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Research Article

COVID-19 and Coagulation Profile: A Retrospective Case Control Study

Ahmed Mohammed Elnour Elkhalif[1, 3], Mohammed Abdul Wahid Almorish[2, *], Abozer Yousif Elderdery[4], Saud Nahar Alruwaili[5], Maryam Musleh Althobiti[6], Siddiqa Mohammed Abbas Hamza[7], Salma Elhadi Ibrahim Mekki[8], Dania Ahmed[9], Jeremy Mills[10]

[1]Department of Public Health, College of Health Sciences, Saudi Electronic University, Riyadh, Kingdom of Saudi Arabi

[2]Department of Hematology, Faculty of Medicine and Health Sciences, Sana'a University, Sana'a, Yemen

[3]Department of Haematology, Faculty of Medical Laboratory Sciences, University of El Imam El Mahdi, Kosti, Sudan

[4]Department of Clinical Laboratory Sciences, College of Applied Medical Sciences, Jouf University, Sakaka, Saudi Arabia

[5]Regional Laboratory, Ministry of Health, Sakaka Aljouf, Saudi Arabia

[6]Department of Clinical Laboratory Science, College of Applied Medical Science, Shaqra University, Shaqra, Saudi Arabia

[7]Department of Pathology, College of Medicine, Umm Alqura University, Algunfuda, Saudi Arabia

[8]Department of Physiology, College of Medicine, Umm Alqura University, Algunfuda, Saudi Arabia

[9]Hampshire Hospitals NHS Foundation Trust and Health Education, Winchester, UK

[10]School of Medicine, Pharmacy and Biomedical Sciences, University of Portsmouth, Portsmouth PO1 2DT, UK

Abstract

The COVID-19 virus can initiate a coagulation cascade leading to clot formation and disseminated intravascular coagulation (DIC), raising alarms among healthcare professionals about managing severe cases and underscoring the need for a comprehensive understanding of its mechanisms and therapeutic strategies. This study examines the coagulation parameters and D-Dimer levels in confirmed COVID-19 patients in contrast healthy controls. A retrospective case control study was conducted at the Riyadh Regional Laboratory Centre in Saudi Arabia, involving 384 confirmed COVID-19 patients and an equivalent control group of non-COVID-19 individuals matched for age, gender and nationality/ethnicity. Data on demographics and laboratory results were extracted from electronic medical records. A comparative examination of coagulation factors utilizing standard methodologies for D-Dimer, Prothrombin Time (PT), activated Partial Thromboplastin Time (APTT) and International Normalized Ratio (INR) levels was conducted between individuals diagnosed with nasopharyngeal swab samples by real time-polymerase chain reaction (RT-PCR) from COVID-19 patients and non-COVID-19 individuals. Our study indicated a significant increase in the mean values of PT, APTT and D-dimer in COVID-19 positive patients than non-COVID-19 individuals. Conversely, the mean values of INR were markedly reduced in COVID-19 positive patients compared to non-COVID-19 individuals. COVID-19 patients exhibit significant abnormalities in blood coagulation profile relative to non-COVID-19 individuals. The research indicates that elevated levels of D-Dimer, PT, and APTT may serve as indicators of disease severity and

*Corresponding author: m.almorish@su.edu.ye (Mohammed Abdul Wahid Almorish), almorish70@gmail.com (Mohammed Abdul Wahid Almorish)

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prognostic markers in COVID-19 patients.

Keywords

COVID-19, Coagulopathy, Activated Partial Thromboplastin Time, D-Dimer, Prothrombin Time

1. Introduction

COVID-19, a highly transmissible positive-strand RNA coronavirus identified in December 2019 in Wuhan, China, has led to over 236.8 million infections and more than 4.8 million fatalities globally as of October 8, 2021, severely disrupting human societies and the global economy [1-3]. COVID-19 was initially identified in the United Arab Emirates on January 29, 2020, subsequently spreading to other Gulf nations. Its detection in Saudi Arabia on March 2, 2020, prompted the cessation of Umrah and various travel activities [4]. From March 2 to June 7, Mohammad H and colleagues documented an average of 1039 daily cases in Saudi Arabia, with a 71.4% recovery rate and a 6.4% decline in mortality. Furthermore, the virus exhibited a higher prevalence among males and adults compared to other demographic groups [5]. The disease spread rapidly, with 1.2% of Al-kharj City's population infected by August 2020 [6]. As a result, the quick transmission of COVID-19 led to numerous health complications, particularly anemia and thrombocytopenia [7, 8].

The virus's interaction with the angiotensin-converting enzyme 2 receptor enables it to impact multiple bodily systems, inducing lung fibrosis that compromises oxygen transport and triggers a cytokine storm, among other issues [9]. The severity of COVID-19 pneumonia correlates with factors such as age, smoking, respiratory failure, and chronic obstructive pulmonary disease [10]. Patients with severe COVID-19 and preexisting chronic conditions face increased risks of pneumonia and acute respiratory distress syndrome (ARDS), leading to elevated mortality rates, indicating a multisystem disease. The predominant symptoms of COVID-19 include fever, cough, dyspnea, wheezing, and increased mucus production [11]. A notable association exists between severe COVID-19 and coagulopathy, with many patients exhibiting coagulation abnormalities similar to other systemic coagulopathies, underscoring the importance of assessing coagulopathy for predicting adverse outcomes [12].

The present investigation examines the diagnostic relevance of D-dimer, PT, PTT, and INR in evaluating COVID-19, emphasizing the nascent role of D-dimer in this context while underscoring adherence to established protocols; furthermore, procalcitonin, C-reactive protein and ferritin emerge as promising prognostic biomarkers for severity assessment, with fluctuations in D-dimer levels potentially aiding in the identification of co-infections and comorbidities, thereby facilitating personalized clinical management and enhancing recovery rates along with reducing mortality [13].

The current study evaluates the diagnostic significance of D-dimer, PT, PTT, and INR in COVID-19 assessment, highlighting D-dimer's emerging importance while adhering to established guidelines; additionally, procalcitonin, C-reactive protein, and ferritin are identified as potential prognostic biomarkers for assessing severity, with changes in D-dimer levels possibly aiding in recognizing co-infections and comorbidities [14], thus promoting tailored clinical management, improving recovery rates, and decreasing mortality.

2. Materials and Methods

2.1. Study Design

A retrospective case control study was conducted at the Riyadh Regional Laboratory Centre in Saudi Arabia from October to November 2020, focusing on hospitalized patients with confirmed COVID-19 diagnoses at King Saud Medical City to compare coagulation parameters, specifically D-Dimer, PT, APTT, and INR, between COVID-19-infected and non-COVID-19 individuals.

2.2. Sample Size and Collection

A total of 384 anonymized COVID-19 patient files were randomly selected from clinical databases to analyse PT, INR, APTT, and D-Dimer. An equivalent group of 384 non-COVID-19 participants, matched by age, gender, and nationality, was also randomly selected as a control group. COVID-19 diagnosis was confirmed through RT-PCR-SARS-CoV-2 assay using extracted nasopharyngeal swab samples [15].

2.3. Exclusion Criteria

Hospitalized COVID-19 positive and negative patients were recruited based on specific inclusion and exclusion criteria. Individuals with significant coagulation-affecting diseases, cardiovascular conditions, liver diseases, alcoholism history and prolonged use of Heparin, aspirin, or Warfarin were excluded.

2.4. Ethical Approval

Ethical approval was secured in accordance with the Helsinki Declaration prior to data collection, following review by the Institutional Review Board at Saudi Electronic University, assigned SEUREC-CHS20113-REC Number.

2.5. Statistical Analysis

Raw data were processed and analyzed using SPSS Software version-26 (IBM Corp., Armonk, USA). Variables were expressed as percentages, frequencies, or means and standard deviations (SD), followed by normality tests and t-tests for group comparisons. Statistical significance was established at p-value is considered significant <0.05.

3. Results

Our findings reveal that 207 patients (53.9%) are males and 177 (46.1%) females across both study and control groups, with ages ranging from 18 to 90 years. The mean age was 48.44±18.8 years for the COVID-19 patients and 48.93±18.9 years for the non-COVID-19 individuals. The majority of samples were from Saudi citizens (252, 65.6%) followed by over 20 other nationalities (132, 34.4%) residing in KSA, as shown in Table 1. The study indicates a significant rise in D-dimer levels (4.94±1.04µg/ml vs. 0.23µg/ml ±0.03), ($p < 0.001$), a significant prolonged in PT mean values (13.92±3.64s vs. 13.31±4.27s) ($p < 0.035$), and APTT mean values (35.08±10.32s vs. 33.16±8.71s) ($p < 0.006$) in COVID-19 patients relative to non-COVID-19 individuals. Conversely, the INR mean values were statistically lower in COVID-19 positive patients compared to their negative counterparts (1.13±2.4 vs. 1.21±8.71) ($p < 0.003$). Table 2

Table 1. *Socio-demographic characteristics of COVID-19 patients and controls.*

Variables	COVID-19 patients (N=384) N (%)	Controls (N=384) N (%)
Gender		
Males	207 (53.9)	207 (53.9)
Females	177 (46.1)	177 (46.1)
Age (18-90Yrs)		
Mean ± SD	48.44±18.8	48.93±18.9
Nationality		
Saudi	252 (65.6)	252(65.6)
Non-Saudi	132 (34.4)	132 (34.4)

Key: SD= Standard Deviation; other nationalities include Palestinian, Nepali, Nigerian, Eritrean, Iraqi, Jordanian, Afghani, Ghanaian, Indonesian, Tunisian, New Guinea, and Kenyan.

Table 2. *Coagulation profile of Covid-19 patients versus controls.*

Parameters	Independent variables	Mean (± SD)	*P*-value
APTT (s)	COVID-19 patients	35.08 (10.3)	< 0.006*
	Non-COVID-19 control	33.2 (8.7)	
PT (s)	COVID-19 patients	13.9 (3.6)	< 0.035*
	Non-COVID-19 control	13.3 (4.3)	
INR	COVID-19 patients	1.13 (2.4)	< 0.003*
D-Dimer (µg/ml)	Non-COVID-19 control	1.21 (8.7)	< 0.001*
	COVID-19 patients	4.94 (1.04)	

Parameters	Independent variables	Mean (± SD)	*P*-value
	Non-COVID-19 control	0.23 (0.03)	

*Significance at the level p ≤0.05, (s) seconds

4. Discussion

COVID-19, a virulent pathogen with extensive pathophysiological implications, can lead to significant organ damage in patients, particularly through the development of ARDS characterized by widespread alveolar injury and hyaline membrane formation [16]. Immuno-thromboinflammation significantly impacts various stages of haemostasis and fibrinolysis in COVID-19 patients, characterized by elevated von Willebrand factor and reduced ADAMTS13 levels [3, 4]. This condition leads to enhanced platelet activity and formation of platelet-thrombi, while transitioning from a hypercoagulable to a hypocoagulable state as coagulation factors diminish due to coagulopathy and liver impairment [5, 6]. Additionally, COVID-19 alters fibrinolysis, initially causing hypo fibrinolysis that evolves to hyperfibrinolysis as the disease progresses, influenced by inflammatory mediators and the dynamics of plasminogen activation [11].

The current research demonstrates a marked elevation of D-dimer concentrations in patients with COVID-19 compared to those without the infection. D-dimer, a byproduct of fibrin degradation by plasmin, indicates clot breakdown. Significant increases in D-dimer levels correlate with poor clinical outcomes and can serve as a thrombosis identification parameter [17, 18]. Previous studies indicate a connection between abnormal coagulation parameters and heightened thromboembolic risk in severe COVID-19 cases [19, 20]. Consequently, regular monitoring and timely identification of coagulation abnormalities are vital for comprehending disease progression and mitigating thrombotic complications to enhance clinical outcomes [21, 22]. Effective COVID-19 management relies on stratifying disease pathophysiology and administering suitable therapies [23, 24]. Thus, the diagnostic application of coagulation markers could aid in assessing COVID-19 severity and improving disease management. Inflammatory responses to infections may elevate D-dimer levels in COVID-19 patients, resulting in endothelial dysfunction that promotes thrombin generation and hypoxic events [25, 26]. Early in COVID-19 infection, studies consistently report increased D-dimer and fibrinogen levels [27-29]. Other studies have established a correlation between elevated D-dimer levels and the severity of COVID-19, implying an increased risk for thrombotic cardiovascular complications such as blood clot formation [1, 16, 30, 31]. These findings suggest that monitoring D-dimer alongside other coagulation markers from the onset of illness can enhance medical management, particularly given the association of heightened levels with severe cases and mortality rates [28, 32]. Hence, the utilization of coagulation markers, particularly D-dimer levels present a promising avenue for enhancing the diagnostic assessment of COVID-19 severity. The intricate relationship between inflammatory responses and coagulation pathways underscores the potential for these markers to not only reflect the severity of the disease but also inform therapeutic strategies.

The present research indicates a significant elevation in PT and APTT mean values in COVID-19 patients relative to non-COVID-19 individuals, whereas INR mean values were found to be statistically reduced in those testing positive for COVID-19 compared to their negative counterparts. The observed increase in coagulation parameters corresponds with our results [1, 33]. PT and PTT are vital coagulation tests for detecting coagulation abnormalities, facilitating DIC identification, and correlating with clinical outcomes. Additionally, prothrombin, a serine protease, converts fibrinogen to fibrin and its overproduction is associated with heightened plasma thrombin, triggering the coagulation cascade and thrombosis [34]. An analysis of 201 hospitalized patients in China found that prolonged PT at admission correlated with ARDS development. When compared to non-COVID -19, COVID-19 patients demonstrate elevated PT, antithrombin, fibrinogen, and platelet counts, alongside reduced APTT and D-dimer levels [35, 36]. Prior study have noted mild PT/INR prolongation and slightly decreased APTT levels, with elevated fibrinogen and D-dimer frequently seen in severe COVID-19 cases [1]. A study by Elieh and their colleagues indicated that D-dimer, fibrinogen, PT, APTT, protein S, fibrin degradation products and protein Care prognostic indicators for disease severity, with their efficacy determined by p-values. Disruptions in proteins C and S, which regulate the activation of factors V and VIII, may compromise coagulation homeostasis [37]. These findings underscore the necessity for rigorous assessment of coagulation parameters in COVID-19 patients, potentially influencing management and therapeutic approaches. Additional investigation is required to clarify the mechanisms behind these alterations and their possible effects on patient outcomes.

Limitations of the study

This retrospective case control study possesses significant limitations. The lack of real-time patient observation in this retrospective design may lead to incomplete data representation. Variability in laboratory assessment data across patient files may reflect clinical relevance and severity based on specific clinical features. Critical COVID-19 reports were

absent in some files, thereby diminishing the reliability of individual evaluations. Additionally, there were instances where patient medical and prescription histories were not accessible. Nonetheless, we advocate for randomized clinical studies to ascertain the optimal dosage and regimen of thromboprophylaxis for COVID-19 patients.

5. Conclusion

A significant correlation and disparity in coagulation and fibrinolysis markers (D-Dimer, PT, APTT, and INR) were identified between COVID-19 and non-COVID-19 individuals, highlighting the abnormal coagulation profiles in those infected individuals. Consequently, early detection is crucial for recognizing at-risk individuals and mitigating complications, thereby making anticoagulant therapies essential for preventing thrombotic issues in early-stage COVID-19 infection, and enhancing overall clinical outcomes.

Abbreviations

APTT	Activated Partial Thromboplastin Time
ARDS	Acute respiratory distress syndrome
DIC	Disseminated intravascular coagulation
INR	International Normalized Ratio
PT	Prothrombin Time
RT-PCR	Real time- polymerase chain reaction

Data Availability Statement

The datasets utilized and examined in the present study can be requested from the corresponding author.

Conflicts of Interest

The authors declare no conflicts of interest.

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