Original Research Article

Prevalence and impact of coagulation dysfunction in patients with COVID-19 in Yazd

Zohreh AkhoundiMeybodi [1], Maryam Dehghan [2], Seyed Alireza Mousavi [1], Mahmood Vakili [3], Noor Foroghi nasab [4], Seyed Hossein Shahcheraghi [1], Mahdie Hamidfar [1], Faezehsadat Heidari [1], Bijan jafarnia [1], Kazem Ansari [5,*]

[1]Infectious Diseases Research Center, Shahid Sadoughi Hospital, Shahid Sadoughi University of Medical Sciences, Yazd, Iran; [2]Department of Internal Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran; [3]Department of Community Medicine, School of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran; [4]Shahid Sadoughi University of Medical Sciences, Yazd, Iran; [5]Nano-Biotech Foresight Company Biotechnology Campus, Yazd Stem Cells and Regenerative Medicine Institute, Yazd, Iran

***Corresponding author:** Kazem Ansari, Nano-Biotech Foresight Company Biotechnology Campus, Yazd Stem Cells and Regenerative Medicine Institute, Yazd, Iran. E- mail: kazemansari.1372@gmail.com*

DOI: 10.22034/HBB.2022.11

Received: February 14, 2022; **Accepted:** May 9, 2022

ABSTRACT

Covid-19 patients have coagulation complications resulting in poor prognosis. Therefore, this study aimed to investigate the prevalence of coagulation disorders in patients with Covid-19 admitted to Shahid Sadoughi Hospital in Yazd. This study was a cross-sectional study that all patients admitted with a diagnosis of Covid-19 from the beginning of February 2020 to the end of April 2020 were examined for the frequency of coagulation dysfunctions. A total of 441 patients with Covid-19 were included in the study with a mean age of 55.4 years that 47.8 %, 25.6 % and 6.8 % had impaired Prothrombin Time (PT), Partial Thromboplastin Time (PTT) and International Normalized Ratio (INR), respectively.

***Keywords*:** Covid-19, coagulation, Yazd

INTRODUCTION

In late December 2019, an outbreak of mysterious disease known as 2019 novel coronavirus disease (COVID-19) occurred in Wuhan, Hubei, China and quickly became a worldwide epidemic. [1] SARS-CoV- 2 is single-stranded RNA beta-

coronavirus, positive-sense and enveloped viruse [2]. In the early stages of infection, clinical characteristics is associated with nonspecific symptoms such as fatigue, fever and dry cough [3]. The most common clinical manifestation of COVID-19 patients include fever, cough, Fatigue, dyspnea [4]. World Health Organization reported that more than 188 million people infected by covid-19 and more than 4 million have died by July 15th, 2021 [5].

Previous studies showed that SARS-CoV-1 and MERS-CoV infections caused coagulation disorders and hematologic manifestations [6]. COVID-19 can make patients more susceptible to venous and arterial thrombotic disease due to excessive inflammation, endothelial dysfunction and platelet activation [7]. Previous studies reported that abnormal coagulation parameters and coagulopathy as the most important biomarkers for poor prognosis in patients with COVID19 [8-10]. The purpose of this study was to evaluate the prevalence of coagulation dysfunction in covid-19 patients in Yazd.

MATERIALS AND METHODS

We studied 441 consecutive patients with RT-PCR confirmed COVID-19 admitted to Shahid Sadoughi Hospital, being the first referral center of COVID-19 in Yazd Province, from February to March 2020. Diagnosis of COVID-19 was made according to the Real-time PCR. Patients underwent routine drug therapy for covid-19. The samples for coagulation tests were collected from patients at hospital admission. The coagulation parameters include the Prothrombin Time (PT), activated Partial Thromboplastin Time (aPTT) and International Normalized Ratio (INR) values which were measured using Coatron M2 coagulation analyzer (TECO Medical Instruments, Germany). Written informed consent was obtained from every participant.

Statistical methods

Statistical analysis was performed using SPSS statistical software package version 22 (SPSS Inc., Chicago, USA). Categorical variables were compared using $\chi 2$ test, and quantitative variables were compared using student's t-test and ANOVA. Univariate analyses and multivariate analyses were performed. The quantitative data were presented as mean ± Standard Deviation (SD) and p value <0.05 was considered statistically significant.

Ethics approval

The ethics committee of Shahid Sadoughi University of Medical Sciences approved the study (Ethics code: IR.SSU.REC.1400.141) and the study was

in accordance with the principles of the declaration of Helsinki II.

RESULTS

A total of the 441 hospitalized SARS-Cov-2 patients consisted of 220 males and 221 females with median age of 55.4 ±2.9 (range18-98 years) and 131 (27.9 %) were died in the hospital. The laboratory findings are also shown in Table 2. The most common coagulation finding was prolonged prothrombin time. As shown in Table 3 there was statistically significant relationship between coagulation parameters (PT, PTT and INR) and age and these abnormal coagulation parameters were more in older patients. As shown in Table 4 there was statistically significant relationship between coagulation parameters (PT, PTT and INR) and gender and these abnormal coagulation parameters were more common in men.

Table 1. Demographic characteristics of the participants

Gender	male	220 (49.9 %)
	female	221 (50.1 %)
Severity of disease	Mild	180 (40.8 %)
	Moderate	81 (18.4 %)
	severe	180 (40.8 %)
Mortality	survivors	310 (70.3 %)
	non-survivors	131 (29.7)

Table2. Laboratory findings on admission of COVID-19 patients

Parameters	**Frequency (%)**
PT (s; normal range 9.00-13.00)	230 (52.2)
Increased	211 (47.8)
APTT (s; normal range 20.00-40.00)	328 (74.4)
Increased	113 (25.6)
INR (normal range 0.70-1.30)	411 (93.2)
Increased	30 (6.8)

Table3. Laboratory findings on admission and age of COVID-19 patients

Parameters	Age(Mean±SD)	p-value
PT (s; normal range 9.00-13.00)	47.14±20.13	0.011
Increased	64.49±17.77	
APTT (s; normal range 20.00-40.00)	51.95±20.63	0.002
Increased	65.60±18.27	
INR (normal range 0.70-1.30)	54.41±20.64	0.035
Increased	69.63±19.60	

Table4. Laboratory findings on admission and gender of COVID-19 patients

Parameters	Male	Female	p-value
PT (s; normal range 9.00-13.00)	102	128	0.022
Increased	118	93	
APTT (s; normal range 20.00-40.00)	154	174	0.049
Increased	66	47	
INR (normal range 0.70-1.30)	198	213	0.013
Increased			

The results of the study showed that there was a significant relationship between all three coagulation markers and disease severity (Table5).

DISCUSSION

This study investigated of coagulation dysfunction in patients with Covid-19 and its relationship with disease severity, gender and age. The results of this study showed that the mortality rate of Covid-19 in hospitalized patients was 27.9 %. A study by Martínez *et al.* reported that the mortality rate of hospitalized patients was 30.1 % [11]. In the Wang et al. study mortality rate of hospitalized patients was 38.9 % [12]. In a study conducted by Nasrollahzadeh *et al.* in Tehran, the mortality rate of hospitalized patients was reported to be 21.9 % [13].

In our study, patients with prolonged PT, PTT, and INR had higher mortality rates. Long et al. reported in their study that PT and D-dimer levels were increased in a high percentage of patients who died. They concluded that coagulation dysfunctions were more common in severe patients and D-dimer and PT can be used as significant indicators in prognosis of COVID-19 patients [14].

Findings from the research of Luo et al. showed that PT and INR levels were significantly higher in dead Covid-19 patients than in the survived Covid-19 patients, whereas in contrast to our study, the PTT levels were higher in the survived patients. They also showed that PT levels in patients with Covid-19 can independently predict mortality in patients [15].

In the Tang *et al.* study, overall mortality was 11.5 %, which was found significantly higher D-dimer levels and longer levels of Fibrin Degradation Product (FDP), PT, and PTT in dead patients compared with survivors at admission [16].

Baranovskii et al. revealed that PT was significantly longer in patients who transferred to the ICU compared with stable patients admitted to the ward, while there was no statistically significant difference in fibrinogen and INR at admission among COVID-19 patients who transferred to the ICU and stable COVID-19 patients [17].

Table5. Laboratory findings on admission and severity of COVID-19 patients

Parameters	Mild	Moderate	Severe	p-value
PT (s; normal range 9.00-13.00)	160	66	102	0<001
Increased	20	15	78	
APTT (s; normal range 20.00-40.00)	160	66	102	0<001
Increased	20	15	78	
INR (normal range 0.70-1.30)	180	79	152	0<001
Increased	0	2	28	

In two different studies by Huang and Tang, contrary to our study, reported that the aPTT in severe and stable COVID-19 patients was similar and had no significant association with disease severity or mortality [16,18]. A study by Chen et al. showed that aPTT was normal in most patients with COVID-19, and that only 6 % of patients develop prolonged aPTT [19]. In a systematic review and meta-analysis Lin and colleagues reported that the coagulation dysfunction (high d-dimer, low platelet and fibrinogen upon admission) is closely related to the severity of COVID-19 patients and may serve as risk factor for increased severity of the disease [20].

The cause of these coagulation disorders, especially in critically ill patients, is that by the entry of SARS-CoV-2 through the Angiotensin 2 Converting receptor (ACE2) into the surface of mucosal epithelial cells, its Pathogen-related Molecular Pattern (PAMP). The system is quickly recognized by the immune system, and the immune response is activated to clear the virus. However, an overactive immune response

can trigger a cytokine storm. As a result, cytokine storms damage vascular endothelium, activate the coagulation system, and inhibit fibrinolytic and anticoagulant systems. Excessive thrombosis in the vascular system leads to Diffuse Intravascular Coagulation (DIC) and ultimately to microcirculation dysfunction and multiple organ dysfunction syndrome.

CONCLUSION

Coagulation dysfunction were more common in older patients, males and critically ill patients. Therefore, coagulation parameters (PT, PTT and INR) can be used to determine the prognosis of patients.

ACKNOWLEGEMENT

The authors would like to thank all the study participants. They are also grateful to the all staff for their support and cooperation.

REFERENCES

[1]. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*, 2020, 30183-85.

[2]. Adhikari B, Marasini BP, Rayamajhee B, Bhattarai BR, Lamichhane G, Khadayat K, Adhikari A, Khanal S, Parajuli N. Potential roles of medicinal plants for the treatment of viral diseases focusing on COVID-19: A review. *Phytother Res.* 2021; 35(3): 1298-1312.

[3]. Zu ZY, Jiang MD, Xu PP, Chen W, Ni QQ, Lu GM, Zhang LJ. Coronavirus disease 2019 (COVID-19): a perspective from China. *Radiology*. 2020; 296(2): 15-25.

[4]. Alimohamadi Y, Sepandi M, Taghdir M, Hosamirudsari H. Determine the most common clinical symptoms in COVID-19 patients: a systematic review and meta-analysis. *J Prev Med Hyg*. 2020; 61(3): 304.

[5]. Ribeiro MH, Silva RG, Larcher JH, Mariani VC, Coelho LD. Ensemble learning models coupled with urban mobility information applied to predict COVID-19 incidence cases. In modeling, control and drug development for COVID-19 outbreak prevention. *Springer, Cham.* 2022, 821-58.

[6]. Ng KH, Wu AK, Cheng VC, Tang BS, Chan CY, Yung CY, Luk SH, Lee TW, Chow L, Yuen KY. Pulmonary artery thrombosis in a patient with

severe acute respiratory syndrome. *Postgrad Med J.* 2005, 1; 81(956): 3.

[7]. Assiri A, Al-Tawfiq JA, Al-Rabeeah AA, Al-Rabiah FA, Al-Hajjar S, Al-Barrak A, Flemban H, Al-Nassir WN, Balkhy HH, Al-Hakeem RF, Makhdoom HQ. Epidemiological, demographic, and clinical characteristics of 47 cases of Middle East respiratory syndrome coronavirus disease from Saudi Arabia: a descriptive study. *Lancet Infect Dis.* 2013; 13(9): 752-61.

[8]. Al-Samkari H, Karp Leaf RS, Dzik WH, Carlson JC, Fogerty AE, Waheed A, Goodarzi K, Bendapudi PK, Bornikova L, Gupta S, Leaf DE. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. *Blood.* 2020; 136(4): 489-500.

[9]. Annunziata A, Imitazione P, Polistina GE, Lanza M, Coppola A, Fiorentino G. Pulmonary embolism in Covid-19: coagulation parameters, close monitoring to prevent?. *Turk. Thorac. J*. 2020; 21(4): 287.

[10]. Savioli F, Rocha LL. Coagulation profile in severe COVID-19 patients: what do we know so far*?.Rev Bras Ter Intensiva*. 2020; 32: 197-99.

[11]. Olivas-Martínez A, Cárdenas-Fragoso JL, Jiménez JV, Lozano-Cruz OA, Ortiz-Brizuela E, Tovar-Méndez VH, Medrano-Borromeo C, Martínez-Valenzuela A, Román-Montes CM, Martínez-Guerra B, González-Lara MF. In-hospital mortality from severe COVID-19 in a tertiary care center in Mexico City; causes of death, risk factors and the impact of hospital saturation. *Plos one*. 2021, 16(2): 245772.

[12]. Wang L, He WB, Yu XM, Hu DL, Jiang H. Prolonged prothrombin time at admission predicts poor clinical outcome in COVID-19 patients. *World J Clin Cases*. 2020; 8(19): 4370.

[13]. Nasrollahzadeh Sabet M, Khanalipour M, Gholami M, Sarli A, Rahimi Khorrami A, Esmaeilzadeh E. Prevalence, Clinical Manifestation and Mortality Rate in COVID-19 Patients With Underlying Diseases. *J Arak Uni Med Sci*. 2020; 23(5): 740-49.

[14]. Long H, Nie L, Xiang X, Li H, Zhang X, Fu X, Ren H, Liu W, Wang Q, Wu Q. D-dimer and prothrombin time are the significant indicators of severe COVID-19 and poor prognosis. *Biomed Res Int*. 2020.

[15]. Luo HC, You CY, Lu SW, Fu YQ. Characteristics of coagulation

alteration in patients with COVID-19. *Ann Hematol.* 2021; 100(1): 45-52.

[16]. 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): 844-47.

[17]. Baranovskii DS, Klabukov ID, Krasilnikova OA, Nikogosov DA, Polekhina NV, Baranovskaia DR, Laberko LA. Prolonged prothrombin time as an early prognostic indicator of severe acute respiratory distress syndrome in patients with COVID-19 related pneumonia. *Curr Med Res Opin.* 2021; 37(1): 21-25.

[18]. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The lancet.* 2020; 395(10223): 497-506.

[19]. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Yu T. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *The lancet.* 2020; 395(10223): 507-13.

[20]. Lin J, Yan H, Chen H, He C, Lin C, He H, Zhang S, Shi S, Lin K. COVID-19 and coagulation dysfunction in adults: A systematic review and meta-analysis. *J Med Virol*. 2021, 93(2): 934-44.