ORIGINAL ARTICLE

Prosthetic heart valves and the COVID-19 pandemic era: What should we be concerned about?

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Abstract

Background: The disturbance in the international normalized ratio (INR) in patients receiving warfarin therapy is of concern. We aimed to evaluate coagulation features in hospitalized patients under warfarin treatment for prosthetic heart valves during the novel coronavirus disease 2019 (COVID-19) pneumonia pandemic.

Methods: Between 20 February and 28 March 2020, 10 patients (7 males) who were under warfarin therapy for prosthetic heart valves were hospitalized after a diagnosis of COVID-19 in Tehran Heart Center, Tehran, Iran. The clinical, paraclinical, and in-hospital outcomes were described. The patients were followed for 4 weeks.

Results: The median age was 62 years. All the patients received antiviral treatment, either lopinavir/ritonavir or oseltamivir. The serum level of high-sensitivity C-reactive protein ranged between 0.24 and 15.24 mg/dL. Alanine aminotransaminase was normal in all the patients except for two, with levels 1.6 and 4.2 times above normal values. The INR increased in all the patients. One (10%) patient died in the hospital. No bleeding, ischemic, or thrombotic events occurred during the hospital stay and within the 4-week follow-up.

Conclusions: Antiviral therapy in patients with COVID-19 with prosthetic heart valves might be an issue responsible for an uncontrolled INR. Liver injury may happen in a minority of patients. Bridging in these patients during the antiviral treatment might be required and because of significant INR fluctuations, it might be safer to prescribe antiviral treatment in an inpatient setting.

KEYWORDS
coronavirus, COVID-19, international normalized ratio, lopinavir/ritonavir, prosthetic heart valve, warfarin

1 | INTRODUCTION

Patients with prosthetic valve replacement with coronavirus disease 2019 (COVID-19) infection are a challenging subset of patients to manage. Very little is known regarding the outcome of COVID-19 infection in these patients. The patients are challenging not just because of concomitant cardiovascular risk factors but also because of the presence of liver function abnormalities. Regular testing for the international normalized ratio (INR) in these patients who receive warfarin is critical, and meanwhile, concomitant infection is a great concern. It is already well-established that COVID-19 can not only cause atypical pneumonia and respiratory distress but also accompany abnormal liver function tests. Increased aspartate aminotransferase and alanine aminotransferase (liver enzymes) could be explained by

the effect of COVID-19 on the liver itself and/or the prescription of antiviral therapies in hospitalized patients.[1-5] In the case of severe COVID-19 and the use of recommended antiviral therapies, such as lopinavir/ritonavir (KALETRA) and oseltamivir, a high INR is encountered in patients who use warfarin, even though without a change in the warfarin dosage. Very little is known about the interaction of anticoagulation drugs and antiviral drugs patients with prosthetic heart valves are often required to be treated with. Although interim guidance for the management of coagulopathy in patients with COVID-19 has been published,[6] the resultant clotting profile in patients with prosthetic heart valve are largely unknown. A consensus has yet to emerge as to the approach toward these patients with COVID-19.

In this study, we describe a case series of patients with prosthetic heart valves and concomitant COVID-19 and seek to explore the challenges involving coagulation abnormalities.

2 | METHODS

This study involved human participants and was in accordance with the ethical standards of the institutional research committee and the 1964 Helsinki Declaration. The study protocol was approved by the Research Ethics Committee of Tehran University of Medical Sciences, Tehran, Iran (code: IR.TUMS.VCR.REC.1399.117). Between 20 February and 28 March 2020, a total of 140 hospitalized patients with clinically diagnosed COVID-19, according to the World Health Organization's interim guidance,[7] were admitted to Tehran Heart Center, affiliated with Tehran University of Medical Sciences.[8] COVID-19 was confirmed by either real-time polymerase chain reaction (RT-PCR) assay or characteristic findings in chest computed

tomography (CT). Of these, 10 patients had a prosthetic valve replacement and were enrolled in this study. The clinical, paraclinical, and in-hospital outcomes were recorded. Chest CT was done on a SIEMENS 16-slice CT scanner with a slice thickness of 5 mm, and the images were reviewed by a radiology specialist.

The INR was recorded on admission and during the course of hospitalization. With the detection of an uncontrolled INR, warfarin was held and antiviral treatment was continued until the occurrence of expected recovery. The patients were in close electrocardiographic monitoring and the antiviral treatment was stopped in case of QT prolongation. Daily INR measurement and close observation against bleeding events were done. When the INR dropped down to the target level, according to the type of prosthetic valve, either warfarin or heparin was initiated.

Laboratory tests including the admission data of the white blood cell count; the percentage of lymphocytes; the levels of hemoglobin, alanine transaminase, aspartate aminotransferase, lactate dehydrogenase, and creatinine, and high-sensitivity C-reactive protein; and RT-PCR results were recorded. The patients were followed for 4 weeks after hospital discharge.

3 | RESULTS

Of the 10 patients, 7 (70%) were men, and the median age of all the patients was 62 years (range = 32-82 years). The demographic and clinical characteristics of each patient are listed in Table 1. Four (40%) patients were smokers, and nine (90%) had at least one comorbidity. The most prevalent comorbidity was hypertension (50%). All the patients had a prosthetic heart valve and were using warfarin. KALETRA was prescribed for eight patients, and the other two

TABLE 1 Summary of the demographic and clinical characteristics and outcomes of the study patients with a prosthetic heart valve and novel Wuhan coronavirus pneumonia

Case no	Sex	Age, y	Presenting sign	Habits and comorbidities	History of cardiac surgery	LVEF (%)	Antiviral treatment	Outcome
1	M	82	Dyspnea	HTN	CABG + AVR	55	HCQ/oseltamivir	Recovered
2	M	68	Dyspnea/cough	DM	CABG + AVR	35	KALETRA	Recovered
3	M	68	Chest pain/dyspnea/fever	DM, HTN	CABG + AVR	15	HCQ/oseltamivir	Recovered
4	M	67	Cough/chills	HTN, CS	CABG + AVR	25	HCQ/KALETRA	Recovered
5	F	44	Dyspnea/cough/fever	HTN	MVR	55	KALETRA	Died
6	M	37	Dyspnea	HLP, CS	MVR + AVR + TVR	45	HCQ/KALETRA	Recovered
7	F	64	Chest pain/cough/fever	HTN, HLP,CS	CABG + MVR + AVR	55	KALETRA	Recovered
8	M	43	Dyspnea	CS	MVR + TVR	65	HCQ/KALETRA	Recovered
9	F	32	Dyspnea/chest pain cough/fever	...	MVR + AVR + TVR	55	KALETRA	Recovered
10	M	60	Chest pain/dyspnea	HLP, CS	CABG + MVR	40	KALETRA	Recovered

Abbreviations: AVR, aortic valve replacement; CABG, coronary artery bypass graft; CS, cigarette smoking; DM, diabetes mellitus; F, female; HCQ, hydroxychloroquine; HLP, hyperlipidemia; HTN, hypertension; LVEF, left ventricular ejection fraction; M, male; MVR, mitral valve replacement; TV, tricuspid valve; TVR, tricuspid valve replacement.

patients were treated with oseltamivir, either with or without hydroxychloroquine. The median hospital stay was 9 days.

Out of the 10 patients, 1 (10%) died. This patient was a woman who expired 5 days after admission for acute respiratory distress syndrome, with transthoracic echocardiography showing no specific findings. Intubation due to respiratory distress and placement on mechanical ventilation proved ineffectual. Two patients had a history of triple valve replacement (mitral, aortic, and tricuspid) but both made a satisfactory recovery. The results of the biochemistry lab tests including the INR, measured after a mean duration of 5 days of antiviral initiation, and spiral chest CT are presented in Table 2. The results of RT-PCR, taken on admission, were positive for six patients, and the other four patients had contact history with confirmed COVID-19 cases and chest CT characteristics compatible with the infection.

The entire study population had normal alanine aminotransferase except two patients, who had an alanine aminotransferase level of 1.6 and 4.2 times the normal value. The 10th and 6th patients had negative and positive RT-PCR results, respectively. Lactate dehydrogenase was measured in six patients: it ranged between 72 and 779 U/L and was higher than 280 U/L in four patients. Subtherapeutic INR values on admission were detected in seven patients, but they reached above 5 after a mean of 5.30 ± 1.64 days (median = 5.5 days) from antiviral therapy commencement. None of the patients had thrombocytopenia on admission (platelet count $< 100 \times 10^6/\mu L$). RT-PCR was positive in six and negative in four patients. Comparisons between the two groups based on the RT-PCR results showed that the mean INR on admission was 2.3 ± 0.6 for the test-positive and 1.6 ± 0.3 for the test-negative patients. The mean INR increased to 14 ± 9.5 and 6.3 ± 2.6 in the patients with positive RT-PCR and negative RT-PCR, respectively.

Nine patients, who recovered and were discharged, were followed through telephone contacts. None of them had bleeding, ischemic, or thrombotic events within the 4-week follow-up.

4 | DISCUSSION

Patients with prosthetic heart valves, given their propensity to the thrombotic state, face a lifetime use of warfarin. It is possible that these patients in the COVID-19 pandemic continue consuming warfarin and checking their INR at a lower frequency to reduce possible exposure to infection. In the present case series, we focused on the demographic characteristics, coagulopathy results, and outcomes of patients with prosthetic heart valves hospitalized with COVID-19.

Our observation revealed that 20% of the study patients had a liver injury, presented as increased alanine aminotransaminase, which is consistent with the results of the previous studies,[2] who reported 14-53% rate of liver injury among their patients during the hospital stay. As demonstrated previously, 40% of patients with COVID-19 were identified to have an increased INR and an elevated lactate dehydrogenase level during the course of the disease.[3,5] It is suggested that increased lactate dehydrogenase has the potential to predict the severe form of the disease.[9] This enzyme was measured in six of our

patients and exhibited a rise in four (66%) of them. Our only case of in-hospital mortality had increased lactate dehydrogenase

While COVID-19 presents with fever and other constitutional symptoms, the differential diagnosis of infectious endocarditis also has to be borne in mind in the presence of a prosthetic heart valve. In our study, four patients had a fever on admission, but none fulfilled the modified Duke criteria as a definite or suspected case for infectious endocarditis.[10,11] Only 2 of 10 patients had increased prosthetic mitral valve gradients without significant transvalvular or paravalvular leakage. The two patients also had no apparent vegetation in transthoracic echocardiography. The mildly increased gradient was probably contributed to tachycardia and fever. With respect to contact history and COVID-19 consistent with chest CT findings, the patients were treated with KALETRA, although their RT-PCR was negative. These two patients were recovered.

Warfarin toxicity could be one of the major challenges in patients with a prosthetic heart valve. A suggested mechanism for warfarin toxicity and an increased INR in these patients could be explained by the side effects of antiviral treatment or the infection itself. As the infection can cause hepatic injury via an inflammatory state, the abnormality in the INR occurs even in the absence of antiviral treatment.[12] Zhou et al[13] reported that coagulopathy was present in 50% of their patients with COVID-19 who died. Although our patients had a high INR at baseline, none of them had bleeding events, as stated in the current guidelines.[6,14] The correction of coagulopathy was not required in the present case series; however, there is no exact recommendation to approach a high INR in COVID-19 patients with a prosthetic heart valve.

The interaction between antiviral treatment and warfarin is also of concern. Early reports were in favor of the important role of KALETRA in the treatment of the novel Wuhan viral pneumonia.[15] KALETRA is one of the protease inhibitors of cytochrome P450, administered to patients with COVID-19 to reduce the viral load.[16] An increase in the level of transaminase 7 days after KALETRA administration has been reported,[17] and the interaction between warfarin and KALETRA have been mentioned in previous cases.[17,18] Possible interactions between oseltamivir and warfarin have also been reported, which could present with a rise in the INR.[19] Among our patients, eight were treated with KALETRA, and the other two patients were treated with oseltamivir.

At the same time, COVID-19 makes patients prone to the thrombotic state, which is a matter of great concern in patients with prosthetic heart valves. The inflammatory state in COVID-19 can give rise to a hypercoagulable state; in addition, the binding of the coronavirus to angiotensin-converting enzyme-2 receptors causes endothelial cell damage.[20] Moreover, the transient rise of antibodies related to antiphospholipid syndrome has been shown in patients with COVID-19.[21,22] However, this rise may not be accompanied by thrombosis.[21] All these mechanisms could predispose patients to the thrombotic state, which could explain the subtherapeutic INR on admission in 70% of our cases. Indeed, COVID-19 due to inflammatory response could produce a hypercoagulable state, resulting in a subtherapeutic INR. Such

TABLE 2 Laboratory and spiral chest CT findings in the patients with a prosthetic heart valve and novel Wuhan coronavirus pneumonia

Case No	INR[a]	INR[b]	Time interval[c], d	WBC count	Lymph (%)	Plt count	CRP, mg/dL	ALT, IU/L	AST, IU/L	LDH, IU/L	Cr, mg/dL	PCR	Main CT findings	Distribution of chest CT findings
1	1.59	20.4	3	7700	16	192 000	1.43	12	21	72	1.23	+	Centrilobular density	Unilateral, left lower lobe
2	2.14	>30	6	11 710	12.7	526 100	15.24	23	34	...	2.1	+	No specific finding	...
3	1.94	4	5	2320	39.4	251 000	14.14	...	...	...	1.6	−	GGO	Diffuse bilateral
4	2.71	8.5	6	12 810	16.9	205 000	0.24	14	23	186	1.16	+	GGO	Diffuse bilateral, mild bilateral PE
5	1.39	>10	5	25 610	10.2	433 000	8.2	15	35	547	0.8	−	GGO	Unilateral, left upper lobe
6	2.1	7.1	3	1920	36.1	116 200	8.92	177	27	521	1.14	+	GGO	Bilateral diffuse, mild bilateral PE
7	1.86	>30	6	8400	7.8	369 000	1.82	15	36	606	0.65	+	Consolidation	Unilateral, subpleural in left lower lobe
8	3.23	5.4	7	5200	46.1	290 000	16.5	12	36	779	0.6	+	GGO	Bilateral, subpleural, and basilar
9	1.37	5.8	8	7400	35.1	156 000	5.29	31	26	...	0.52	−	Consolidation	Bilateral, subpleural, and basilar
10	1.87	5.31	4	10 510	15.5	236 000	9.54	68	38	...	0.7	−	GGO	Diffuse, bilateral, and subpleural

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cr, Creatinine; CRP, C-reactive protein; CT, computed tomography; GGO, ground-glass density; INR, international normalized ratio; LDH, lactate dehydrogenase; lymph, lymphocyte; PCR, polymerase chain reaction; Plt, platelet; WBC, white blood cell.

[a]On admission.

[b]During antiviral therapy.

[c]Time-to-peak INR from the initiation of antiviral treatment.

patients are, therefore, prone to valve thrombosis, clot formation, and valve malfunction. None of our patients had bleeding events and were, thus, not subjected to the correction of coagulopathy. In addition, all our patients had a high INR within 5.3 days after starting antiviral treatment.

In light of our findings, it is reasonable to hospitalize all patients with a prosthetic heart valve and COVID-19 and perform bridging anticoagulation during the course of antiviral treatment whenever necessary. Close monitoring for bleeding and ischemic events by checking daily INR and the prothrombin time is suggested, as well. According to previous reports, coagulopathy is correlated with poor prognosis; however, based on our findings, we would posit that a high INR in the case of antiviral drug interaction with warfarin is not correlated with adverse events in COVID-19. Nevertheless, antiviral treatment has a serious interaction with warfarin, which causes an increase in the INR and at least theoretically renders the patient prone to bleeding.

4.1 | Limitations

The salient limitation of this study is its small sample volume; accordingly, we would recommend larger scale studies with longer follow-ups to evaluate the prognostic factors of the severity and outcome of COVID-19 in patients with prosthetic heart valve infection.

5 | CONCLUSION

The present study adds important insights into the outcome of COVID-19 in patients with a prosthetic heart valve. The current guidelines do not include a definite recommendation for bridging therapy in COVID-19 patients with a prosthetic heart valve. Bridging in these patients during the antiviral treatment course might be required and because of significant INR fluctuations, it might be safer to prescribe antiviral treatment in an inpatient setting. Coagulopathy in COVID-19 patients with a prosthetic heart valve in itself does not imply a poor prognosis.

CONFLICT OF INTERESTS
The authors declare that there are no conflict of interests.

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