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Original Article

Internal Medicine Section

Significance of Haematological Variates in Determining Risk of Cardiovascular Complications Post SARS-CoV-2 Infection: A Prospective Cohort Study

ZIA-UL-SABAH[1], JAVED IQBAL WANI[2], SHAHID AZIZ[3], MOHAMMAD MUZAFFAR MIR[4], HUMAYOUN KHAN DURRANI[5], MUAD ALI ALFAYEA[6], AYYUB ALI PATEL[7], TARIQ RASOOL[8]

ABSTRACT

Introduction: Coronavirus Disease-2019 (COVID-19) is an ongoing global pandemic. Changes in haematological variables in patients with COVID-19 are emerging as important features of the disease. These changes in haematological variables may provide significant clues in the prognosis post Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infection.

Aim: To determine the significance of various haematological variables in cardiac outcomes post SARS-CoV-2 infection.

Materials and Methods: This was a prospective cohort study conducted at Prince Faisal bin Khalid Cardiac Centre, Abha, Kingdom of Saudi between March 2021 and October 2021. A total of 59 patients who were infected with SARS-CoV-2 with or without cardiac complaints were involved. Demographic, clinical, and laboratory data were recorded. Leukocyte counts, Neutrophil Counts, Lymphocyte counts, Neutrophil to Lymphocyte Ratio (NLR), platelet counts, Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT), and D-Dimer were assessed and compared between subjects who developed Cardiovascular Complications (CVC+ group) and the subjects who did not develop CVC post SARS-CoV-2 infection (CVC-group). Statistical analyses were performed using R scripting language and R Studio (version 1.2.5033, Orange Blossom). For continuous variables, t-test (for normally distributed) and Mann-Witney U test (for non normally distributed) were employed. For categorical data, Chi-square test (χ^2) was used. A p-value <0.05 was considered significant.

Results: Among all the haematological variables assessed, Neutrophil counts (p<0.0001), NLR (p<0.0001), and PT (p<0.0001) were highly significant for developing CVC post SARS-CoV-2 infection. Additionally, Leukocyte counts (p=0.028), Lymphocyte counts (p=0.0002), APTT (p=0.036), and D-dimer (p=0.022) also showed statistical significance for developing CVC post-SARS-CoV-2 infection.

Conclusion: Haematological testing is easily available, inexpensive, and provides almost instant results. Therefore, assessing haematological variables like Leukocyte counts, Neutrophil counts, Lymphocyte counts, NLR, PT, APTT, and D-Dimer values post SARS-CoV-2 infection can help doctors identify patients at higher risk of developing CVC and guide their interventions accordingly. This can potentially help in reducing the occurrence of cardiovascular complications.

Keywords: Acute cardiovascular syndrome, Acute respiratory distress syndrome, Catecholamine surge, Cytokine storm, Myocarditis, Renin-angiotensin-aldosterone system, Severe acute respiratory syndrome coronavirus-2

INTRODUCTION

Coronavirus Disease-2019 (COVID-19), although primarily a respiratory system disease [1,2], has now been demonstrated to interfere with and affect the cardiovascular system, leading to myocardial damage [3] and other cardiac and endothelial dysfunctions [4]. While COVID-19 patients with pre-existing cardiac conditions experience more severe respiratory distress symptoms, it is now established that cardiac damage can occur without respiratory manifestations [5,6] post-SARS-CoV-2, the virus that causes COVID-19 infection [7,8]. It has been demonstrated that the SARS-CoV-2 virus affects the cardiovascular system via Angiotensin-Converting Enzyme-2 (ACE-2) receptors [3,4]. SARS-CoV-2 gains entry and controls the host cell by exploiting the S-spike protein and ACE-2 receptor conformations [1,9,10].

The primary immune response to this compromise of ACE-2 receptors by the S-Spike protein of SARS-CoV-2 virus is that the immune system, as a first response, works to trap and eliminate the virus. If the SARS-CoV-2 virus succeeds in evading the primary response, it then multiplies and disseminates into organs with higher expression of ACE-2 receptors, such as the lungs, cardiovascular system, endothelial cells, and kidneys. This triggers the secondary response of the immune system, wherein severe inflammation of the affected organ is achieved [8].

This severe systemic inflammatory response results in the cytokine storm or cytokine release syndrome (release of excessive levels of cytokines). This leads to multiple tissue injuries, including vascular, endothelial, and cardiac myocyte damage [9-12]. The cytokine storm has also been demonstrated to result in Acute Respiratory Distress Syndrome (ARDS) and end-organ damage [13-16]. It has also been observed that SARS-CoV-2 may directly infect the myocardium, resulting in myocarditis. However, in the majority of cases of myocardial damage, the surge in cardiometabolic demand in response to systemic infections and hypoxia caused by ARDS is the main suspect [11]. Acute Cardiovascular Syndrome (ACS) has also been attributed to a catecholamine surge [14] and coronary thrombosis [14]. Various types of arrhythmias have also been shown to be the result of hypokalaemia in patients with COVID-19, due to the SARS-CoV-2 interaction with the Renin-Angiotensin-Aldosterone System (RAAS) [10,11].

Since the spectrum of cardiac manifestations is very wide, ranging from arrhythmias to myocardial damage, it is imperative to be able to identify patients who have a high probability of developing cardiac complications post-SARS-CoV-2 infection. This would allow for the prescription of personalised, targeted, and preventive treatment regimens to alleviate cardiac complications. However, there is a paucity of available literature regarding the values of haematological parameters

at the time of admission to a healthcare facility in determining the probability of cardiac complications post-SARS-CoV-2 infection.

Prognostic significance of neutrophil count, neutrophil-to-lymphocyte ratio, C-Reactive Protein (CRP), D-Dimer, and platelets in SARS-CoV-2 infection is available in the literature [17]. Therefore, the present study was undertaken to determine the significance of various haematological variables at the time of admission in assessing the cardiac outcomes post-SARS-CoV-2 infection.

MATERIALS AND METHODS

This prospective cohort study was conducted at Prince Faisal-bin-Khalid Cardiac Centre, Abha, Kingdom of Saudi Arabia, from March 2021 to October 2021. The study was approved by the Institutional Ethics Committee of King Khalid University, Abha, Kingdom of Saudi Arabia (ECM#2021-4701).

Sample size calculation: For sample size calculation, the finite population corrections for proportions version of Cochran's equation was used [18], and the calculated sample size for the study was 59.

Inclusion criteria: Patients above 18 years of age who tested positive for COVID-19 based on a real-time Reverse Transcription-Polymerase Chain Reaction (RT-PCR) assay on respiratory specimens or had been diagnosed in the community, and consented to the study were included.

Exclusion criteria: Patients with prior documented Myocardial Infarction (MI), heart failure, and those who did not give their consent were excluded from the study.

Study Procedure

Data regarding demographic information (age, gender), medical history (hypertension, diabetes mellitus, and heart disease), and haematological variables such as leukocyte counts, neutrophil counts, lymphocyte counts, Neutrophil-to-Lymphocyte Ratio (NLR), coagulation variables data including Prothrombin Time (PT), platelet counts, Activated Partial Thromboplastin Time (APTT), and D-Dimer levels, along with COVID-19 vaccination status, were recorded from patients at the time of presentation to the healthcare facility [Table/Fig-1].

Variables	CVC (Post SARS-CoV-2 infection)		p-value
	+	-	
N (Total=59)	19 (32.2)	40 (67.8)	<0.05
Age (Years)	68.1±13.3	58.3±11.9	
Sex			
Male	14 (73.68)	19 (52.5)	0.0583
Female	05 (26.32)	21 (47.5)	
H/HTN			
+	15 (78.95)	12 (30)	<0.05
-	04 (21.05)	28 (70)	
H/DM			
+	11 (57.89)	14 (35)	0.0963
-	08 (42.11)	26 (65)	
Pre-existing heart disease			
+	11 (57.89)	12 (30)	<0.05
-	08 (42.11)	28 (70)	
Leucocyte count, $\times 10^9$/L	6.34 (4.75-7.44)	5.57 (5.29-6.12)	<0.05
Neutrophil count, $\times 10^9$/L	4.89 (3.54,5.78)	3.32 (2.93,3.87)	<0.05
Lymphocyte count, $\times 10^9$/L	0.93 (0.58,1.19)	1.25 (1.22,1.46)	<0.05
NLR, $\times 10^9$/L	6.68 (6.46,6.78)	2.7 (2.66,2.8)	<0.05
PLT count, $\times 10^9$/L	157.2 (57.56-189.83)	187 (137.50-265.62)	<0.05
PT (s)	17.80 (14.5-20.78)	13.31 (11.34-13.82)	<0.05
APTT (s)	37.43 (33.12-47.20)	33.01 (30.43-37.80)	<0.05
D-dimer (mg/L)	2.39 (0.89-8)	0.44 (0.20-0.78)	<0.05
Vaccination status {Oxford/Astra Zeneca (ChAdOx1S)}			
2-Doses	06 (32)	16 (40)	0.56
1-Dose	11 (58)	20 (50)	0.57
Not vaccinated	02 (10)	04 (10)	1.00

[Table/Fig-1]: Patient demographics and haematological variables at the time of presentation.
Data are expressed as median (IQR) or % format. The χ^2 test was used for categorical variables, while t-test (for normally distributed) and Mann-Whitney U test (for non normally distributed) were employed for continuous variables. CVC: Cardiovascular complications; HTN: Hypertension, DM: Diabetes mellitus

Haematological testing was conducted using Roche's cobas m511 analyser, and coagulation parameter testing was performed using Roche's t 511 coagulation analyser. For outcome data, the patients were followed for a period of six months postdischarge from the hospital. The cohort was divided into two groups: one that developed cardiovascular complications (CVC+) and the other that did not develop any cardiovascular complications (CVC-). The cardiovascular conditions were classified according to the International Classification of Diseases, 10th Revision, Clinical Modification Codes (ICD10-CM-Code) [19]. The haematological parameters recorded were compared across the two groups using appropriate statistical methods.

STATISTICAL ANALYSIS

The R scripting language and the accompanying R studio (Version 1.2.5033, Orange Blossom) were used to perform all analyses. R is an open-source scripting language better suited for statistical computing, widely used by researchers and academia. For continuous variables, the t-test (for normally distributed data) and Mann-Whitney U test (for non normally distributed data) were employed. For categorical data, the chi-square test was used. A p-value <0.05 was used for all analyses to reject the null hypothesis that the studied haematological variables at the time of presentation have no prognostic power in determining cardiac complications in COVID-19 patients. Continuous variables are presented in either the mean±Standard Deviation (SD) or median (IQR) format, and categorical variables are presented as percentages.

RESULTS

The cohort was predominantly male 33 (55.93%), with an average age of 62.57±12.45. Additionally, 27 (45.76%) were hypertensive, 25 (42.37%) diabetic, and 23 (38.98%) had pre-existing heart ailments. A total of 19 patients developed complications: five had Atrial Fibrillation (AF), four had myocarditis, six had unstable angina, and four had MI [Table/Fig-2].

Cardiovascular damage	Number of patients n=19	ICD10-CM-Code
Atrial fibrillation	5	I48
Myocarditis	4	I40
Unstable angina	6	I24
Myocardial infarction	4	I21, I22

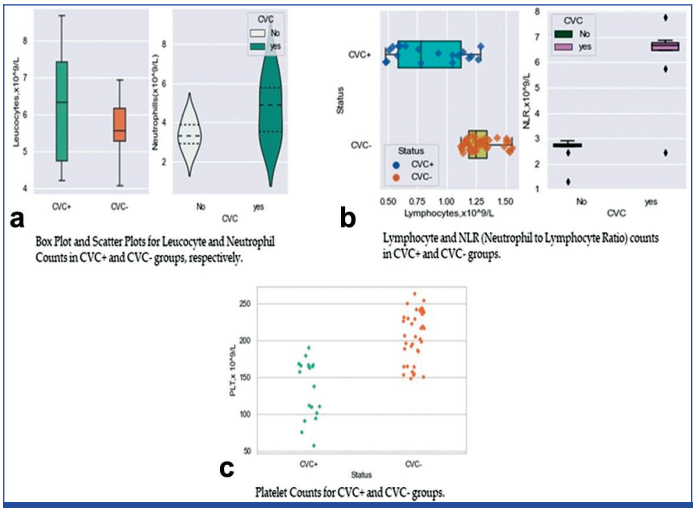
[Table/Fig-2]: Cardiovascular complications observed in the CVC+ group.
ICD-10-CM Code: International classification of diseases, Tenth Revision, Clinical modification codes

During the study, in the CVC+ group [Table/Fig-1], the mean age was 68.1±13.3 years compared to 58.3±11.9 years in the CVC- group (p-value=0.006). Similarly, in the CVC+ group, 14 (73.68%) were males, and 5 (26.32%) were females, while in the CVC- group, there were 21 (52.5%) males and 19 (47.5%) females (p-value=0.125). Likewise, in the CVC+ group, 15 (78.95%) vs. 12 (30%) in the CVC- group were hypertensive (p-value=0.005), 11 (57.89%) vs. 14 (35%) were diabetic (p-value=0.099), and 11 (57.89%) vs. 12 (30%) had pre-existing heart conditions (p-value=0.041). In the CVC+ group, 6 (32%) were vaccinated with two doses, 11 (58%) with a single dose of Oxford/AstraZeneca (ChAdOx1-S) recombinant COVID-19 vaccine, and 2 (10%) were not vaccinated. In the CVC- group, out of 40 subjects, 20 (50%) had a single dose, 16 (40%) had two

doses of Oxford/AstraZeneca (ChAdOx1-S) recombinant COVID-19 vaccine, and 4 (10%) were unvaccinated.

The median leukocyte count at admission in the CVC+ group was higher at 6.34 (4.75-7.44)×10^9/L compared to 5.57 (5.29-6.12)×10^9/L in the CVC- group (p-value=0.028; [Table/Fig-1,3]). Additionally, the median Neutrophil count in the CVC+ group was 4.89 (3.54-5.78)×10^9/L, while in the CVC- group, it was 3.32 (2.93-3.87)×10^9/L (p-value <0.0001; [Table/Fig-1,3]). Similarly, the median lymphocyte counts in the CVC+ group at admission were 0.93 (0.58-1.19)×10^9/L vs. 1.25 (1.22-1.46)×10^9/L in the CVC-group (p-value=0.0002; Table1, Figure2). More importantly, the median NLR in the CVC+group was 6.68 (6.46-6.78) compared to 2.7 in the CVC-group (p-value <0.0001; [Table/Fig-1,3]). The median platelet count in the CVC+group was 157.2 (57.56-189.83)×10^9/L, while in the CVC- group, it was 187 (137.50-265.62)×10^9/L (p-value=0.269) [Table/Fig-1,2].

Regarding coagulation parameters [Table/Fig-1,3], PT was significantly different, and APTT, D-Dimer were also different across the two groups CVC+ and CVC-. The median (IQR) PT (s), APTT(s), and D-Dimer (mg/L) were 17.80 (14.5-20.78) in the CVC+ group vs. 13.31 (11.34-13.82) in the CVC- group (p-value <0.0001), 37.43 (33.12-47.20) in the CVC+ group vs. 33.01 (30.43-37.80) in the CVC- group (p-value=0.036), and 2.39 (0.89-8) in the CVC+ group against 0.44 (0.20-0.78) in the CVC-group (p-value=0.022), respectively. Five patients in the CVC+ group had prolonged APTT (i.e., APTT >43.55 seconds) compared to none in the CVC- group.



[Table/Fig-3]: a) Box and Scatter Plots for Leukocyte and Neutrophil Counts in CVC+ and CVC- groups. b) Lymphocyte and NLR (Neutrophil-to-Lymphocyte Ratio) counts in CVC+ and CVC- groups. c) Platelet counts for CVC+ and CVC- groups.

DISCUSSION

The university hospital-based prospective cohort study presents compelling evidence that haematological variables at presentation, such as neutrophils (p-value <0.0001), NLR (p-value <0.0001), leukocytes (p-value=0.028), and lymphocytes (p-value=0.0002), as well as coagulation variables PT (p-value <0.0001), APTT (p-value=0.036), and D-Dimer (p-value=0.022), show a significant association with CVC post-SARS-CoV-2 infection. In this cohort of 59 individuals, those who developed post-COVID-19 CVC were more likely to exhibit leucocytosis, neutrophilia, lymphopaenia, and elevated NLR compared to those who did not develop CVC post-COVID-19. Previous studies have also suggested prognostic value in ACS for white blood cell count, its differential, and NLR [20-22].

Regarding coagulation variables at the time of admission, the study identifies a strong association between PT, APTT, and elevated D-Dimer levels with post-COVID-19 adverse cardiovascular events. Among the 19 patients in the CVC+ group, five developed AF, four myocarditis, six unstable angina, and four MI. Some reports have indicated arrhythmias, particularly AF, as a common form in COVID-19 infections [23,24]. Additionally, studies [25,26] have shown that patients without prior arterial blockages can experience MI due to oxygen deprivation of cardiomyocytes caused by COVID-19 infection. COVID-19 has also been linked to life-threatening myocarditis, even in individuals with no underlying risk factors [27,28].

Emphasising that haematological and coagulation variables can predict CVCs in COVID-19, the present study indirectly suggests that the risk of CVC extends well beyond the acute phase of SARS-CoV-2 infection. Earlier studies have explored the risk index of CVC in the acute phase of COVID-19 [29-31]. While the mechanisms of post-SARS-CoV-2 CVC are not well-established [32], conjectural mechanisms include prolonged damage due to direct viral invasion of cardiomyocytes [33], dysregulation of RAAS, elevated cytokine release [34], endothelial cell inflammation and infection, transcriptional modification of cells in heart tissue [35,36], complement activation, complement-mediated coagulopathy, microangiopathy [37], and fibrosis and scarring of cardiac tissue via activation of Transforming Growth Factor (TGF)-β signalling through the Supressor of Mothers Against Decapentaplegic (SMAD) pathway [38]. The anomalous, pertinacious hyper activated immune response [31,33] has also been propounded as possible explanations of extrapulmonary (including cardiovascular) post-COVID-19 ramifications [35,39]. The reason for continued triggering of inflammatory-immune-pro-coagulant triad, has also been hypothesised to the amalgamation of SARS-CoV2 genome into Deoxyribonucleic Acid (DNA) of infected cell type [40]. The study suggests that the hypothesised mechanisms need further investigation and understanding to facilitate better prevention and treatment protocols for post-COVID-19 CVC.

The key strength of the present study lies in demonstrating that, despite the enigmatic and ever-dynamic nature of COVID-19, routine haematologic and coagulation variables have significant prognostic power in forecasting post-COVID-19 cardiovascular outcomes.

Limitation(s)

Firstly, the study was single-centric, and the demographic component was limited to a particular geography (Kingdom of Saudi Arabia), which may restrict the generalisation of the findings. Lastly, as the SARS-CoV-2 virus continues to mutate with new variants emerging, it is possible that the epidemiology of CVC may also change with these new mutations.

CONCLUSION(S)

The present study identifies neutrophil, leukocyte, and lymphocyte counts, NLR, PT, APTT, and D-Dimer as significant haematological variables for CVC following SARS-CoV-2 infection. Considering the enigmatic nature of COVID-19, having rapid, routine, and easily obtainable prognostic biomarkers could be game-changers in predicting the post-COVID-19 infection outcome, facilitating the identification of patients at higher risk of post-COVID-19 cardiovascular events. This would enable attending clinicians to prescribe preventive modalities.

Authors contribution: Conceptualisation: ZS and JI; Methodology: MM and SA; Software: HD; Formal analysis: TR; Writing-review and editing: AP; Writing-original draft preparation: MA; Visualisation: All authors. All authors have read and agreed to the published version of the manuscript.

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PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Medicine, College of Medicine, King Khalid University, Abha, Aseer, Saudi Arabia; Consultant Cardiologist, Prince Faisal-bin-Khalid Cardiac Centre, Abha, Kingdom of Saudi Arabia. **Orcid id: 0000-0003-4473-7373.**
2. Associate Professor, Department of Medicine, College of Medicine, King Khalid University, Abha, Aseer, Kingdom of Saudi Arabia.
3. Assistant Professor, Department of Medicine, College of Medicine, King Khalid University, Abha, Aseer, Kingdom of Saudi Arabia; Consultant Physician, Department of Medicine, Aseer Central Hospital, Abha, Aseer, Kingdom of Saudi Arabia. **Orcid id: 0000-0001-7398-8273.**
4. Professor, Department of Clinical Biochemistry, College of Medicine, University of Bisha, Bisha, Aseer, Kingdom of Saudi Arabia.
5. Assistant Professor, Department of Medicine, College of Medicine, King Khalid University, Abha, Aseer, Kingdom of Saudi Arabia.
6. Senior Resident, Department of Medicine, Aseer Central Hospital, Aseer, Kingdom of Saudi Arabia.
7. Assistant Professor, Department of Clinical Biochemistry, College of Medicine, King Khalid University, Abha, Aseer, Kingdom of Saudi Arabia.
8. Teaching Assistant, Department of Mathematics, Central University of Kashmir, Ganderbal, Jammu and Kashmir, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Tariq Rasool,
Teaching Assistant, Department of Mathematics, Central University of Kashmir, Ganderbal-190006, Jammu and Kashmir, India.
E-mail: tariqcukashmir@gmail.com; zsabah@kku.edu.sa

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- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

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