that AUCs of D-Dimer were 0.742, 0.818, and 0.851 in three times of test, respectively as per ROC analyses for mortality risk. Further the authors observed that as the disease progresses, changes in CT imaging closely related to increase in levels of d-dimer and concluded that in COVID-19 patients, D-Dimer levels gradually increased throughout the disease, indicating a hyperfibrinolytic state.[63]

3.2 Fibrinogen

It is a positive acute phase reactant and its level rises in response to systemic inflammation. During injury, fibrinogen is converted enzymatically into fibrin by thrombin and this fibrin forms the clot. Serum levels of fibrinogen have been assessed in various studies and levels have been compared in severe vs. Mild cases, ICU vs. Non-ICU cases.(Table 3) Pierpaolo di Miccoet al observed significantly raised fibrinogen levels in COVID-19 patients as compared to controls (622 vs. 455 mg/dl) and concluded that Fibrinogen levels increase early in COVID-19 patients and can be used as a marker for risk stratification for detecting patients at increased risk to develop SARS.[59] In a retrospective cohort study by Xiaojie Bi Indices of Coagulation Function between Severe and Non-severe COVID patients were compared and significantly higher fibrinogen was observed in severe group (4.23 g/L vs. 3.07 g/L). The study further highlighted that Fibrinogen Albumin ratio (FAR) and Platelet count were closely associated with progression of the disease and FAR levels return to normal after recovery from illness.[65] Similar findings of significantly raised fibrinogen levels in severe COVID-19 cases was observed by Ying Zhou, Jianhong Fu, Yi Han, Yong Gao and David M Smadja.[62, 66-69]

However in a retrospective case series by Hui Long et al, the dynamic changes of Fibrinogen and other parameters were tested and significantly increased levels of Fibrinogen were observed in severe and critically ill patients, with 70.3% of severe and critical patients (52/74) >4.00 g/L. The dynamic changes in Fibrinogen levels revealed lower levels in deceased cases than in survivors suggesting that coagulation process is dynamic in COVID-19 patients with a state of hypercoagulating initially and fibrinolysis later.[63]

3. 3 Platelet Count

Platelets circulate within blood and bind together on recognizing damaged blood vessels. Platelet count is a simple biomarker, associated with severity of disease and higher risk of mortality in COVID-19 patients in ICU. (Table 4)In a retrospective cohort study by Xiaojie Bi et al thrombocytopenia was observed in severe COVID-19patients when compared to non- severe cases and it was postulated that Platelet count with optimal cutoff of $135x10^9$ /L was an independent risk factor for disease progression. The authors further stated that with progression of the disease, there was a rapid decrease in the platelet count. Thrombocytopenia seen in severe COVID-19 patients has been linked with activation of Fibrinolysis and use of corticosteriods.[65]In an another retrospective cohort study by Yanli Liu et al association between various platelet parameters and mortality riskin COVID-19 patients was studied and it was found that mortality associated with Thrombocytopenia was almost three times higher than in patients without thrombocytopenia. Further it was suggested that with an increment of 50×10^9 /L in platelets; there was was 40% decrease in mortality.[67] David M Smajda et al from France also compared various laboratory parameters in COVID-19 patients and controls but noted no significant difference in platelet count in the two groups.[68] Giuseppe Lippi et al in a meta analysis on thrombocytopenia and severe COVID-19concluded that platelet count is simple, rapid and readily available laboratory parameterthat discriminates between COVID-19 patients with and without severe disease.[69]

3.4 Prothrombin Time

It is an assay that evaluates extrinsic and common pathway of coagulation. We could identify 28 studies on evaluation of PT in COVID-19 patients. (Table 5) Significantly raised PT was seen in COVID-19 patients (with ARDS, in non-survivors, in ICU patients, in severe patients). In a retrospective case series by Hui Long, the dynamic changes in PT were tested, correlated with CT imaging, clinical classifications, and it was concluded that PT along with D-dimer can be used as indicators for predicting mortality in

COVID-19.[63] Ning Tang et al in their study on 183 patients; observed longer PT in non-survivors as compared to survivors on admission(13.6 vs. 15.5 seconds).[58] Similar findings of raised PT in severe COVID patients was observed by Ying Zhou and Yi Han et al. [62,70]

3.5 APTT (Activated Partial Thromoplastin Time)

It measures the overall speed at which blood clots by intrinsic and common pathway of coagulation.We identified 25 studies on analysis of APTT in COVID-19 patients. (Table 6)Tao Li et al concluded thatvarious Coagulation abnormalities including prolonged APTT is common in COVID-19 patients and it requires continuous vigilance and timely interventions.[64]

3.6 INR (International Normalised Ratio):

INR is ratio of a patient's PT to control sample, raised to the power of the ISI (International Sensitivity index) value for the analytical system being used.We could identify 5 studies which analyzed INR in COVID-19 patients. (Table 7) Yanghong Zhang compared coagulation parameters including INR amongst COVID-19 patients and controls and noted INR (1.03 vs 0.97) in COVID-19 patients vs controls respectively. On comparing INR in the aggravated patients vs. non - aggravated group INR (1.07 vs 1.02) was obtained. Further Correlation analysis between parameters of coagulation function with liver function revealed that INR was positively correlated with AST, TBiL, DBiL, LDH, and CRP indicating that coagulation in COVID-19 patients is influenced by liver function and inflammation.[60]

3.3 Fibrin Degradation Products (FDP)

FDP are components of blood produced by clot degeneration. When the clot and fibrin net dissolves, fragments of protein are released into the body. These fragments are fibrin degradation products. We were able to identify 5 studies which analyzed FDP in COVID-19 patients. (Table 8)Ning Tang et al in retrospective cohort study observed significantly elevated FDP levels in non-survivors as compared to survivors on admission; and concluded that abnormal coagulation results, especially markedly elevated D-dimer and FDP are common in deaths with NCP and that coagulopathy may be associated with prognosis, and guide clinical treatment.[58] Yongli Zhang et al compared lab findings in critical (32) and non-critical (67) COVID-19 cases and concluded that FDP > 6.7 ug/mL was relatively dangerous and demonstrated a manifestation of critical illness.[71] Based on the study by Tao Li et al on COVID-19 patients and controls, it was concluded that SARS-CoV-2 had an important effect on the hematopoietic system and hemostasis. Coagulation abnormalities such as increased FDPsrequire vigilance and timely interventions.[64]

3.4 Thrombin time (TT)

It is a screening coagulation test used to assess fibrin formation from Fibrinogen in plasma. We could enlist 4 studies on COVID-19 and analysis of TT(Table 9). Yong Gao et al compared various lab parameters including TT in 43 COVID-19 patients with 15 severe and 28 mild cases and observed that TT in severe group was significantly higher than that in mild group (15.87 vs. 14.5 seconds). It was further highlighted that when TT is used for detection, the AUC for predicting severity was 0.711.[72] Similar findings were obtained by Kun Wang et al on comparison of TT between survivors and non-survivors in the training cohort.[73]Yanghong Zhang however; observed no difference in the TT value between patients in aggravated and non-aggravated group.[60]

3.5 Anti thrombin

Antithrombin (AT) is a circulating plasma protein that functions as an important regulator of blood coagulation. It inactivates several enzymes of the coagulation cascade including thrombin and factor Xa.Yanghong Zhang et al compared AT levels healthy controls and COVID patients with aggravated and non-aggravated disease. Significantly reduced AT levels were observed in severe COVID-19 patients than in healthy controls suggesting that severe COVID-19 patients possess coagulation dysfunction.[60]

4. Discussion

COVID-19 is a pandemic and continues to increase the burden on medical facilities across the world. Common symptoms of COVID-19 include fever, cough, fatigue, loss of smell and taste. Majority of the cases present with mild symptoms but in some cases there is progression to ARDS leading to death. The major concern associated with COVID-19 is the fatality associated with infection and to prevent such an adverse incident there is an urgent need to identify lab tests/ biomarkers that effectively and timely determine the likelihood of progression to severe/critical form of the disease in COVID-19 patients. Growing evidence from various studies suggest that deranged coagulation is common in seriously ill COVID-19.[12-57]

Coagulation is the process by which blood changes from a liquid state to a gel like state and as a result blood clot is formed and there is cessation of blood loss from a damaged vessel. The mechanism of coagulation involves activation, adhesion and aggregation of platelets, as well as deposition and maturation of fibrin. ToshiakaIba et al summarized the pathogenesis of coagulopathy in COVID -19 and postulated that SARS-CoV-2 binds ACE2 receptors present on the endothelium and as a result the level of angiotensin II increases and there is vasoconstriction. Further, binding of SARS-CoV-2 releases plasminogen activators and there is extensive cell damage, upregulation of expression of tissue factor and downregulation of protein C. Cytokine storm induced by SARS-CoV-2 stimulates tissue factor expression and activates the extrinsic coagulation cascade. The endothelium damaged due to inflammation readily binds the platelets activated by various cytokines in circulation. The state of hypercoagulability and severe systemic inflammation leads to microangiopathy, thrombosis and various thromoembolic complications seen in critically ill COVID-19 patients suggesting a bidirectional link between inflammation and coagulation.[3,74] Richard C. Becker in a recent review stated that in COVID-19 patients; coagulopathy in the form of thrombin and fibrin generation is a result of disruption in three arms of Virchow's triad i.e

abnormal blood flow, injury to the blood vessels (endothelial cell damage) and due to raised levels of pro-inflammatory cytokines, activated platelets and viral RNA circulating in the blood.[75]

Ning Tang et al from Wuhan, China studied the various coagulation parameters amongst the survivors and non-survivors of NCP and noted that non-survivors had significantly higher D-dimer and FDP levels, longer PT and APTT as compared to survivors. Further it was observed that 71.4% of non-survivors and 0.6% of survivors met the criteria of DIC and concluded that DIC is common in non-survivors of NCP and elevated levels of D-dimer and FDP has role in guiding therapy and evaluating prognosis.[58]Yanhong Zhang et al compared blood coagulation data from aggravated and non-aggravated COVID-19 patients and controls and observed elevated FIB, PT, APTT, INR, FDP, D-Dimers and reduced AT value in COVID-19 patients when compared to controls and in aggravated group than non-aggravated group. Coagulation parameters in COVID-19 patients were found to be closely related to parameters of liver function and inflammation and so it was concluded that coagulation dysfunction in COVID-19 may be due to liver injury and/or inflammatory storm.[60]

D-dimer appear in blood after lysis of cross-linked fibrin and raised levels indicate activation of coagulation and fibrinolysis. Based on reasearch data findings; Litao Zhang et al from Wuhan found that D-dimer had the highest C-index of 0.883 and concluded that D-dimer >2.0 µg/mL as optimum cutoff can be used as a biomarker to predict in-hospital mortality in COVID-19 patients with a sensitivity of 92.3% and a specificity of 83.3%.[61] In an another study; Hui Long et al suggested that in COVID-19 patients, the coagulating process is dynamic in nature with an initial state of hypercoagulatibility followed by activation of fibrinolysis. D-Dimers arising out of fibrinolysis continues to increase gradually throughout the disease and its levels correlated with CT imaging in predicting the progression of disease.[63]

The results of this review highlight that severe COVID-19 patients have various coagulation abnormalities due to which there are many thromboembolic complications which are associated with respiratory deterioration and death. Early recognition of development of such complications is currently the need of the hour for curbing the mortality associated with COVID-19 infection. Various evidences from available literature point towards derangements in coagulation parameters which include raised D-dimers, elevated Fibrinogen, prolonged PT, APTT and thrombocytopenia (Table 10). The coagulopathy seen in such patients further leads to pulmonary microvascular thrombosis, thromboembolic complications and fibrin deposition in broncho-alveoli thereby causing impaired gas exchange.

5. Limitations

This review has many limitations. Most of the studies included in this meta-analysis are from Wuhan, China and around the same time period; hence it is quite possible that the same patients have been enrolled in more than one study. Further articles enlisted in this meta-analysis include several groups of COVID-19 patients- worsened, improved; requiring O2, not requiring O2; ICU, non-ICU; alive, deceased; with ARDS, without ARDS; survivors, nonsurvivors etc raising the element of heterogeneity amongst the studies included. Furthermore, the co-morbidities in severe COVID-19 patients was studied in only a few studies. Only articles published in English language were included in the study.

6. Conclusion

COVID-19 is a newly emerging zoonotic disease and has reached a pandemic stage. Around one-fifth of COVID-19 patients have severe or life-threatening infections that requires immediate interventions such as oxygen therapy or mechanical ventilation. It is therefore imperative to know which patients are likely to develop severe disease to reduce the mortality associated with infection. Patients with severe COVID-19 exhibit derangement in various laboratory parameters including abnormalities in coagulation profile. Coagulopathy in COVID-19 patients has been found to be associated with an increased risk of death. Various evidences such as elevated levels of D-dimers, Fibrinogen, prolonged PT, APTT and thrombocytopenia can be helpful for clinicians for risk stratification and for early prediction of progression to severe and fatal form of COVID-19 and for guiding treatment.

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