



On admission hemoglobin and albumin, as the two novel factors associated with thrombosis in COVID-19 pneumonia

Somayeh Sadeghi^{1,2}, Peiman Nasri^{3,4}, Maryam Nasirian^{2,5}, Maryam Sadat Mirenayat⁶, Arash Toghiani⁷, Mohammadsaeid Khaksar⁸, Elahe Nasri², Ali Safaei⁹, Hamed Fakhim², Elham Raofi⁸, Koorosh Nemati¹⁰, Hurie Hashemi⁸, Elaheh Keivany^{8*}

¹Acquired Immunodeficiency Research Center, Al-Zahra Hospital, Isfahan University of Medical Sciences, Isfahan, Iran

²Infectious Diseases and Tropical Medicine Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

³Metabolic Liver Disease Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

⁴Child Growth and Development Research Center, Research Institute for Primordial Prevention of Non-Communicable Disease, Isfahan University of Medical Sciences, Isfahan, Iran

⁵Epidemiology and Biostatistics Department, Health School, Isfahan University of Medical Sciences, Isfahan, Iran

⁶Chronic Respiratory Diseases Research Center (CRDRC), National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University, Tehran, Iran

⁷School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

⁸Department of Internal Medicine, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

⁹Isfahan Cardiovascular Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran

¹⁰Department of Clinical Toxicology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

ARTICLE INFO

Article Type:

Original

Article History:

Received: 16 September 2021

Accepted: 1 November 2021

Published online: 7 February 2022

Keywords:

Thrombosis

COVID-19

Blood coagulation

Albumin

Hemoglobin

ABSTRACT

Introduction: The unrelenting storm of coronavirus disease (COVID-19) since late 2019 has turned into a crucial health matter of the globe. There is increasing evidence in terms of a hypercoagulable state by this infection.

Objectives: The current study aims to clarify the association between thromboembolic events in COVID-19 and the patient, the infection and in-hospital related characteristics.

Patients and Methods: The current case-control study has been conducted on 243 COVID-19 pneumonia patients including 83 cases with thrombotic events and 160 controls without thrombosis. The thrombotic events included deep venous thrombosis (DVT) (n=9), pulmonary thromboembolism (PTE) (n=48), acute myocardial infarction (AMI) (n=17), cerebrovascular accidents (CVA) (n=4) and arterial thrombosis (n=5). On admission, hemodynamic parameters, on admission laboratory assessments, mobility during hospitalization, type of oxygenation, intensive care unit (ICU) admission requirement and duration of ICU and also hospital stay were recorded in the checklist.

Results: According to logistic regression assessment, on admission O₂ saturation (OR: 0.97, 95% CI: 0.94-0.99), hemoglobin level (OR: 0.87, 95% CI: 0.77-0.97) and albumin level (OR: 0.53, 95% CI: 0.3-0.86) were independently correlated with thrombosis due to COVID-19. Other factors, including demographic, infection severity, laboratory and in-hospital characteristics, were not significantly associated with thrombotic events.

Conclusion: Based on this study's findings, hemoglobin and albumin levels were the independent factors associated with the thrombotic events in COVID-19 patients.

Implication for health policy/practice/research/medical education:

The results of this study help physicians recognize the patients with COVID-19 pneumonia who are at increased risk of thromboembolic events and thus prevent their occurrence.

Please cite this paper as: Sadeghi S, Nasri P, Nasirian M, Mirenayat MS, Toghiani A, Khaksar M, Nasri E, Safaei A, Fakhim H, Raofi E, Nemati K, Hashemi H, Keivany E. On admission hemoglobin and albumin, as the two novel factors associated with thrombosis in COVID-19 pneumonia. J Renal Inj Prev. 2022; 11(2): e31957. doi: 10.34172/jrip.2022.31957.

Introduction

The unrelenting storm of coronavirus disease of 2019 (COVID-19), which has emerged since December 2019, has turned into a crucial health matter of the globe. This infection has involved over 90 million people worldwide and led to death in approximately two million cases. This pandemic's exact pathophysiology is unknown still and scientists are searching for efficient management approaches to this infection (1).

COVID-19 is an acute complex systemic disorder which presentation varies from mild influenza-like symptoms to catastrophic conditions by interstitial pneumonia progressing to acute respiratory distress syndrome (ARDS), sepsis and multi-organ failure (2). Increasing evidence is going on regarding hypercoagulable states among those infected with COVID-19, also known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The epidemiological studies have stated a wide range of 7.7%-49% for thrombotic events incidence in COVID-19 infected patients, including deep vein thrombosis (DVT), pulmonary thromboembolism (PTE), ischemic cerebrovascular accident (CVA), acute myocardial infarction (AMI) and arterial thrombosis (3-5). An increase in the inflammatory factors, endothelial dysfunction, and thromboinflammation propagated by angiotensin-converting enzyme-2 are the potential factors presumed to play a role in coagulopathy pathogenesis (6).

Although numerous studies have been conducted to assess the prevalence, etiology and features of thromboembolic events due to SARS-CoV-2, the knowledge in this regard is limited (7).

Objectives

The current study aims to clarify the correlation between thromboembolic events incidence in COVID-19 and the patient, infection, and in-hospital related characteristics.

Patients and Methods

Study design

The current case-control study has been conducted on 243 patients admitted at Amin and Alzahra hospitals (affiliated to Isfahan University of Medical Sciences) due to SARS-CoV-2 from May to June 2020. The included patient consisted of 83 cases with thrombotic events and 160 individuals as controls with no thrombotic event, matched according to presence of COVID-19 pneumonia.

First, the study protocol was explained to the patients, or their legal guardians; then, the participants became aware of the study and signed the written consent accordingly.

The case group was selected from the patients with any thrombotic event, like DVT, ischemic CVA, PTE or AMI whose COVID-19 infection was approved by a positive polymerase chain reaction (PCR) test and also presence of signs of COVID-19 pneumonia in the imaging. The inclusion of the patients was conducted employing a convenience sampling.

Additionally, all patients in the control group had positive results for PCR test and radiographic signs of COVID-19 pneumonia, but with no thrombotic event. The control group was matched to the cases with a 2:1 proportion.

The previous history of coagulopathies and a recent history of thrombotic events (DVT, PTE, CVA or AMI) within a month prior to the hospital admission were determined as the exclusion criteria.

Diagnosis of thrombotic events

DVT diagnosis was made according to the patients' clinical manifestations (8) and confirmed through Doppler ultrasonography. To make a PTE diagnosis, computed tomographic pulmonary angiography was conducted for those referred with the symptoms compatible with PTE (9). Acute MI (myocardial infarction) was determined as ST-segment elevation myocardial infarction (STEMI) or non-STEMI. Typical chest pain for cardiac ischemia plus an elevation in highly-sensitive troponin levels as a sensitive and specific cardiac biomarker was defined as acute MI. STEMI in two or more echocardiogram leads indicating the involvement of a particular epicardial territory or new-onset left bundle branch block; otherwise, assumed as the non-STEMI. Hemiplegia, facial hemiparesis or dysarthria with a CT (computed tomography) scan compatible with an ischemic CVA was the CVA determinants.

All patients received the required COVID-19 treatment and anticoagulant according to Iran's national guidelines.

Data collection

The demographic data including age, gender and smoking and full medical history were imported into the study checklist.

The patients' examinations in the period of hospitalization were recorded too. The assessments included the admission levels of hemodynamic parameters [oxygen saturation (O₂ sat), pulse rate (PR), systolic blood pressure (SBP) and diastolic blood pressure (DBP)] and the on admission laboratory assessments (polymorphonuclear cells absolute count (PMN), absolute lymphocyte count (lymph count), hemoglobin (Hb), platelet (PLT) count, troponin level, fibrin degradation product (FDP), fibrinogen, d-dimer, ferritin, C-reactive protein (CRP), prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR), albumin (Alb) and lactate dehydrogenase (LDH).

Anticoagulation in the studied group was classified as no anticoagulation, prophylactic, intermediate and therapeutic dose. Type of anticoagulation prior to thrombotic event was considered in the case group. Prophylactic doses were 5000 IU of subcutaneous unfractionated heparin (UFH) (twice daily) or 40 mg of subcutaneous low molecular weight heparin (LMWH) (once daily) or 10 mg of oral rivaroxaban (daily). Intermediate doses included 7500 IU of subcutaneous

UFH (twice daily) or 60 mg of subcutaneous LMWH (daily) or 40 mg of subcutaneous LMWH (twice daily). The therapeutic doses were determined as 80 IU/kg of IV UFH followed by infusion of 18 IU/kg/h or 1 mg/kg of subcutaneous LMWH (twice daily) or 15 mg of oral rivaroxaban (twice daily).

The hospitalization-related characteristics were gathered too. These data were mobility during the hospitalization [complete bed rest (CBR) or relative bed rest (RBR)], type of ventilation (non-invasive ventilation/ intubation), intensive care unit (ICU) admission requirement, length of hospitalization, the time between hospitalization to ICU admission and death incidence.

Data analysis

The obtained data were entered into the Statistical Package for Social Sciences (SPSS; version 14.0, SPSS Inc., Chicago, IL, USA). The descriptive data were presented in mean, standard deviation, median and range for the continuous variable and also absolute numbers and percentages for categorical variables. The chi-square test or Fisher's exact test was utilized to compare the categorical variables between the groups. The continuous variables were compared using a t-test. Binary logistic regression analysis was applied to estimate the odds ratio and find the association between the assessed factors and thrombotic events in the crude model and adjusted model for age and gender. A *P* value of less than 0.05 was considered as a significant level.

Results

This study has been conducted on patients with COVID-19 pneumonia, including two groups of cases (*n*=83) with and controls (*n*=160) without thrombotic events. The cases consisted of 48 (57.8%), 9 (10.8%), 17 (20.5%), 4 (4.8%) and 5 (6.0%) with PTE, DVT, AMI, CVA and arterial thrombosis, respectively.

The thrombotic events occurred in 51 patients (61.5%) on admission or within the first two days of hospitalization. The mean period between COVID-19 symptoms onset and a thrombotic event incidence was 8.2 ± 8.6 days (median; 7 days). Forty-three (51.8%) of the cases required ICU admission, among which thrombosis occurred in 26 cases (60.5%). Further information is presented in [Table 1](#).

The gender distribution of thrombotic events revealed insignificant differences according to the type of the events; however, the comparison of the cases with controls revealed a significantly higher prevalence of females among the case group (*P*=0.025). None of the comorbid conditions were associated with thrombotic events (*P*>0.05). The patients' mobility and anticoagulation status were remarkably different between the cases and control (*P*<0.0001). It is also worth noting that all the cases with CVA and arterial thrombosis had not received any form of anticoagulation (*P*<0.001). Detailed information in terms of the comparison between cases and controls is

Table 1. The characteristics of the thrombotic cases (*n*=83)

| Characteristics | |
|---|------------------|
| Time from admission to thrombosis incidence-day | |
| Mean (SD) | 4.9 (10.4) |
| Median (Range) | 1 (0-72) |
| Thrombotic event incidence on admission, <i>n</i> (%) | 51 (61.5)* |
| Time from onset of COVID-19 symptoms to thrombosis incidence-day | |
| Mean (SD) | 8.2 (8.6) |
| Median (Range) | 7 (0-40) |
| ICU admission | 43 (51.8) |
| Thrombosis incidence in ICU, <i>n</i> (%) | 26/43 (60.5) |
| Interval between ICU admission to thrombosis incidence-day (<i>n</i> =26) | |
| Mean (SD) | 5.8 (8.8) |
| Median (Range) | 3 (0-37) |
| Time interval between thrombosis incidence to ICU admission-day (<i>n</i> =17) | |
| Mean (SD) | 3.6 (5.7) |
| Median (Range) | 2 (1-25) |
| Thrombosis type, <i>n</i> (%) | |
| PTE | 48 (57.8) |
| DVT | 9 (10.8) |
| AMI | 17 (20.5) |
| CVA | 4 (4.8) |
| Arterial thrombosis | 5 (6.0) |
| D-dimmer at time of thrombosis diagnosis | |
| Mean (SD) | 4858 (3377) |
| Median (Range) | 3885 (654-14969) |

PTE, pulmonary thromboembolism; DVT, deep vein thrombosis; AMI, acute myocardial infarction; CVA, cerebrovascular accident; ICU, intensive care unit.

* Thrombosis diagnosis within less than two days after admission (*n*=5) was defined as on admission thrombosis.

demonstrated in [Table 2](#).

As illustrated in [Table 3](#), the intubation requirement rate was significantly more in CVA cases than other groups of patients with thrombotic events (*P*=0.048). The most prolonged period of hospitalization belonged to the cases with arterial thrombosis, whereas the shortest period between hospitalization to ICU admission was found in CVA cases (*P*=0.044).

[Table 4](#) demonstrates the hemodynamic and laboratory characteristics of the cases versus controls. The mean oxygen saturation in the case group was remarkably lower than controls (*P*=0.031); however, the comparison among the groups regarding the categorized oxygen saturation revealed an insignificant difference (*P*=0.768).

The laboratory evaluations revealed significant differences between the groups in terms of PMN count, Hb level, PLT count, D-dimer, albumin, and LDH levels (*P*<0.05).

The comparison of troponin level regardless of the thrombotic event type was accompanied by significantly higher levels in the case group (*P*=0.027); however, after

Table 2. The comparison of demographic and medical characteristics between cases and controls

| | Thrombosis form | | | | | P-Value | Total Case (n=83) | Control (n=160) | P value |
|------------------------|-----------------|-------------|-------------|-------------|---------------------------|---------|-------------------|-----------------|----------|
| | PTE (n=48) | DVT (n=9) | AMI (n=17) | CVA (n=4) | Arterial thrombosis (n=5) | | | | |
| Gender/male, n (%) | 15 (31.3) | 4 (44.4) | 3 (17.7) | 3 (75.0) | 2 (40.0) | 0.219 | 27 (32.5) | 76 (47.5) | 0.025* |
| Age (y), Mean (SD) | 59.7 (17.9) | 62.8 (22.3) | 64.8 (15.1) | 69.5 (18.3) | 64 (34.8) | 0.172 | 61.8 (18.9) | 59.0 (17.6) | 0.239 |
| Age group, n (%) | | | | | | 0.606 | | | 0.871 |
| <18 | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | | 0 (0) | 1 (0.63) | |
| 18-29 | 2 (4.2) | 1 (11.1) | 0 (0) | 0 (0) | 1 (20.0) | | 4 (4.82) | 7 (4.38) | |
| 30-59 | 22 (45.8) | 3 (33.3) | 9 (52.9) | 1 (25.0) | 1 (20.0) | | 36 (43.4) | 65 (40.6) | |
| ≥60 | 24 (50.0) | 5 (55.5) | 8 (47.1) | 3 (75.0) | 3 (60.0) | | 43 (51.8) | 87 (54.3) | |
| ESRD, n (%) | 1 (2.1) | 0 (0) | 2 (11.8) | 0 (0) | 0 (0) | 0.520 | 3 (3.6) | 13 (8.1) | 0.179 |
| COPD, n (%) | 1 (2.1) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0.904 | 1 (1.2) | 6 (3.8) | 0.261 |
| Malignancy, n (%) | 0 (0) | 0 (0) | 1 (5.9) | 0 (0) | 0 (0) | 0.507 | 1 (1.2) | 10 (6.3) | 0.073 |
| CVA, n (%) | 3 (6.3) | 0 (0) | 1 (5.9) | 1 (25.0) | 1 (20.0) | 0.376 | 6 (7.2) | 8 (5.0) | 0.479 |
| DM, n (%) | 9 (18.8) | 0 (0) | 6 (35.3) | 2 (50.0) | 3 (60.0) | 0.045* | 20 (24.1) | 37 (23.1) | 0.865 |
| IHD, n (%) | 10 (20.8) | 2 (22.2) | 6 (35.3) | 1 (25.0) | 2 (40.0) | 0.324 | 21 (25.3) | 25 (15.6) | 0.068 |
| PTE, n (%) | 1 (2.1) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0.935 | 1 (1.2) | 1 (0.63) | 0.635 |
| Smoking-n (%) | 5 (10.4) | 2 (22.2) | 2 (11.8) | 1 (25.0) | 0 (0) | 0.761 | 10 (12.1) | 17 (10.6) | 0.738 |
| CBR-n (%) | 39 (81.3) | 7 (77.8) | 15 (88.2) | 0 (0) | 0 (0) | 0.643 | 70 (84.3) | 101 (63.1) | 0.001* |
| RBR, n (%) | 21 (43.7) | 5 (55.6) | 4 (23.5) | 0 (0) | 5 (20.0) | 0.056 | 31 (37.4) | 83 (51.9) | 0.031* |
| Anticoagulation, n (%) | | | | | | | | | |
| No anticoagulation | 23 (47.9) | 7 (77.8) | 16 (94.1) | 4 (100) | 5 (100) | 0.001* | 55 (66.3) | 32 (20.0) | <0.0001* |
| Prophylactic dose | 18 (37.5) | 2 (22.2) | 0 (0) | 0 (0) | 0 (0) | 0.011* | 20 (24.1) | 97 (60.3) | <0.0001* |
| Intermediate dose | 1 (2.1) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0.947 | 1 (1.2) | 11 (6.9) | 0.053 |
| Therapeutic dose | 6 (12.5) | 0 (0) | 1 (5.9) | 0 (0) | 0 (0) | 0.587 | 7 (8.4) | 20 (12.5) | 0.339 |

PTE, pulmonary thromboembolism; DVT, deep vein thrombosis; AMI, acute myocardial infarction; CVA, cerebrovascular accident; ESRD, end-stage renal disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; IHD, Ischemic heart attack; CBR, complete bed rest; RBR, relative bed rest.

χ^2 test for categorical variable and independent *t* test for a continuous variable were significant if *P* value < 0.05.

Table 3. The comparison of hospitalization characteristics between cases and controls

| | Thrombosis form | | | | | P value | Total Case (n=83) | Control (n=160) | P value |
|--|-----------------|------------|------------|------------|---------------------------|----------|-------------------|-----------------|---------|
| | PTE (n=48) | DVT (n=9) | AMI (n=17) | CVA (n=4) | Arterial thrombosis (n=5) | | | | |
| NIV, n (%) | 8 (16.7) | 2 (22.2) | 0 (0) | 0 (0) | 1 (20.0) | 0.340 | 11 (13.3) | 19 (11.9) | 0.757 |
| Intubation, n (%) | 7 (14.6) | 2 (22.2) | 3 (17.6) | 3 (75.0) | 2 (40.0) | 0.048* | 17 (20.5) | 83 (23.7) | 0.564 |
| ICU, n (%) | 23 (47.9) | 3 (33.3) | 10 (58.8) | 0 (0) | 3 (60.0) | 0.222 | 43 (51.8) | 84 (52.5) | 0.918 |
| Death, n (%) | 7 (14.6) | 1 (11.1) | 6 (35.3) | 2 (50.0) | 1 (20.0) | 0.204 | 17 (21.5) | 31 (19.4) | 0.837 |
| Time from hospitalization to ICU admission (day) | | | | | | | | | |
| Mean (SD) | 7.5 (13.6) | 2.0 (2.0) | 1.2 (1.6) | 0.7 (0.9) | 2.0 (1.7) | <0.0001* | 4.6 (10.4) | 3.9 (5.5) | 0.616 |
| Median (Range) | 2 (0-58) | 2 (0-4) | 0.5 (0-4) | 0.5 (0-2) | 1 (1-4) | 0.538 | 2 (0-58) | 2 (0-33) | 0.265 |
| Hospitalization length (day) | | | | | | | | | |
| Mean (SD) | 14.5 (13.7) | 12.8 (8.0) | 8.5 (7.8) | 9.8 (6.5) | 19.4 (15.3) | 0.044* | 13.1 (12.1) | 13.8 (10.5) | 0.668 |
| Median (Range) | 10 (2-67) | 10 (5-30) | 5 (0-25) | 8 (4-19) | 16 (9-46) | 0.541 | 9 (0-67) | 11 (1-83) | 0.227 |
| Time to discharge (day) | | | | | | | | | |
| Mean (SD) | 14.7 (13.9) | 13.7 (7.9) | 11.1 (8.1) | 6.5 (3.5) | 12.8 (4.3) | 0.041* | 13.7 (11.9) | 13.3 (11.0) | 0.842 |
| Median (Range) | 10 (2-67) | 10 (7-30) | 8 (0-25) | 6 (4-9) | 12 (9-17) | 0.760 | 10 (0-67) | 10 (1-83) | 0.931 |
| Time to death (day) | | | | | | | | | |
| Mean (SD) | 12.9 (12.4) | 5 (0) | 3.8 (4.8) | 13.0 (8.5) | 46 (0) | 0.021* | 11.2 (13.0) | 15.8 (7.9) | 0.153 |
| Median (Range) | 6 (2-31) | 5 (5-5) | 1.5 (1-13) | 13 (7-19) | 46 (46-46) | 0.148 | 5 (1-46) | 16 (2-34) | 0.110 |

PTE, pulmonary thromboembolism; DVT, deep vein thrombosis; AMI, acute myocardial infarction; CVA, cerebrovascular accident; NIV, Non-invasive ventilation; ICU, intensive care unit.

χ^2 test for categorical variable and independent t test for a continuous variable were significant if $P < 0.05$.

Table 4. The comparison of on admission maximum-values of hemodynamic and laboratory parameters between the cases and controls

| | Case (n=83) | Control (n=160) | P value |
|---|---------------|-----------------|---------------------|
| O ₂ sat, Mean (SD) | 83.6 (11.4) | 86.3 (8.1) | 0.031* |
| O ₂ sat group, n (%) | | | |
| ≤90% | 60 (72.3) | 116 (72.5) | |
| >90% to ≤93% | 11 (13.3) | 17 (10.6) | 0.768 |
| ≥94% | 12 (14.5) | 27 (16.9) | |
| PR (BPM), n (%) | 93.6 (18.8) | 92.6 (19.8) | 0.707 |
| RR, n (%) | 23.9 (6.8) | 23.7 (6.2) | 0.773 |
| Systolic BP (mm Hg), n (%) | 124.8 (19.1) | 124 (20.6) | 0.850 |
| Diastolic BP (mm Hg), n (%) | 77.9 (13.9) | 75.6 (14.4) | 0.241 |
| PMN count (cells/mL), n (%) | 8311 (4253) | 6737 (4872) | 0.013* |
| Hb (g/dL), n (%) | 12.3 (2.6) | 13.0 (2.1) | 0.021* |
| Lymph count (cells/mL), n (%) | 1344 (905) | 1236 (887) | 0.372 |
| PLT (×10 ³ /μL) ^b , n (%) | 220.5 (96.9) | 193.5 (94.4) | 0.037* |
| Troponin (ng/mL), Mean (SD) | 1721 (6723) | 51.4 (172.9) | 0.027* ^a |
| Troponin (ng/mL), Mean (SD) ^p | 238.8 (492.5) | 51.4 (172.9) | 0.607 ^a |
| FDP (μg/mL), Mean (SD) | 26.2 (6.1) | 24.60 (12.1) | 0.639 |
| Fibrinogen (mg/dL), Mean (SD) | 276.6 (115.1) | 326.9 (116.3) | 0.034 |
| D-dimer (μg/L), Mean (SD) | 4803 (3735) | 2830 (2997) | <0.0001* |
| Ferritin (μg/L), Mean (SD) | 765 (596) | 715 (580) | 0.598 |
| CRP (mg/L), Mean (SD) | 75.5 (43.3) | 66.1 (46.4) | 0.166 |
| PT (s), Mean (SD) | 15.2 (6.9) | 13.7 (5.5) | 0.089 |
| PTT (s), Mean (SD) | 33.1 (9.3) | 34.1 (12.5) | 0.544 |
| INR, Mean (SD) | 1.37 (0.67) | 1.22 (0.55) | 0.060 |
| ALB (g/dL), Mean (SD) | 3.3 (0.52) | 3.5 (0.61) | 0.009* |
| LDH (U/L), Mean (SD) | 1349 (1802) | 861 (456) | 0.046* ^a |

* χ^2 test for categorical variable and independent t test (or median test^a) for a continuous variable were significant if P value < 0.05.

^b Cases without MI (n = 66) were compared with control.

eliminating those with AMI, the two groups were similar ($P = 0.607$).

According to Table 5, oxygen saturation, Hb and albumin levels were the only markers inversely associated with thrombotic events.

Discussion

In the current case-control study, we tried to assess the clinical, laboratory and in-hospital characteristics of the patients with thrombotic events following a SARS-CoV-2 infection and find the predisposing factors that make a person prone to thrombotic events. Over 60% of the cases admitted in ICUs, experienced the thrombotic event after ICU admission. There are several studies representing the high incidence of these events in critically ill patients too (3,5). Nevertheless, 61.5% of the COVID-19 infected patients had a thrombotic event on-admission or presented it within the first two days. A paucity of knowledge is available regarding the characteristics of COVID-19 for increasingly developing these events.

The studies on general populations insisted on the role

of medical conditions including hypertension, diabetes mellitus, chronic pulmonary disorders, chronic renal disorders, and active malignancy on thrombotic events incidence (10), which has been notified in patients with SARS-CoV-2 (3). However, none of the comorbid conditions was remarkably different between cases and controls in this study. We assume that better insight may be provided in larger populations.

Among the hemodynamic parameters, oxygen saturation was found the only independent factor associated with the thrombotic events. SARS-CoV-2 pneumonia can lead to improper oxygenation due to acute respiratory distress itself. In addition, inappropriate respiration disables a person from exertion and is causative for immobilization, as well (11). It should be noted that approximately 63% of the cases were admitted due to PTE, a condition accompanied by a decrease in oxygen saturation and CVA, which required intubation due to a similar condition. Therefore, a two-sided association should be considered between the oxygen saturation and thrombotic events.

We found on-admission Hb level as an inverse factor

Table 5. Logistic regression assessments of related factor to thrombosis incidence

| | Odds ratio (95% CI) | |
|-------------------------------------|---------------------|-----------------------|
| | Crude | Adjusted ^a |
| Oxygen saturation,% | 0.97 (0.94-0.99)* | 0.96 (0.93-0.99)* |
| PMN absolute count, cells/mL | 1.00 (1.00-1.00)* | 1.00 (0.99-1.00) |
| Hemoglobin, g/dL | 0.87 (0.77-0.97)* | 0.86 (0.77-1.01) |
| Lymphocyte absolute count, cells/mL | 1.00 (0.99-1.00) | 1.00 (0.99-1.00) |
| Platelet count, 10 ³ /μL | 1.00 (1.00-1.00)* | 1.00 (0.99-1.00) |
| Troponin, ng/ml | 1.00 (1.00-1.00)* | 1.00 (1.00-1.00)* |
| D-dimer, μg/L | 1.00 (1.00-1.00)* | 1.00 (1.00-1.00)* |
| Albumin, g/dL | 0.53 (0.32-0.86)* | 0.66 (0.39-1.10) |
| Lactate dehydrogenase, U/L | 1.00 (1.00-1.00)* | 1.00 (1.00-1.00)* |

^a Adjusted for gender and anticoagulation dose.

* Odds Ratio was considered significant in 0.05 level, using logistic regression

associated with thrombotic events, which has not been noted previously. Furthermore, most of the studies represented an insignificant difference between those with thromboembolic events and the control groups (10-12).

It is hypothesized that low Hb level, which represents low blood viscosity, reduces stress formation on the endothelial bed of the vessels and, in turn, inhibits the function of the anti-thrombotic mechanism (13). Therefore, patients with lower Hb levels are prone to thrombotic events due to impaired endothelial function as one of the Virchow triad (14). Recent investigations on COVID-19 have notified increased risk of thromboembolism development due to diverse factors such as the imbalance between oxidative and anti-oxidative processes, accumulation of pro-inflammatory and pro-thrombotic factors and endothelial dysfunction (15). It seems that mentioned factors accompanying low levels of Hb reinforce the cascade of thrombosis formation.

Contrary to most of the investigations insisting on the standalone role of low- Hb levels on thrombosis in-hospital and long-term adverse events (16-18), studies in the literature have rarely evaluated the predictive value of Hb level for thrombotic events developing. Yamashita et al reported exceptional lower levels of Hb among the patients with venous thromboembolism and in accordance with other presentations, found a predictive role for this index for in-hospital outcomes, long-term adverse events and all-cause mortality (19). A similar reverse association was presented by Can et al (13). On the other hand, Kalra et al hesitate to confirm whether low Hb has a role in cardiovascular events and/or is a marker of comorbidities (17). This poor correlation was noted for thromboembolism accordingly (20). Therefore, the attitude about Hb's role in the development of thrombotic events is not unanimous and requires further investigations.

D-dimer was shown to be directly correlated with thrombotic events in our study. It is traditionally known as a marker of inflammation, coagulation activation and hyperfibrinolysis. The studies assessing these events in COVID-19 patients insisted on the elevated levels of this marker among those who experience a thrombotic event during a course of COVID-19 infection (12,21). In addition, Lodigiani et al represented a rapid increase in D-dimer levels among non-survivors of thrombosis in COVID-19 patients (4). Helms and colleagues noted that a rapid rising D-dimer level despite anticoagulation is a reflection of clot formation and a probable thrombotic event. They even recommended imaging assessments for patients with a sudden increase in D-dimer along with the deterioration of the clinical course of the disease (22). The significance of D-dimer is to the extent that guidelines for anticoagulant therapy in this infection have mentioned elevated D-dimer as a factor for high dose anticoagulant treatment (23).

Plasma albumin is the other factor found inversely associated with thrombosis in COVID-19 infection. To the best of our knowledge, despite all the notifications regarding the hypercoagulable state in SARS-CoV-2 infection, albumin level has not been well studied. Zhang et al determined the proportion of fibrinogen-to-albumin as a determinant for the risk of thrombosis development (24).

The increased probability of thrombosis in hypoalbuminemia has been well-established in chronic conditions such as nephrotic syndrome or cirrhosis (25); however, most of our patients were gathered from the general population infected by COVID-19. Nevertheless, studies on the general population have stated a significant association between albumin levels with venous thromboembolism incidence (26) and its severity (27). Further studies on other thrombotic events presented similar correlations (28,29).

To evaluate the role of low albumin levels as a risk factor for thrombosis formation, Mirsaeidi et al concluded that it acts as a representative of inflammation status (30). This theory has been confirmed by presenting an inverse correlation between serum albumin level with CRP and estimated erythrocyte sedimentation (28,27). In other studies, an antagonistic role of oxidation, stagnant, thrombosis and leukocyte adhesion has been considered for albumin (31). Further investigations, particularly in the critical group of COVID-19 patients, are required.

According to the findings of this study in terms of a significant association between anticoagulant prophylaxis and thrombosis formation and due to the recommendations of the other investigations of SARS-CoV-2 infected patients, prophylactic anticoagulation is strongly recommended, particularly in critical patients (32). It should also be noted that high number of cases in "no anticoagulation" group may be due to this fact that thrombotic events occurred on admission and no

anticoagulation was received by them prior to admission. The significance of prophylaxis is clarified, knowing the high incidence of thrombosis even among those under anticoagulation (4). Therefore, detailed investigations are recommended to determine the ultimate anticoagulant dosage in the target populations.

Conclusion

Based on this study's findings, Hb and albumin levels were the independent factors associated with thrombotic events in COVID-19 patients.

Limitations of the study

There were few limitations in this study including retrograde data collection, exclusion of some of the cases during study and incompleteness of some of the data.

Authors' contribution

SS, MSK and EK were the principal investigators of the study. SS, EN, MN, PN and HF were included in preparing the concept and design. SS, MN, MSM, AT, ER, KN, HH and AS revisited the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The Ethics Committee of Isfahan University of Medical Sciences approved this study. The institutional ethical committee at Isfahan University of Medical Sciences approved all study protocols (IR.MUI.MED.REC.1399.692). Accordingly, written informed consent was taken from all participants before any intervention. This study was extracted from M.D., thesis of Mohammadsaeid Khaksar at this university. Besides, ethical issues (including plagiarism, data fabrication and double publication) were completely observed by the authors.

Funding/Support

This study was not supported by any institute.

References

- Depalo D. True COVID-19 mortality rates from administrative data. *J Popul Econ.* 2021;34:253-74. doi: 10.1007/s00148-020-00801-6.
- Tu H, Tu S, Gao S, Shao A, Sheng J. Current epidemiological and clinical features of COVID-19; a global perspective from China. *J Infect.* 2020;81:1-9. doi: 10.1016/j.jinf.2020.04.011.
- Helms J, Tacquard C, Severac F, Leonard-Lorant I, Ohana M, Delabranche X, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive Care Med.* 2020;46:1089-98. doi: 10.1007/s00134-020-06062-x.
- Lodigiani C, Iapichino G, Carenzo L, Cecconi M, Ferrazzi P, Sebastian T, 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. doi: 10.1016/j.thromres.2020.04.024.
- Thomas W, Varley J, Johnston A, Symington E, Robinson M, Sheares K, et al. Thrombotic complications of patients admitted to intensive care with COVID-19 at a teaching hospital in the United Kingdom. *Thromb Res.* 2020;191:76-7. doi: 10.1016/j.thromres.2020.04.028.
- Hajra A, Mathai SV, Ball S, Bandyopadhyay D, Veyseh M, Chakraborty S, et al. Management of Thrombotic Complications in COVID-19: An Update. *Drugs.* 2020;80:1553-62. doi: 10.1007/s40265-020-01377-x.
- Wu T, Zuo Z, Yang D, Luo X, Jiang L, Xia Z, et al. Venous thromboembolic events in patients with COVID-19: a systematic review and meta-analysis. *Age Ageing.* 2021;50:284-93. doi: 10.1093/ageing/afaa259.
- Kruger PC, Eikelboom JW, Douketis JD, Hankey GJ. Deep vein thrombosis: update on diagnosis and management. *Med J Aust.* 2019;210:516-24. doi: 10.5694/mja2.50201.
- Nagamalesh UM, Prakash VS, Naidu KCK, Sarthak S, Hegde AV, Abhinay T. Acute pulmonary thromboembolism: Epidemiology, predictors, and long-term outcome - A single center experience. *Indian Heart J.* 2017;69:160-4. doi: 10.1016/j.ihj.2016.08.010.
- Agno W, Becattini C, Brighton T, Selby R, Kamphuisen PW. Cardiovascular risk factors and venous thromboembolism: a meta-analysis. *Circulation.* 2008;117:93-102. doi: 10.1161/circulationaha.107.709204.
- 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;395:1054-62. doi: 10.1016/s0140-6736(20)30566-3.
- Santoliquido A, Porfidia A, Nesci A, De Matteis G, Marrone G, Porceddu E, et al. Incidence of deep vein thrombosis among non-ICU patients hospitalized for COVID-19 despite pharmacological thromboprophylaxis. *J Thromb Haemost.* 2020;18:2358-63. doi: 10.1111/jth.14992.
- Can C, Topacoglu H, Ucku R. Investigation of relationship between blood hemoglobin level and acute pulmonary embolism in emergency setting. *Int Med J.* 2013;20:584.
- Irace C, Scarinci F, Scordia V, Bruzzichessi D, Fiorentino R, Randazzo G, et al. Association among low whole blood viscosity, haematocrit, haemoglobin and diabetic retinopathy in subjects with type 2 diabetes. *Br J Ophthalmol.* 2011;95:94-8. doi: 10.1136/bjo.2009.172601.
- Iba T, Levy JH, Levi M, Thachil J. Coagulopathy in COVID-19. *J Thromb Haemost.* 2020;18:2103-9. doi: 10.1111/jth.14975.
- Jiménez D, Escobar C, Martí D, Díaz G, César J, García-Avello A, et al. Association of anaemia and mortality in patients with acute pulmonary embolism. *Thromb Haemost.* 2009;102:153-8. doi: 10.1160/th09-01-0003.
- Kalra PR, Greenlaw N, Ferrari R, Ford I, Tardif JC, Tendera

- M, et al. Hemoglobin and Change in Hemoglobin Status Predict Mortality, Cardiovascular Events, and Bleeding in Stable Coronary Artery Disease. *Am J Med.* 2017;130:720-30. doi: 10.1016/j.amjmed.2017.01.002.
18. Khan MF, Shamael I, Zaman Q, Mahmood A, Siddiqui M. Association of Anemia with Stroke Severity in Acute Ischemic Stroke Patients. *Cureus.* 2018;10:e2870. doi: 10.7759/cureus.2870.
 19. Yamashita Y, Morimoto T, Amano H, Takase T, Hiramori S, Kim K, et al. Influence of baseline anemia on long-term clinical outcomes in patients with venous thromboembolism: from the COMMAND VTE registry. *J Thromb Thrombolysis.* 2019;47:444-53. doi: 10.1007/s11239-018-1791-2.
 20. Harringa JB, Bracken RL, Nagle SK, Schiebler ML, Patterson BW, Svenson JE, et al. Anemia is not a risk factor for developing pulmonary embolism. *Am J Emerg Med.* 2017;35:146-9. doi: 10.1016/j.ajem.2016.09.068.
 21. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med.* 2020;180:934-43. doi: 10.1001/jamainternmed.2020.0994.
 22. Helms J, Severac F, Merdji H, Anglés-Cano E, Meziani F. Prothrombotic phenotype in COVID-19 severe patients. *Intensive Care Med.* 2020;46:1502-3. doi: 10.1007/s00134-020-06082-7.
 23. Thachil J, Tang N, Gando S, Falanga A, Cattaneo M, Levi M, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. *J Thromb Haemost.* 2020;18:1023-6. doi: 10.1111/jth.14810.
 24. Zhang DP, Mao XF, Wu TT, Chen Y, Hou XG, Yang Y, et al. The Fibrinogen-to-Albumin Ratio Is Associated With Outcomes in Patients With Coronary Artery Disease Who Underwent Percutaneous Coronary Intervention. *Clin Appl Thromb Hemost.* 2020;26:1076029620933008. doi: 10.1177/1076029620933008.
 25. Johnson DW, Jones GR, Mathew TH, Ludlow MJ, Chadban SJ, Usherwood T, et al. Chronic kidney disease and measurement of albuminuria or proteinuria: a position statement. *Med J Aust.* 2012;197:224-5. doi: 10.5694/mja11.11468.
 26. Folsom AR, Lutsey PL, Heckbert SR, Cushman M. Serum albumin and risk of venous thromboembolism. *Thromb Haemost.* 2010;104(1):100-4. doi: 10.1160/th09-12-0856.
 27. Omar HR, Mirsaeidi M, Rashad R, Hassaballa H, Enten G, Helal E, et al. Association of Serum Albumin and Severity of Pulmonary Embolism. *Medicina (Kaunas).* 2020;56:26. doi: 10.3390/medicina56010026
 28. Kunutsor SK, Seidu S, Katechia DT, Laukkanen JA. Inverse association between serum albumin and future risk of venous thromboembolism: interrelationship with high sensitivity C-reactive protein. *Ann Med.* 2018;50:240-8. doi: 10.1080/07853890.2018.1441537.
 29. Tian M, Li Y, Wang X, Tian X, Pei LL, Wang X, et al. The Hemoglobin, Albumin, Lymphocyte, and Platelet (HALP) Score Is Associated With Poor Outcome of Acute Ischemic Stroke. *Front Neurol.* 2020;11:610318. doi: 10.3389/fneur.2020.610318.
 30. Mirsaeidi M, Omar HR, Sweiss N. Hypoalbuminemia is related to inflammation rather than malnutrition in sarcoidosis. *Eur J Intern Med.* 2018;53:e14-e6. doi: 10.1016/j.ejim.2018.04.016.
 31. Lam FW, Cruz MA, Leung HC, Parikh KS, Smith CW, Rumbaut RE. Histone induced platelet aggregation is inhibited by normal albumin. *Thromb Res.* 2013;132:69-76. doi: 10.1016/j.thromres.2013.04.018.
 32. 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. *Lancet Haematol.* 2020;7:e362-e3. doi: 10.1016/s2352-3026(20)30109-5.

Copyright © 2022 The Author(s); Published by Nickan Research Institute. This is an open-access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.