Blood Coagulation Parameters in Patients with Severe COVID-19

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Short Report

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Abstract

Background: Infection with coronavirus disease 2019 (COVID-19) could be complicated with coagulopathy and high risk of thromboembolic events.

Methods: Coagulation parameters were analyzed in 74 confirmed severe COVID-19 patients admitted to the intensive care unit of Farabi University Hospital, Kermanshah, Western Iran.

Results: Around 42% of patients had abnormal prothrombin time (PT) and international normalized ratio (INR). The rate of abnormal coagulation parameters in the mean age 76.6±7.7 and 46.6±10.3 years were 62 and 38%, respectively. Patients with comorbidities had significantly longer PT and higher INR that increased the rate of mortality to around 77% in these individuals. The abnormal pattern of coagulation parameters was highly associated with comorbidities and poor prognosis.

Conclusions: Our study demonstrated abnormal coagulation parameters and a high rate of coagulopathy in hospitalized patients with COVID-19 that was associated with age, comorbidities and mortality which should be considered in management of these patients.

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that is responsible for coronavirus disease 2019 (COVID-19) resulted in systemic inflammatory response and imbalance between homeostatic mechanisms of procoagulant and anticoagulant and is complicated with thrombotic complications [1]. Around 40% of hospitalized patients with COVID-19 are at high risk for development of venous thromboembolism (VTE) [2]. Among non-ICU COVID-19 French patients receiving thromboprophylaxis the incidence of VTE and pulmonary embolisms were 22.5 and 10%, respectively [3]. Abnormal coagulation factors in Chinese patients with COVID-19 were associated with poor prognosis [4]. In the present study coagulation parameters among consecutive severe intensive care unit (ICU) admitted patients from Kermanshah, Western Iran is reported and are compared between survivors and non-survivors.

Methods

We studied 74 consecutive patients with confirmed COVID-19 admitted to the ICU of Farabi Hospital of Kermanshah University of Medical Sciences as the second referral center of COVID-19 in Kermanshah Province of Iran from March 7 to May 12, 2020. Diagnosis of COVID-19 was made according to the chest CT scan and/or real time PCR. The samples for coagulation tests were collected at hospital admission. The prothrombin time (PT), aPTT, fibrinogen, and international normalized ratio (INR) were measured using Coatron M2 coagulation analyzer (TECO Medical Instruments, Germany). D-dimer was measured by a Siemens device (Germany) using *chemiluminescence* method.

A two-tailed student's t test and ANOVA were used to compare quantitative data between survivors and non-survivors. Using the χ^2 test the categorical variables were compared between groups. The P-value <0.05 was considered as statistically significant. The SPSS (SPSS Inc., Chicago, IL, USA) statistical software package version 16.0 was used for statistical analysis.

Results

Studied patients consisted of 74 severely affected individuals with COVID-19 (mean age 65.1±17.1 years) including 44 males and 30 females. Twenty-six patients (35.1%) required tracheal intubation (64.1% non-survivors and 2.9% survivors, p<0.001). Fifty-one out of 74 patients (around 69%) had comorbidities (hypertension, diabetes mellitus, coronary artery disease, cancer, renal transplantation, chronic obstructive pulmonary disease, and osteomyelitis). There were 46 patients (around 62%) aged 65 to 90 years (76.6±7.7 years) with the PT 16.2±4.6 sec and the INR 1.52±0.74 compared to 28 patients (38%) below 65 years with the mean age of 46.6±10.3 years and the PT level of 14.6±1.8 sec (p=0.051) and the INR 1.26±0.26 (p=0.052).

Table 1 indicates the levels of coagulation factors measured at admission in studied patients. Lower level of platelet (PLT) count was detected among non-survivors compared to survivors, also patients with comorbidities had lower PLT count than patients without comorbidities (Table 1). Two (one man and a woman, 70 and 68 years old, respectively) out of three patients with PLT count $\leq 36 \times 10^3/\mu L$ died. Around 30% (22 individuals) had PLT<$150 \times 10^3/\mu L$.

The PT was 15.6±3.9 (12.5-35.4) sec in all patients. The PT was longer in non-survivors than survivors (Table 1). Around 42% of the patients (31 individuals) had abnormal PT and INR (>14.5 sec, and >1.2, respectively). There were 5 patients with PT 27-35 sec (INR 1.7-5.1) that all except one died. The only case with critical value of INR 5.1 was a 76 years female with PT 35.4 sec, and D-dimer 15 µg/ml required tracheal intubation who died after 6 days hospitalization. Also, a significantly higher PT was observed in patients with comorbidities compared to those without comorbidities (Table 1). Comparing patients with concomitant presence of two comorbidities with those lack of comorbidity indicated the PT level of 17.5±6.1 vs.14.4±1.64 sec (p=0.045) and INR 1.8±1.1 vs.1.22±0.21 (p=0.03). The mean level of D-dimer available from 16 severe patients with COVID-19 was 5.1±7.3 (0.1-25) µg/ml that in non-survivors was higher than survivors (Table 1). The aPTT and fibrinogen levels in all patients were 39.1±9.2 (25-68) sec and 3.37±1.80 (135-751) g/L, respectively (Table 1). The abnormal pattern of coagulation parameters (lower PLT, higher PT, aPTT, INR, and D-dimer) observed in 30 out of 39 patients (around 77%) with comorbidities who died compared to 9 non-survived patients without comorbidities.

Discussion

Thrombocytopenia was detected in around 30% of patients with lower PLT count in older patients, patients with comorbidities and in non-survivors. The longer PT and higher INR was found in 42% of patients especially in patients older than 65 years with increased comorbidities and mortality, also the

PT>27 sec was fatal. Thrombocytopenia and abnormal coagulation parameters (PT, INR, D-dimer) could be considered as important indicators of severe COVID-19 that is associated with mortality. High levels of D-dimer have been associated with 28-day mortality among patients with infection or sepsis. The systemic pro-inflammatory cytokines contribute to plaque rupture through local inflammation, procoagulant factors induction, and haemodynamic alterations are mechanisms which are involved in predisposition to ischaemia and thrombosis [5]. The most hemostatic abnormalities in patients with COVID-19, requiring more mechanical ventilation, ICU admission, or death, were mild thrombocytopenia and increased levels of D-dimer indicating the presence of some forms of coagulopathy with increased risk of thrombotic events [2]. Using the cut-off value of D-dimer 1.5μg/mL for prediction of VTE 8 out of 16 (50%) our patients had VTE. In a report from 81 severe COVID-19 Chinese admitted ICU there were 20 (25%) with VTE [6].

No prolonged aPTT (more than 70 sec) was observed in our patients that might explain the absence of disseminated intravascular coagulation (DIC) bleeding in patients. In some patients with COVID-19 there was an associated coagulopathy but even in those patients with DIC, bleeding was not manifested since these abnormalities could be the result of the profound inflammatory response that did not result in bleeding [7]. In Caucasian patients with COVID-19 on low molecular weight heparins (LMWHs) thrombo-prophylaxis the overt DIC rarely developed and in rare COVID-19 patients with DIC it was almost appeared in late stage disease. A term of pulmonary intravascular coagulopathy was suggested for bilateral pulmonary inflammation observed in COVID-19 patients to distinct from DIC [8].

Based on recommendation of the international society on thrombosis and haemostasis, in patients with markedly increased D-dimer (3-4 folds increased), hospital admission should be considered even in the absence of other symptoms and all hospitalized COVID-19 patients with this elevation should receive thromboprophylaxis, or full therapeutic-intensity anticoagulation [9]. The prophylactic daily LMWHs, or twice daily subcutaneous unfractionated heparin has been proposed by the WHO interim guidance [2] except for those have active bleeding or PLT count < 25×10^9/L [10]. Severe hospitalized COVID-19 patients from Kermanshah received LMWHs (enoxaparin 40 mg/day for body mass index (BMI) < 30 kg/m^2, 60 mg/day for BMI 30-40 kg/m^2 and 40 mg twice daily in patients with BMI > 40 kg/m^2) in addition to antiviral therapy after hospitalization.

Conclusion

Our report indicated the age higher than 65 years was associated with high rate of comorbidities, abnormal level of coagulation parameters and poor prognosis. Also, we detected a high rate of coagulopathy (around 42%) in severely affected patients with COVID-19. Further, severe COVID-19 patients had low levels of PLT, high PT and INR that were associated with poor prognosis. The abnormal pattern of coagulation parameters was highly associated with comorbidities and mortality. The coagulation tests such as PLT, PT, PTT, D-dimer, and fibrinogen should be performed at hospital admission in patients suspected or confirmed to have COVID-19 infection to provide useful prognostic

information. These patients should be treated with pharmacologic VTE prophylaxis unless there were specific contraindications.

Declarations

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Author contributions

B. Sayad provided clinical data and revised the manuscript. Z. Rahimi processed statistical data and drafted the manuscript.

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Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

This retrospective study involved human participants was in accordance with the ethical standards of the institutional and national research committee and was in accordance with the principles of the Declaration of Helsinki II.

Informed consent was obtained from patients. The Ethics Committee of Kermanshah University of Medical Sciences approved the study (Ethics code: IR.KUMS.REC.1399.049) and the study was in accordance with the principles of the Declaration of Helsinki II in the manuscript.

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Tables

Table 1. Coagulation parameters in patients with severe COVID-19

Variable	ALL patients (n=74)	Survivors (n=35)	Non-survivors (n=39)	Patients without comorbidities (n=23)	Patients with comorbidities (n=51)
		Mean±SD	Mean±SD, P	Mean±SD	Mean±SD, P
Age (years)	65.1±17.1 (23-90)	63.6±18.7	66.5±15.5, 0.48	55.2±16	69.4±15.8, 0.001
Sex (male/female)	44/30	21/14 (47.7/46.7%)	23/16 (52.3/53.3%)	17/6 (38.6/20%)	27/24 (61.4/80%)
PLT counts ($\times 10^3/\mu L$)	207.8±111.5 (13.5-707)	223.9±124.1	193±9.8, 0.24	218.7±117.7	186.9±97.3, 0.22
PT (sec)	15.6±3.9 (12.5-35.4)	15.1±2.8	16±4.6, 0.29	14.4±1.6	16.1±4.4, 0.024
aPTT (sec)	39.1±9.2 (25-68)	39±10.5	39.1±8.2, 0.98	38.2±11.2	39.4±8.5, 0.68
INR	1.42±0.62 (1-5.1)	1.4±0.47	1.5±0.72, 0.39	1.22±0.22	1.50±0.7, 0.02
D-dimer (µg/ml)	5.1±7.3 (0.1-25) n=16	4.8±9.9	5.3±5.9, 0.92	5.1±7	5.1±7.6, 0.99
Fibrinogen (g/L)	3.37±1.80 (135-751) n=16	3.38±2.39	3.36±1.28, 0.98	2.69	3.45±1.9, 0.71

PLT: platelet, PT: prothrombin time, aPTT: activated partial thromboplastin time, INR: international normalized ratio