Course of COVID-19 Based on Admission D-Dimer Levels and Its Influence on Thrombosis and Mortality

Vaasanthi Rajendran, Sowmya Gopalan, Priyadarshini Varadaraj, Viswanathan Pandurangan, Lakshmi Marappa, Aiswarya M. Nair, Sudha Madhavan, Rajkumar Mani, Emmanuel Bhaskara

Abstract

Background: Arterial and venous thrombosis is one of the major complications of coronavirus disease 2019 (COVID-19) infection. Studies have not assessed the difference in D-dimer levels between patients who develop thrombosis and those who do not.

Methods: Our study retrospectively assessed D-dimer levels in all virus confirmed hospitalized patients between May to September, 2020. Patients were divided into three groups: group 1 with normal D-dimer of < 0.5 µg/mL, group 2 with elevation up to six folds, and group 3 with more than six-fold elevation. Statistical analysis was done using SPSS software 23.0.

Results: Seven hundred twenty patients (group1 (n = 414), group 2 (n = 284) and group 3 (n = 22)) were studied. Eight thrombotic events were observed. Events were two with stroke, two non-ST elevation myocardial infarction and one each of ST elevation myocardial infarction, superior mesenteric artery thrombosis with bowel gangrene, arteriovenous fistula thrombus and unstable angina. No significant difference (P = 0.11) was observed between median D-dimer levels among patients who developed thrombosis (1.34) and those who did not develop thrombosis (0.91). Twenty-nine patients died. The adjusted odds of death among those with a six-fold or higher elevation in D-dimer was 128.4 (95% confidence interval (CI): 14.2 - 446.3, P < 0.001), while adjusted odds of developing clinical thrombosis was 1.96 (95% CI: 0.82 - 18.2, P = 0.18).

Conclusions: Our study observed a 1.1% in-hospital incidence of clinical thrombosis. While, a six-fold elevation in D-dimer was significantly associated with death; the same was not a strong predictor of thrombosis; an observation which implies that dose of anticoagulation should not be based on absolute D-dimer level.

Keywords: COVID-19; D-dimer; Thrombosis; Death, Anticoagulation
Thrombosis and D-Dimer in COVID-19

Materials and Methods

This was a retrospective study at a tertiary care center in Chennai, South India of all hospitalized patients between May to September, 2020 (period corresponding to first pandemic wave in India) with reverse transcriptase-polymerase chain reaction (RT-PCR) of nasopharyngeal/oropharyngeal swab confirmed SARS-CoV-2 infection.

Physical case records having clinical and laboratory details, centralized laboratory database having results of laboratory tests, imaging database having digital images and radiologist report were perused by one of the study authors and recorded in a standard data entry template. Patients' identities were reversibly de-identified during data entry. All adults aged > 18 years and who had at least one baseline D-dimer test were included. Patients who were: 1) discharged within 24 h; 2) prematurely discharged on their request; and 3) patients who expired at or shortly after arrival to emergency room were excluded. D-dimer assay was performed within 24 h of admission, using immunoturbidimetry technique with a Sysmex CS 2400 machine; a value of < 0.5 µg/mL was considered as normal. Baseline D-dimer test was done prior to anticoagulant initiation. Test was periodically repeated during hospitalization as per treating clinician opinion in those with an initial abnormal value or in those who had requirement for supplementary oxygen.

Baseline characteristics such as age, gender, symptoms, comorbidities, need for oxygen, laboratory testing (neutrophil to lymphocyte ratio (NLR), CRP, ferritin, and LDH), place of admission (ward or intensive care), drugs administered; specifically use of heparin (unfractionated or low-molecular-weight), antiplatelet agents (aspirin or clopidogrel) and oral anticoagulant drugs were recorded by one of the study investigators.

All relevant clinical details of thrombotic events were recorded. The study was approved by the Institutional Ethics Committee (IEC) of Sri Ramachandra Institute of Higher Education and Research with waiver of consent (IEC-NI/20/ Aug/75/53), and was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration.

Patients were divided into three groups based on the value of baseline D-dimer level: group 1 with normal D-dimer (< 0.5 µg/mL), group 2 with D-dimer elevation up to six folds (0.51 - 3.0 µg/mL) and group 3 more than six-fold elevation (> 3.0 µg/mL). These cutoffs were chosen on the basis of Cleveland clinic review that suggested that values > 3.0 µg/mL were associated with a higher incidence of either thrombosis or failure of thromboprophylaxis [15]. These groups were compared for clinical features, development of thrombosis, need for intensive care stay and other non-thrombotic complications, in-hospital outcomes and mortality. In patients with clinical suspicion of thrombosis, further laboratory investigations were done to confirm the diagnosis. The confirmatory tests were electrocardiogram, serial troponin T measures for acute coronary syndrome (ST-elevation myocardial infarction (STEMI)/non-ST-segment myocardial infarction (NSTEMI)), computed tomography (CT) of brain in those with stroke and CT angiogram for arterial or venous thrombosis. Severity of illness was considered as mild if peripheral oxygen saturation by pulse oximetry was ≥ 95%, moderate if 90-94% and severe if < 90%.

Categorical variables were expressed as number (%) and continuous variables as mean (standard deviation or median (interquartile range (IQR))). Statistical analysis was done using SPSS software 23.0 and statistical difference in age, gender, prior medical illness, symptoms at presentation, level of oxygen saturation, laboratory parameters and mortality was assessed with t-test, one-way analysis of variance with Tukey’s post hoc test, Chi-square test, Wilcoxin rank sum test as per data form. Odds ratio (adjusted for differences in age, gender and prior chronic medical illness in the compared groups) with 95% confidence interval (CI) and test of significance was calculated for death and in-hospital development of thrombosis by standard statistical methods. A P value of < 0.05 was considered significant.

Results

Seven hundred twenty patients were studied. Table 1 elaborates the baseline characteristics of study participants classified as groups based on level of D-dimer elevation.

Group 3 patients were older (P = 0.0005), and were more frequently male (P = 0.01). Diabetes (P = 0.02) and hypertension (0.03) was more prevalent in group 3; no significant difference in coronary artery disease and lung disease was observed across groups.

Cough (P = 0.008) and breathlessness (P = 0.0005) were more frequent in group 3; no significant difference was observed in frequency of fever, sore throat, headache, vomiting, diarrhea and anosmia between groups. Most of group 1 (87.7%), group 2 (65.1%) had mild illness and most of group 3 (45.4%) had severe illness. Sixty-seven of 720 required ICU: group 1 (14 of 414) 3.3%, group 2 (41 of 284) 14.4% and group 3 (12 of 22) 54.5%. Group 3 had significantly higher NLR (P = 0.0005), ferritin (P = 0.001), LDH (P = 0.0005) and CRP (P = 0.0005) compared to groups 1 and 2.

Table 2 compares the parameters between survivors and non-survivors in the study groups. Non-survivors in group 1 had significant higher prevalence of diabetes mellitus (P = 0.04); while it was not significant in group 2 (P = 0.34) and group 3 (P = 0.16). Non-survivors in group 2 had higher preva-
lence of hypertension (P = 0.02); while it was not significant in group 1 (P = 0.67) and group 3 (P = 0.79). Non-survivors in group 1 (P < 0.001) and group 2 (P = 0.005) more frequently required oxygen therapy at hospitalization; while oxygenation requirement between survivors and non-survivors were not significantly different in group 3 (P = 0.08).

A total of 284 received anticoagulant therapy with either unfractionated heparin or low-molecular-weight heparin (145 in mild, 98 in moderate and 51 in severe). None was given novel oral anticoagulants. Eight of 720 (1.1%) had arterial or venous thrombosis. Mean age of those with thrombosis was 67.36 (range: 40 - 93) years; six were male. Six patients had prior chronic medical illness (diabetes mellitus (n = 3), hypertension (n = 4), chronic kidney disease (n = 2), coronary artery disease (n = 3), stroke (n = 1), chronic obstructive pulmonary disease (n = 1)). Mean D-dimer at hospitalization was 2.25 (range: 0.5 - 9.66). Three presented to hospital with features of arterial thrombosis without symptoms of COVID-19 (two strokes and one STEMI). Five patients developed thrombotic events in hospital while on prophylactic anticoagulant therapy (superior mesenteric artery thrombosis with bowel gangrene (n = 1), arteriovenous (AV) fistula thrombus in a hemodialysis patient (n = 1), NSTEMI (n = 2) and unstable angina (n = 1)). There was no deep vein thrombosis or pulmonary embolism.

Table 1. Baseline Characteristics of Study Population

| Clinical parameter                  | Group 1 (n = 414) | Group 2 (n = 284) | Group 3 (n = 22) | P value |
|-------------------------------------|-------------------|------------------|------------------|---------|
| Age, mean ± SD (years)              | 44.4 ± 15.1       | 50.1 ± 16.4      | 58.2 ± 12.1      | 0.0005  |
| Gender, n (%)                       |                   |                  |                  |         |
| Male                                | 254 (61.4)        | 149 (52.5)       | 17 (77.3)        | 0.012   |
| Female                              | 160 (38.6)        | 135 (47.5)       | 5 (22.7)         |         |
| Comorbidities, n (%)                |                   |                  |                  |         |
| Diabetes mellitus                   | 137 (33.1)        | 111 (39.1)       | 13 (59.1)        | 0.021   |
| Coronary artery disease             | 21 (5.1)          | 24 (8.5)         | 1 (4.5)          | 0.188   |
| Hypertension                        | 104 (25.1)        | 89 (31.3)        | 10 (45.5)        | 0.038   |
| Lung disease                        | 15 (3.6)          | 18 (6.3)         | 1 (4.5)          | 0.251   |
| Oxygen saturation at admission, mean ± SD | 97.4 ± 2.2 | 95.9 ± 4.3 | 87.3 ± 13.8 | 0.0005 |
| Presenting symptoms, n (%)          |                   |                  |                  |         |
| Fever                               | 307 (74.1)        | 212 (74.6)       | 18 (81.8)        | 0.73    |
| Sore throat                         | 117 (28.3)        | 62 (21.8)        | 3 (13.6)         | 0.07    |
| Cough                               | 119 (28.7)        | 111 (39.1)       | 10 (45.4)        | 0.008   |
| Breathlessness                      | 37 (8.9)          | 69 (24.3)        | 12 (54.5)        | 0.0005  |
| Vomiting/diarrhea                   | 32 (7.7)          | 20 (7.0)         | 2 (9.1)          | 0.906   |
| Anosmia                             | 19 (4.5)          | 15 (5.3)         | 1 (4.5)          | 0.914   |
| Ageusia                             | 16 (3.9)          | 7 (2.5)          | 0                | -       |
| Headache                            | 22 (5.3)          | 9 (3.2)          | 1 (4.5)          | 0.401   |
| Myalgia                             | 57 (13.8)         | 25 (8.8)         | 0                | -       |
| Fatigue                             | 6 (1.4)           | 8 (2.8)          | 0                | -       |
| Severity of illness, n (%)          |                   |                  |                  |         |
| Mild                                | 363 (87.7)        | 185 (65.1)       | 6 (27.3)         | 0.0005  |
| Moderate                            | 39 (9.4)          | 67 (23.6)        | 6 (27.3)         |          |
| Severe                              | 12 (2.9)          | 32 (11.3)        | 10 (45.5)        |          |
| Investigations, mean ± SD           |                   |                  |                  |         |
| NLR                                  | 2.7 ± 3.6         | 3.9 ± 5.6        | 10.2 ± 12.1      | 0.0005  |
| Serum ferritin (ng/mL)              | 175.4 ± 208.6     | 263.7 ± 541.1    | 418.0 ± 396.6    | 0.001   |
| LDH (IU/L)                           | 254.1 ± 87.1      | 311.6 ± 162.1    | 456.9 ± 268.1    | 0.0005  |
| Sodium (mEq/L)                      | 136.5 ± 3.1       | 135.5 ± 3.9      | 132.6 ± 5.9      | 0.0005  |
| Albumin (g/dL)                      | 4.0 ± 0.4         | 3.7 ± 0.5        | 3.3 ± 0.7        | 0.0005  |
| CRP (mg/dL)                          | 2.2 ± 3.6         | 5.0 ± 7.9        | 6.5 ± 5.2        | 0.0005  |

SD: standard deviation; NLR: neutrophil to lymphocyte ratio; LDH: lactate dehydrogenase; CRP: C-reactive protein.
No significant difference (P = 0.11) was observed between median (IQR) D-dimer level among patients who developed thrombosis (1.34, IQR: 0.573, 1.042 - 1.615) and those who did not develop thrombosis (0.91, IQR: 0.643, 0.721 - 1.364).

Twenty-nine patients died. Median (IQR) D-dimer among non-survivors (0.96, IQR: 1.45, 0.56 - 2.01) was significantly (P < 0.001) higher than survivors (0.41, IQR: 0.5, 0.25 - 0.75). The adjusted odds of death (adjusted for age, gender and comorbidities) among those with a six-fold or higher elevation in D-dimer was 128.4 (95% CI: 14.2 - 446.3, P < 0.001), while odds of developing clinical thrombosis (adjusted for age, gender and comorbidities) was 1.96 (95% CI: 0.82 - 18.2, P = 0.18).

Discussion

Critical illness is associated with a higher risk of thrombosis due to various factors such as immobilization, arterial and central venous lines, and nutritional deficiencies, etc [16]. However in COVID-19, hypercoagulable state is also due to a link between inflammation and thrombosis.

Cytokine storm that is seen in a small proportion of individuals causes release of interleukins, tumor necrosis factor and chemokines leading to activation of neutrophils, macrophages and platelets culminating in a prothrombotic state [17]. There is also a localized coagulopathy in the pulmonary vasculature due to inflammation in the alveoli, a phenomenon called microvascular COVID-19 lung vessels obstructive thrombo-inflammatory syndrome or MicroCLOTS which can lead to micro-thrombotic complications [18].

Our study observed a 1.1% (8 of 720) in-hospital incidence of clinical arterial or venous thrombosis. We also observed a 45.4% prevalence of severe disease in those with higher than six-fold D-dimer elevation. The fact that 54.6% of patients who had higher than six-fold elevation in D-dimer had no or minimal hypoxia, and occurrence of only one of the eight thrombotic events (AV fistula thrombosis with D-dimer of 9.66) indicates that D-dimer may not be an ideal predictor of clinical thrombosis. Further, we observed that the odds of death among patients with six-fold or higher elevation in D-dimer were much higher and significant than the odds of thrombosis (128.4 against 1.96); though, this observation is limited by the small event rate of our study. Furthermore, published studies have not elaborated the absolute D-dimer in patients who developed thrombosis [19].

Seven of eight thrombotic events occurred in patients who had normal or up to six-fold elevation in D-dimer (mean: 1.19). The mortality among those who developed thrombosis was 50% (4 of 8) compared to an overall study mortality of 4% (29 of 720). We diagnosed thrombosis based on evaluation following clinical suspicion, and duplex ultrasound surveillance for deep venous thrombosis was not a part of our protocol. Studies from ICUs using regular assessment with duplex ultrasound for screening even in the absence of clinical suspicion have observed a higher proportion of deep vein thrombosis (56.3% vs. 11.0%, P<0.001) [20]. Hence, we may have underestimated the venous thrombosis in the ICU, and it is likely that pulmonary embolism may have contributed to the overall mortality.

In conclusion, incidence of in-hospital thrombosis was 1.1% with a 50% mortality among the affected. Absolute value of D-dimer was not a strong predictor of thrombosis; an observation which implies that dose of anticoagulation should not be based on absolute D-dimer level. Limitations include the retrospective nature of the study, absence of a screening protocol for asymptomatic deep vein thrombosis. More studies are required to confirm our observation on occurrence of thrombosis independent of the D-dimer level.

Acknowledgments

None to declare.

Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

Waiver of informed consent was obtained from the ethics committee as it was a retrospective observational study.

Author Contributions

Vaasanthi Rajendran, Priyadarshini Varadaraj, Viswanathan Pandurangan, Lakshmi Marappa, Aiswarya M. Nair, Sudha Madhavan, and Rajkumar Mani: design feasibility assessment, acquisition of data, analysis and interpretation, and final approval of manuscript. Sowmya Gopalan: overall supervision, concept and design, analysis and interpretation of data, drafting of manuscript. Emmanuel Bhaskar: overall supervision, concept and design, analysis and interpretation of data, revision of manuscript and final approval.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

References

1. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;18(4):844-847.
### Table 2. Comparison of the Parameters Between Survivors and Non-Survivors in Each Group

| Parameter                                      | Group 1 |                      | Group 2 |                      | Group 3 |                      | P value |
|-----------------------------------------------|---------|----------------------|---------|----------------------|---------|----------------------|---------|
|                                               | Survived (n = 409) | Died (n = 5) | P value | Survived (n = 266) | Died (n = 18) | P value | Survived (n = 16) | Died (n = 6) | P value |
| Age, mean ± SD                                | 44.2 ± 15.1 | 61.8 ± 8.5 | 0.009   | 48.7 ± 15.6 | 70.4 ± 15.2 | < 0.001 | 58.2 ± 14.0 | 58.3 ± 5.5 | 0.98    |
| Gender, n (%)                                 |         |                      |         |                      |         |                      |         |
| Male                                          | 249 (60.9) | 5 (100.0) | 0.075   | 138 (51.9) | 11 (61.1)  | 0.448    | 14 (87.5)  | 3 (50.0)  | 0.067   |
| Female                                        | 160 (39.1) | 0           |         | 128 (48.1) | 7 (38.9)   |          | 2 (12.5)   | 3 (50.0)  |         |
| Prior medical illness, n (%)                  |         |                      |         |                      |         |                      |         |
| Diabetes mellitus                             | 133 (32.5) | 4 (80.0)  | 0.048   | 103 (38.7) | 9 (50.0)   | 0.34     | 8 (50.0)   | 5 (83.3)  | 0.166   |
| Hypertension                                  | 102 (24.9) | 2 (40.0)  | 0.678   | 79 (29.7)  | 10 (55.6)  | 0.022    | 7 (43.7)   | 3 (50.0)  | 0.79    |
| Coronary artery disease                       | 20 (4.8)  | 1 (20.0)   | 0.526   | 15 (5.6)   | 9 (50.0)   | < 0.001  | 1 (6.2)    | 0           |         |
| Chronic lung disease                          | 14 (3.4)  | 1 (20.0)   | 0.455   | 16 (6.0)   | 2 (11.1)   | 0.38     | 1 (6.2)    | 0           |         |
| Oxygen saturation, mean ± SD                  | 97.4 ± 2.0 | 91.8 ± 6.3 | < 0.001 | 96.5 ± 3.7 | 88.4 ± 5.7 | < 0.001  | 91.0 ± 7.9 | 77.2 ± 21.1 | 0.032   |
| Needing supplementary oxygenation at admission|         |                      |         |                      |         |                      |         |
| Yes                                           | 46 (11.2) | 5 (100.0) | < 0.0001 | 185 (69.6) | 18 (100.0) | 0.005    | 10 (62.5)  | 6 (100.0) | 0.085   |
| No                                            | 363 (88.8) | 0           |         | 81 (30.4)  | 0           |         | 6 (37.5)   | 0           |         |
| Investigation                                 |         |                      |         |                      |         |                      |         |
| NLR, mean ± SD                                | 2.5 ± 2.2 | 16.7 ± 24.2 | < 0.001 | 3.2 ± 3.6 | 12.7 ± 14.9 | < 0.0001 | 6.9 ± 8.7 | 18.8 ± 16.1 | 0.035   |
| CRP (mg/dL), mean ± SD                        | 2.1 ± 3.5 | 8.4 ± 7.7   | 0.0001  | 4.6 ± 7.8 | 11.8 ± 6.5 | 0.0002   | 5.9 ± 4.7 | 7.7 ± 6.6 | 0.468   |
| LDH (IU/L), mean ± SD                         | 232.0 ± 83.8 | 413.0 ± 169.2 | < 0.0001 | 295.5 ± 131.2 | 523.3 ± 319.4 | < 0.0001 | 381.3 ± 216.1 | 646.2 ± 310.9 | 0.0341  |
| D-dimer (µg/mL), mean ± SD                    | 0.3 ± 0.1 | 0.4 ± 0.1   | 0.069   | 1.2 ± 0.8 | 1.1 ± 0.6 | 0.59     | 9.2 ± 5.3 | 16.2 ± 17.1 | 0.148   |
| Ferritin (ng/mL), mean ± SD                   | 170.9 ± 201.5 | 548.9 ± 408.8 | < 0.0001 | 228.1 ± 369.4 | 791.2 ± 1,564.0 | < 0.0001 | 429.8 ± 393.9 | 388.6 ± 439.4 | 0.834   |
| Albumin (g/dL), mean ± SD                     | 4.0 ± 0.4 | 3.5 ± 0.8   | 0.0046  | 3.8 ± 0.4 | 3.3 ± 0.5 | 0.0001   | 3.6 ± 0.5 | 2.7 ± 0.8 | 0.0023  |
| Chest X-ray grade 3*, n (%)                    | 143 (35.1) | 4 (80.0)   | 0.068   | 122 (46.6) | 15 (83.3)  | 0.002    | 10 (62.5)  | 6 (100.0) | 0.085   |
| Complications, n (%)                           |         |                      |         |                      |         |                      |         |
| Thrombotic events                              | 0       | 1 (20)    |         | 3 (1.8)   | 3 (16.7)   | 1 (6.2)   | 0           |         |         |
| Sepsis                                        | 4 (0.9) | 3 (60)    |         | 12 (72.3) | 13 (72.2)  | 2 (12.5)  | 5 (83.3)   |         |         |
| Heart failure                                  | 0       | 0           |         | 3 (1.8)   | 4 (22.2)   | 0         | 0           |         |         |
| Acute kidney injury                            | 7 (1.7) | 3 (60.0)   |         | 12 (73.2) | 8 (44.4)   | 3 (18.7)  | 2 (33.3)   |         |         |

*aInvolvement of more than one zone in chest X-ray.
2. Porfidia A, Valeriani E, Pola R, Porreca E, Rutjes AWS, Di Nisio M. Venous thromboembolism in patients with COVID-19: Systematic review and meta-analysis. Thromb Res. 2020;196:67-74.
3. Klok FA, Kruip M, van der Meer NJM, Arbous MS, Gommers D, Kant KM, Kaptein FHJ, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res. 2020;191:145-147.
4. Middeldorp S, Coppens M, van Haaps TF, Foppen M, Vlaar AP, Muller MCA, Bouman CCS, et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost. 2020;18(8):1995-2002.
5. Oxley TJ, Mocco J, Majidi S, Kellner CP, Shoirah H, Singh IP, De Leacy RA, et al. Large-vessel stroke as a presenting feature of COVID-19 in the young. N Engl J Med. 2020;382(20):e60.
6. Lodigiani C, Iapichino G, Carenzo L, Cecconi M, Ferrazzi P, Sebastian T, Kucher N, et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. Thromb Res. 2020;191:9-14.
7. Ackermann M, Verleden SE, Kuehnel M, Haverc A, Welte T, Laenger F, Vanstapel A, et al. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. N Engl J Med. 2020;383(2):120-128.
8. Yin S, Huang M, Li D, Tang N. Difference of coagulation features between severe pneumonia induced by SARS-CoV2 and non-SARS-CoV2. J Thromb Thrombolysis. 2021;51(4):1107-1110.
9. Carr JM, McKinney M, McDonagh J. Diagnosis of disseminated intravascular coagulation. Role of D-dimer. Am J Clin Pathol. 1989;91(3):280-287.
10. Soni M, Gopalakrishnan R, Vaishya R, Prabu P. D-dimer level in a useful predictor for mortality in patients with COVID-19: Analysis of 483 cases. Diabetes Metab Syndr. 2020;14(6):2245-2249.
11. Huang Y, Lyu X, Li D, Wang L, Wang Y, Zou W, Wei Y, et al. A cohort study of 676 patients indicates D-dimer is a critical risk factor for the mortality of COVID-19. PLoS One. 2020;15(11):e0242045.
12. Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. J Thromb Haemost. 2020;18(6):1421-1424.
13. Maatman TK, Jalali F, Feizpour C, Douglas A, 2nd, McGuire SP, Kinnaman G, Hartwell JL, et al. Routine venous thromboembolism prophylaxis may be inadequate in the hypercoagulable state of severe coronavirus disease 2019. Crit Care Med. 2020;48(9):e783-e790.
14. Favaloro EJ, Thachil J. Reporting of D-dimer data in COVID-19: some confusion and potential for misinformation. Clin Chem Lab Med. 2020;58(8):1191-1199.
15. Mucha SR, Dugar S, McCray K, Joseph D, Bartholomew J, Sacha GL, Militello M. Coagulopathy in COVID-19: manifestations and management. Cleve Clin J Med. 2020;87(8):461-468.
16. Minet C, Potton L, Bonadona A, Hamidfar-Roy R, Somohan CA, Lugosi M, Cartier JC, et al. Venous thromboembolism in the ICU: main characteristics, diagnosis and thromboprophylaxis. Crit Care. 2015;19:287.
17. Du F, Liu B, Zhang S. COVID-19: the role of excessive cytokine release and potential ACE2 down-regulation in promoting hypercoagulable state associated with severe illness. J Thromb Thrombolysis. 2021;51(2):313-329.
18. Bobrova L, Kozlovskaia N, Korotchaeva Y, Bobkova I, Kamysheva E, Moiseev S. Microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome (MicroCLOTS): a new variant of thrombotic microangiopathy? Crit Care Resusc. 2020;22(3):284.
19. Zhan H, Chen H, Liu C, Cheng L, Yan S, Li H, Li Y. Diagnostic value of D-Dimer in COVID-19: a meta-analysis and meta-regression. Clin Appl Thromb Hemost. 2021;27:10760296211010976.
20. Jenner WJ, Kanji R, Mirsadraee S, Gue YX, Price S, Prasad S, Gorog DA. Thrombotic complications in 2928 patients with COVID-19 treated in intensive care: a systematic review. J Thromb Thrombolysis. 2021;51(3):595-607.