Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jptcp.v30i1.5290

ASSOCIATION OF COAGULATION DYSFUNCTION WITH CARDIAC INJURY IN HOSPITALIZED PATIENTS WITH COVID-19

Muizz Zahoor[1], Muhammad Shoaib[2], Saiqa Zahoor[3*], Gul Rukh[4], Hafsa Tariq[5], Hamid Mahabat Khan[6]

[1]PG Trainee, Department of Cardiology, MTI-Hayatabad Medical Complex, Peshawar, Pakistan
[2]PG Trainee, Department of Haematology, MTI-Hayatabad Medical Complex, Peshawar, Pakistan
[3*]Associate Professor, Department of Haematology, MTI-Hayatabad Medical Complex, Peshawar, Pakistan
[4]PG Trainee, Department of Haematology, MTI-Hayatabad Medical Complex, Peshawar, Pakistan
[5]PG Trainee, Department of Haematology, Pak International Medical College, Peshawar, Pakistan
[6]PG Trainee, Department of Haematology, MTI-Hayatabad Medical Complex, Peshawar, Pakistan

***Corresponding Author:** Saiqa Zahoor
*Associate Professor, Department of Haematology, MTI-Hayatabad Medical Complex, Peshawar, Pakistan, Email: saiqazahoor@hotmail.com

Abstract:

Objective: To determine the association of coagulation dysfunction with cardiac injury in hospitalized patients with COVID-19.

Study Design: Descriptive Cross Sectional.

Place and Duration of Study: Department of Hematology, MTI-HayatabadMedical Complex, Peshawar, from Jun 2021 to Dec 2021.

Methodology: A total of 103 patients hospitalized for COVID-19 were included in this study. The sample size was calculated by WHO Sample Size calculator with 7.20% proportion of cardiac injury in hospitalized COVID-19 patients, 5% margin of error and 5% significance level. Cardiac and coagulation biomarkers were recorded at the time of admission and later during hospitalization. To establish association between coagulation dysfunction and cardiac injury, spearman correlation coefficient was used.

Results: Mean age of patients was 57.6±12.36 years. Mean d-dimer was 2.022±2.84 ug/mL, mean fibrin levels were 34.27±54.68 mg/dL and mean fibrinogen was 2.51±1.04 g/L, mean hsTn1 was 5.88±6.51 pg/mL, mean myohemoglobin was 65.49±52.2 ng/mL and mean CK-MB was 16.76±6.67 U/L. Cardiac injury was recorded in 23 (22.3%) patients hospitalized due to COVID-19.

Conclusion: This study demonstrated a significant association of coagulation dysfunction with the development of cardiac injury as markers of coagulation function were found significantly synchronized with the dynamic progression of cardiac biomarkers.

Keywords: COVID-19, Cardiac Injury, Coagulation Dysfunction

INTRODUCTION:

Patients with COVID-19 typically exhibit abnormal coagulation. In individuals with severe COVID-19, fulminant thrombotic problems appear as crucial issues. Coronavirus infection 2019 (COVID-19) has been linked to cardiac damage, which can have fatal consequences. [1,2] According to the World Health Organization, cardiovascular disease is responsible for 12 million deaths annually.[3] Both arterial and venous thrombosis are made more likely because of the effects on the blood's hemostatic system, vasculature, and flow dynamics. The major cause of heart disease is platelet activation and aggregation, which increase the risk of cardioembolic stroke and death by contributing to the production of arterial thrombi and venous thromboembolism. [4] It has been found that between 7.2% and 27.8% of hospitalized COVID-19 patients suffer from cardiac damage.[5] COVID-19-induced heart damage has no readily apparent pathogenic mechanisms. Myocarditis directly caused by the virus through angiotensin-converting enzyme 2 (ACE2),[6,7] the putative viral receptor of SARS- COV-2[8], is just one of several possibilities hypothesized to be potentially related to cardiac damage. However, the link between cardiac injury and variables such as coagulation dysfunciton[9] has not been thoroughly elucidated in our local population. Therefore, the prime objective of this study was to determine the mechanisms of cardiac involvement and its relationship to coagulation dysfunction in hospitalized COVID-19 patients in our local population.

MATERIALS & METHODS:

This descriptive cross-sectional study was conducted at the Department of Hematology, MTI-Hayatabad Medical Complex, Peshawar, from Jun 2021 to Dec 2021. Ethical approval was obtained from the Institutional Research & Ethical Review Board (Ref No. 0026/IREB/DME/HMC/2021. The sample size was calculated by WHO Sample Size calculator with 7.20% proportion of cardiac injury in hospitalized COVID-19 patients, 5% margin of error and 5% significance level. Nonprobability consecutive sampling technique was adopted for data collection.

Inclusion Criteria: Patients of either gender aged 40 to 80 years hospitalized due to COVID- 19 were included in the study.

Exclusion Criteria: Hospitalized patients without COVID-19, patients with history of chronic obstructive pulmonary disease and patients with chronic kidney and liver disease.

Written informed consent was also taken from all the study participants after a complete description. All patients underwent cardiac and coagulation biomarker testing during hospitalization. Cardiac injury was defined as elevation of at least one of the three cardiac biomarkers above the 99th percentile upper reference limit and coagulation dysfunction was defined as elevated D-dimer, increased FDPs and decreased fibrinogen. Clinical data was recorded at the time of cardiac injury after the elevation of cardiac biomarkers during hospitalization. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 23.0. Mean+SD was calculated for quantitative variables while frequencies and percentages were computed for qualitative variables. Spearman correlation coefficient test was applied to establish association between coagulation dysfunction and cardiac injury keeping p-value $\leq$ 0.05 as significance level.

RESULTS:

A total of one hundred and three patients were included in this study. Mean age of patients was 57.6$\pm$12.36 years. As per mean$\pm$SD for coagulation biomarkers, mean d-dimer was 2.022$\pm$2.84 ug/mL, mean fibrin levels were 34.27$\pm$54.68 mg/dL and mean fibrinogen was 2.51$\pm$1.04 g/L and as per mean$\pm$SD for cardiac biomarkers, mean hsTn1 was 5.88$\pm$6.51 pg/mL, mean myohemoglobin was 65.49$\pm$52.2 ng/mL and mean CK-MB was 16.76$\pm$6.67 U/L. Cardiac injury was recorded in 23 (22.3%) patients hospitalized due to COVID-19. (Table-I).

Markers of coagulation dysfunction such as elevated d-dimer, increased fibrin degradation products and decreased fibrinogen were found significantly associated with cardiac biomarkers like hsTn1 (p-value < 0.001), myohemoglobin (p-value < 0.001) and CK-MB (p-value < 0.001) (Table-II).

Table-I: Demographic and Clinical Characteristics of Patients (n=103)

Quantitative Variables	**Mean + SD**
Age (Years)	57.64+12.36
Coagulation Biomarkers	
D-dimer (ug/mL)	2.022 + 2.84
Fibrinogen Degradation Products (mg/dL)	34.27±54.68
Fibrinogen (g/L)	2.51+1.04
Cardiac Biomarkers	
hsTn1 (pg/mL)	5.88 + 6.51
Myohemoglobin (ng/mL)	65.49 + 52.02
CK-MB (U/L)	16.76 + 6.67
Qualitative Variables	
Age Groups, n (%)	
< 60 Years	65 (63.1%)
> 60 Years	38 (36.9%)
Gender Groups, n (%)	
Male	54 (52.4%)
Female	49 (47.6%)
Hypertension, n (%)	
Hypertensive	62 (60.2%)
Normotensive	41 (39.8%)
Smoking, n (%)	
Smoker	62 (60.2%)
Non-Smoker	41 (39.8%)
Diabetes	
Diabetic	59 (57.3%)
Non-Diabetic	44 (42.7%)
Cardiac Injury, n (%)	
Yes	23 (22.3%)
No	80 (77.7%)

Table-II: Association of Coagulation Dysfunction with Cardiac Injury in Hospitalized COVID- 19 patients (n=103)

Coagulation Biomarkers	**Spearman Correlation Coefficient***			
	Cardiac Biomarkers			
	hsTn1 (pg/mL)	**Myohemoglobin (ng/mL)**	**CK-MB (U/L)**	***p*-value**
D-dimer (ug/mL)	.395*	.517*	.488*	< 0.001
FDPs (mg/dL)	.412*	.387*	.471*	< 0.001
Fibrinogen (g/dL)	-.449*	-.528*	-.547*	< 0.001

DISCUSSION:

This study analyzed the development of cardiac injury and its association with the markers of coagulation dysfunction like elevated D-dimer and FDP and decreased fibrinogen. In this regard, a total of 103 patients hospitalized for COVID-19 during the pandemic were studied. Patients with COVID-19 have been reported to have a high rate of cardiac injury, from 7.2% to 27.8% of all hospitalized patients[10], with a higher frequency among those with severe disease requiring intensive care unit (ICU) treatment. Substantial cardiac damage was seen in this investigation because preexisting comorbidities like hypertension and diabetes mellitus have been recognized as independent risk factors for cardiac injury[11] It is worth noting that male patients had a higher incidence of cardiac damage than female patients, which may be attributable to males' higher smoking rates and therefore, according to a recent research[12], ACE2 plasma concentration was higher in men than in women.

Coagulation biomarkers, such as elevated d- dimer, fibrin degradation products, and decreased fibrinogen, were found to be significantly associated with cardiac biomarkers, suggesting a strong correlation between them[13]. Likewise, markers of coagulation demonstrated highly synchronous alterations of D-dimer along with progression to cardiac injury, suggesting a strong correlation between them. In cardiac damage, fibrinogen was shown to be considerably reduced whereas FDP was significantly increased, indicating a hyperfibrinolytic state.

Disseminated intravascular coagulation (DIC) and thrombotic illness, evidenced by higher D- dimer and fibrinogen degradation product levels, have been found to be common in COVID-19, but uncommon in other coronavirus infections[13,14]. Extremely high rates of DIC (71.4% in non-survivors) have been documented in the medical literature[15]. In COVID-19, however, there is a more pronounced rise of D- dimer as compared to thrombocytopenia, suggesting a type of DIC that is distinct from that which happens during sepsis. Patients with preexisting cardiovascular disease may be more prone to developing acute myocardial ischemia due to the formation of an occlusive thrombus during a hypercoagulable condition. As the underlying coagulation malfunction in COVID-19 has become more understood, anticoagulant medication has become increasingly common in the treatment of these patients. Systemic anticoagulation was linked to better survival in hospitalized COVID-19 patients, according to an early large observational cohort study[16]. Hospitalised COVID-19 patients were less likely to die or require intubation when treated with anticoagulation in a recent large retrospective cohort (n = 4389). Even while there was no statistically significant difference between therapeutic and preventive anticoagulation in terms of mortality, the latter was associated with fewer deaths. The effectiveness of anti- coagulation (e.g. heparin or enoxaparin) on COVID-19 individuals with varying degrees of severity has been demonstrated in several small retrospective cohort studies[18,19,20]. The clinical value of these medications will soon be demonstrated by the results of a series of randomized controlled studies assessing the causative effects of anticoagulation in various therapy regimens[21,22,23,24,25]. Anticoagulation treatment may play a beneficial role in the prevention of disease progression and avoidance of cardiac injury, and thus, may improve overall prognosis of patients with this disease. Microvascular endothelial injury and coagulation dysfunction may be novel potential mechanisms of cardiac injury in COVID-19.

Coagulation markers indicated very synchronous modifications of D-dimer alongside progression to cardiac injury, leading us to the conclusion that cardiac injury, represented by elevation of cardiac biomarkers,is a common consequence of COVID-19. Therefore, coagulation malfunction and microvascular endothelial damage may play primary roles in the aetiology of cardiac injury in COVID-19.

There were few limitations to our study, which mainly pertained to its study design with a small sample size that was restricted to a single centered institution, cardiac injury biomarkers were only measured at a single time point, therefore, in order to further validate the direct connection between cardiac injury and coagulation, it requires the clinical association studies of cardiac injury from larger multicentered randomized controlled trials from across the country. Finally, we did not follow/observed the treatment strategies and clinical outcome of these patients during their stay and

at discharge from the hospital.

CONCLUSION:
This study demonstrated significant association of coagulation dysfunction with the development of cardiac injury as markers of coagulation function were found significantly synchronized with the dynamic progression of cardiac biomarkers.

Declaration by Authors
Ethical Approval: Approved **Acknowledgement:** Prof. Dr. Shahtaj Khan for her guidance and continuous support.

Source of Funding: None

Conflict of Interest: The authors declare no conflict of interest.

Author's Contribution:
Following authors have made substantial contributions to the manuscript as under:**MZ:** Conception, study design, drafting the manuscript, approval of the final version to be published.
MS: Data analysis, data interpretation, critical review, approval of the final version to be published.
SZ & GR: Data acquisition, critical review, approval of the final version to be published.**HT & HMK:** Proof readings, write-up, approval of the final version to be published. Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES:
1. Fei Y, Tang N, Liu H, Cao W. Coagulation Dysfunction. Arch Pathol Lab Med. 2020 Oct 1;144(10):1223-1229.
2. Chen L, Hu W, Guo X, Zhao P, Tang J, Gu Y, et al. Association of coagulation dysfunction with cardiac injury among hospitalized patients with COVID-19. Sci Rep. 2021 Feb 24;11(1):4432.
3. World Health Organization. *Global Action Plan for the Prevention and Control of Noncommunicable Diseases 2013-2020*. World Health Organization; 2013.
4. Witt BJ, Gami AS, Ballman KV, et al. The incidence of ischemic stroke in chronic heart failure: a meta-analysis. *J Card Fail*. 2007;13(6):489–496.
5. Guo T, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19) JAMA Cardiol. 2020;5:811–818.doi: 10.1001/jamacardio.2020.1017.
6. Chen L, Li X, Chen M, Feng Y, Xiong C. The ACE2 expression in human heart indicates new potential mechanism of heart injury among patients infected with SARS- CoV-2. Cardiovasc. Res. 2020;116:1097– 1100. doi: 10.1093/cvr/cvaa078.
7. Nicin L. Cell type-specific expression of the putative SARS-CoV-2 receptor ACE2 in human hearts. Eur. Heart J. 2020;41:1804– 1806. doi: 10.1093/eurheartj/ehaa311.
8. Hoffmann M. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020;181:271–280. doi: 10.1016/j.cell.2020.02.052.
9. Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. Nat. Rev. Cardiol. 2020;17:259–260. doi: 10.1038/s41569-020-0360-5.
10. Shi S. Characteristics and clinical significance of myocardial injury in patients with severe coronavirus disease 2019. Eur. Heart J. 2020;41:2070–2079.doi: 10.1093/eurheartj/ehaa408.
11. Chen T. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: Retrospective study. BMJ. 2020;368:m1091. doi: 10.1136/bmj.m1091.
12. Sama IE. Circulating plasma concentrations of angiotensin-converting enzyme 2 in men and women with heart failure and effects of renin-angiotensin-aldosterone inhibitors. Eur. Heart J. 2020;41:1810– 1817. doi: 10.1093/eurheartj/ehaa373.

13. Cao W, Li T. COVID-19: Towards understanding of pathogenesis. CellRes. 2020;30:367–369. doi: 10.1038/s41422-020-0327-4.
14. Bikdeli B. COVID-19 and thrombotic or thromboembolic disease: Implications for prevention, antithrombotic therapy, and follow-up. J. Am. Coll. Cardiol. 2020;75:2950–2973
15. 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;18:844–847. doi: 10.1111/jth.14768.
16. Varga Z. Endothelial cell infection and endotheliitis in COVID-19. Lancet. 2020;395:1417–1418. doi: 10.1016/S0140-6736(20)30937-5.
17. Paranjpe I. Association of treatment dose anticoagulation with in-hospital survival among hospitalized patients with COVID-19. J. Am. Coll. Cardiol. 2020;76:122–124. doi: 10.1016/j.jacc.2020.05.001.
18. Nadkarni GN, et al. Anticoagulation, bleeding, mortality, and pathology in hospitalized patients with COVID-19. J. Am. Coll. Cardiol. 2020;76:1815–1826. doi: 10.1016/j.jacc.2020.08.041.
19. Ayerbe L, Risco C, Ayis S. The association between treatment with heparin and survival in patients with Covid-19. J. Thromb. Thrombolysis. 2020;50:298–301.doi: 10.1007/s11239-020-02162-z.
20. Billett HH. Anticoagulation in COVID-19: Effect of enoxaparin, heparin, and apixaban on mortality. Thromb. Haemost. 2020 doi: 10.1055/s-0040-1720978.
21. Tang N. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with oagulopathy. J. Thromb. Haemost. 2020;18:1094–1099. doi: 10.1111/jth.14817.
22. Bikdeli B, et al. Intermediate versus standard-dose prophylactic anticoagulation and statin therapy versus placebo in critically-ill patients with COVID-19: Rationale and design of the INSPIRATION/INSPIRATION-S studies. Thromb. Res. 2020;196:382–394. doi: 10.1016/j.thromres.2020.09.027.
23. Busani S. Multi-centre, three arm, randomized controlled trial on the use of methylprednisolone and unfractionated heparin in critically ill ventilated patients with pneumonia from SARS-CoV-2 infection: A structured summary of a study protocol for a randomised controlled trial. Trials. 2020;21:724. doi: 10.1186/s13063-020-04645-z.
24. Houston BL. Anti-thrombotic therapy to ameliorate complications of COVID-19 (ATTACC): Study design and methodology for an international, adaptive Bayesian randomized controlled trial. Clin. Trials. 2020;17:491–500. doi: 10.1177/1740774520943846.
25. Lemos ACB. Therapeutic versus prophylactic anticoagulation for severe COVID-19: A randomized phase II clinical trial(HESACOVID) Thromb. Res. 2020;196:359–366. doi: 10.1016/j.thromres.2020.09.026.