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ORIGINAL ARTICLE

Thrombotic Events in Covid-19: Incidence and their Association with Lab Parameters, Vaccination Status and Mortality

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Abstract

Background & Objectives: Major arterial or venous thrombotic complications occur frequently with COVID-19. This risk seems to be present despite no known underlying thrombophilia and even adequate anticoagulation does not diminish its risk. Whilst pulmonary embolism may seem to be the most common thrombotic complication, others may also occur. A vaccination link to thrombotic events in COVID-19 has not been studied to the best of our knowledge.

Methods: In this retrospective cross-sectional study we determined the incidence of total thrombotic events, individual Venous Thromboembolisms (VTE) and Arterial Thromboembolisms (ATE) that occurred in patients requiring ICU admission for COVID-19 in one of Bahrain's main COVID ICU facilities for a period of 6 months. We also aim to determine mortality rate in this group of patients, links with specific baseline characteristics, laboratory parameters and patient vaccination status.

Results: We studied 1597 patients over 6 months, 6% of patients were found to have VTE or ATE with a cumulative incidence of 6.5% thrombotic events. Elevated D dimer >1 was associated with an increased risk of thrombosis and an increased risk of mortality. There was a higher risk of thrombotic events in unvaccinated individuals. All-cause mortality in COVID-19 patients complicated with thrombosis and mortality solely secondary to thrombotic event were both significantly higher in unvaccinated individuals.

Conclusions: Based on the findings of this study, unvaccinated individuals are at significantly higher risk of developing thrombotic events**.** This will assist in enabling physicians to lower their threshold of diagnosing such events. The urgency of lab parameters the swift management of other risk factors and the importance of vaccination against COVID-19 can be further studied.

Keywords: COVID-19, Venous Thromboembolisms, Arterial Thromboembolisms, Mortality, D dimer, Vaccination status

Introduction

Coronaviruses are a large family of enveloped, single stranded ribonucleic acid viruses, identified decades ago but whose clinical significance and epidemic potential were not recognized until the outbreak of severe acute respiratory distress

syndrome CoV (SARS CoV) and Middle Eastern Respiratory Syndrome (MERS) in 2002 and 2012, respectively. Symptoms range from a mild cold to severe respiratory distress with significant mortality rates.[1,2] In late December 2019, a cluster of pneumonia cases of unknown cause, initially linked to seafood and wet animal wholesale market, were reported in Wuhan, Hubei Province, China.[3] Thereafter, many countries reported similar cases, leading to a discovery of a novel CoV. In February 2020, the World Health Organization (WHO) defined the Coronavirus disease-2019 (COVID-19) as a viral illness caused by severe acute respiratory syndrome-coronavirus 2 (SARS CoV-2), the seventh member of CoV to be identified and later deemed it as a pandemic.[4]

One of the most striking features observed in COVID-19 is coagulopathy, with associated high incidences of thrombotic events and complications, predisposing patients to both VTEs and ATEs.[5,8,9-11] Thrombosis in COVID-19 may occur despite thromboprophylaxis with a standard prophylactic or therapeutic dose of low molecular weight heparin (LMWH), suggesting a profound procoagulant state.[12-20] Vaccination against COVID-19 has reduced severity of clinical symptoms, hospitalizations, mechanical ventilation and ICU admissions, and death.[21-24] We predicted that vaccination against COVID-19 may also reduce the risk of thrombotic events in patients with COVID-19. However, to date, we have not found any specific studies that have examined this and aimed to explore this association, if any.

We aimed to determine the percentage of total (objectively diagnosed) thrombotic events (ATEs and VTEs) in our patient population,

the individual rates of VTEs and ATEs: PE, Acute Coronary Syndrome (ACS), Ischaemic Stroke, Bowel Ischaemia, DVT/Limb Ischaemia and Miscellaneous, establish baseline characteristics in these patients (mean age; duration of symptom onset prior to admission; coagulation parameters on admission: D dimer, PT, aPTT, and Platelet count; comorbidities and specific risk factors other than COVID-19 for thrombosis; vaccination status) and ascertain whether or not the above contributed towards these thrombotic events or were associated with higher thrombotic events and/or mortality.

We also aim to secondarily deduce the overall mortality rate in our COVID-19 patients with thrombotic events and mortality rate associated independently with thrombotic events (defined as mortality solely / most likely secondary to the thrombotic event rather than other more prominent contributing factors such as ARDS / respiratory failure secondary to COVID-19, sepsis, multiorgan failure etc.) Additionally, we aim to determine the percentage of our COVID-19 patients with thrombotic events who were vaccinated (1 dose *vs.* 2 doses) vs unvaccinated, to establish if a link is noted, to determine whether mortality rate differed between the two groups.

Materials & Methods

Bahrain Defence Force (BDF) Hospital, Kingdom of Bahrain, opened a Field-Intensive Care Unit (FICU) in April 2020, and was one of the three ICU facilities available at the time for COVID-19 patients in Bahrain. Only male patients were admitted to BDF FICU. The only exceptions were made for ventilated COVID-19 female patients who required extracorporeal membrane oxygenation (ECMO) since it was the only facility in Bahrain to provide it. Majority of patients who were admitted to BDF FICU had severe COVID-19 pneumonia (requiring oxygen support of Non Rebreather Mask/Venturi Mask and above) or those who were on lower oxygen requirements but had significant risk factors for severe disease or evidence of complications of their underlying comorbidities requiring ICU care (e.g. Diabetic Ketoacidosis, Acute on Chronic Renal Failure with complications possibly requiring CRRT, Acute Decompensated Heart Failure, Asthma or Chronic Obstructive Pulmonary Disease exacerbation, Sickle Cell Disease crises) or complications of COVID-19 (eg. Thrombosis).

In this retrospective cross-sectional study, we included all patients admitted to BDF FICU between January 2021 and June 2021. This time period was chosen as it was during this time that the delta variant was prominent, the highest number of new

cases per day / active cases per day / critical cases per day / deaths per day were registered in Bahrain and the vaccination campaign was in full swing.

A total number of 1597 male patients were admitted during this period. All patients were diagnosed with COVID-19 using a reverse transcriptase-polymerase chain reaction (RT-PCR) of patient via a nasopharyngeal swab. Retrospectively, qualitative and quantitative data analysis was done using information gathered from the BDF System database (*Doctors Station*, *JIVEX*, *compiled admissions EXCEL*). Data was scrutinized for age, baseline characteristics, vaccination status, thrombotic events, morbidity and mortality.

Data was collected from time of admission till one of the following: discharge, transfer to another facility / hospital, death. Any thrombotic events that happened after the above are not known.

A thrombotic event was only included if it was confirmed using biochemical or radiologic objective methods: ECG, Troponin I, ECHO for ACS, CTPA diagnosed PE, CT brain diagnosed ischemic stroke, CT abdomen diagnosed bowel ischemia, CT angiography or U/S doppler diagnosed limb ischemia / DVT. All possible thrombotic events based only on clinical suspicion but not proven objectively, were excluded from this study.

Patient characteristics were described using standard descriptive statistics. The data was recorded and organized into Microsoft Excel (Microsoft Corporation, Redmond, WA, USA), and analyzed using SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY). Continuous variables are summarized as (mean ± SD) or median (25^{th}, 75^{th} percentile), and discrete variables as frequencies and percentages. Patient's characteristics were analyzed with mortality by Chi-square test of association or Fisher's Exact test. The univariate analysis was followed by logistic regression. *P* value <0.05 was considered statistically significant. Cumulative incidences were calculated for all thrombotic events and for VTEs and ATEs separately, for all-cause mortality and mortality secondary to thrombotic event independently, and for thrombotic events in vaccinated and unvaccinated population.

This study was approved by the BDF Research & Research Ethics Committee and the Bahrain National Taskforce Medical Research Team / COVID-19 Clinical Research Team.

Results

We included 1597 patients in our study, 96 (6%) of whom had a biochemically and / or radiologically diagnosed ATE or VTE. 8 patients had dual thromboses, leading to a total of 104 thrombotic events, i.e. a cumulative incidence of 6.5%. PE, as also shown in previous studies[12, 15] was the most frequently encountered thrombotic event (37 patients out of 96, 38.5%) followed closely by ACS (35 patients out of 96, 36.5%).

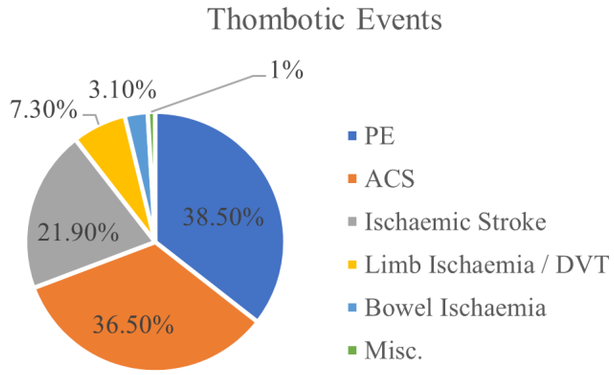

Figure 1: Percentage of individual VTEs / ATEs

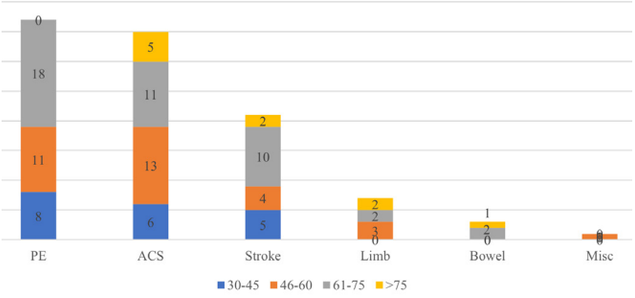

Figure 2: Age Distribution For each Thrombotic Event

A total of 96 patients with thrombotic events were included in the analysis. Their ages ranged from 30-106 with mean age 58.82 +/- 14.47. Some information e.g. Laboratory parameters were not available for all patients on admission hence data was collected from the total number available instead of 96. Symptoms were seen in 64.4% of patients for >5 days duration prior to admission. D dimer of >1 was seen in 79.1% supporting the fact that elevated D dimer on admission is a risk factor

for thrombotic event, whereas elevated PT or APTT or thrombocytopenia did not show a significant association, consistent with previous studies.[25-27] Only 20 out of 96 patients (20.8%) had a prior risk factor for thrombotic event which proves that an underlying risk factor was not necessary for thrombosis in COVID-19 patients. 2 patients had 2 risk factors simultaneously. All patients were started on anticoagulant therapy on admission, majority therapeutic. Thrombotic events developed in 78.1% of patients post admission while on anticoagulant therapy, suggesting that despite adequate anticoagulation, risk of thrombotic event was still very significant.

Of those who developed thrombotic events, 87.5% were not fully vaccinated (2 doses), hence suggesting that unvaccinated individuals are at significantly greater risk of developing thrombotic events secondary to COVID-19. At the time of this study, booster doses were still not available.

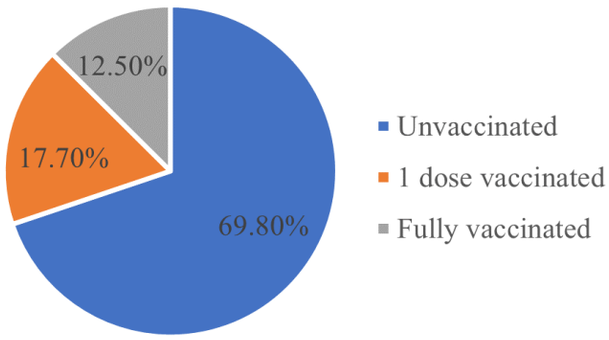

Figure 3: Vaccination status of COVID-19 patients with thrombotic events

Patient characteristics are summarized in Table 1.

Table 1: Descriptive Statistics of Patient's Characteristics

Variable		Frequency (%)
Thrombotic event	PE	37 (38.5)
	ACS	35 (36.5%)
	Stroke	21 (21.9%)
	Limb	7 (7.3)
	Bowel	3 (3.1)
	Misc	1 (1%)
Age (mean ± SD)		**58.82 ± 14.47**
Age	30-45	18 (18.8)
	46-60	30 (31.3)
	61-75	38 (39.6)
	>75	10 (10.4)
Comorbidities	Yes	66 (68.8)
	None	30 (31.3)
Duration of Sx prior to admission (median (25th, 75th Percentile))		**7 (4, 12)**
Duration of Sx prior to admission	> 5 days	58 (64.4)
	≤ 5 days	32 (35.6)
Had a risk factor of thrombosis	Yes	20 (20.8)
	No	76 (79.2)
Risk factor of thrombosis	Prior H/O thrombosis	18 (18.8)
	Bedbound	4 (4.2)
	Recent surgery or trauma	0 (0)
	Active Ca	0 (0)
D dimer (median (25th, 75th Percentile))		**3 (1.28, 12.25)**
D dimer	> 1	68 (79.1)
	≤ 1	18 (20.9)
PT (median (25th, 75th Percentile))		14 (13, 16)
PT	> 15	26 (27.7)
	≤ 15	68 (72.3)

APTT (median (25th, 75th Percentile))		**36 (33, 44.25)**
APTT	> 45	20 (21.3)
	≤ 45	74 (78.7)
Plt (median (25th, 75th Percentile)		**248 (181, 326)**
Plt	≥ 150	84 (88.4)
	< 150	11 (11.6)
Diagnosis	Before admission	21 (21.9)
	After admission	75 (78.1)
Anticoagulation Status	Therapeutic	91 (94.8)
	Prophylactic	5 (5.2)
Vaccination Status	Unvaccinated	67 (69.8)
	1 dose	17 (17.7)
	2 doses	12 (12.5)
Completed two doses	Yes	12 (12.5)
	No	84 (87.5)
Outcome	Expired	43 (44.8)
	Transferred	23 (24)
	Discharged	30 (31.3)
Mortality	Yes	43 (44.8)
	No	53 (55.2)
Mortality secondary to thrombosis	Yes	19 (44.2)
	No	24 (55.8)

Mortality rate stratified by patient's characteristics is displayed in table 2. Significant variables from the univariate analysis were included in the multivariate model.

Table 2: Associations between Patient's Characteristics and Overall Mortality Rate

Variable		N	Mortality (N (%)) P-value	Univariate OR (95% CI)	Multivariate P-value	
PE	No			.001**	Ref.	<.001**
	Yes	37	9 (24.3)		0.176 (0.071, 0.436)	
ACS	No			.065	-	-
	Yes	35	20 (57.1)			
Stroke	No			.198	-	-
	Yes	21	12 (57.1)			
Limb	No			.086†	-	-
	Yes	7	4 (57.1)			
Bowel	No			.697†	-	-
	Yes	3	3 (100)			
Misc	No			>.05†	-	-
	Yes	1	0 (0)			
Age	30-60	48	14 (29.2)		Ref.	.010*
	61-109	48	28 (58.3)		3.540 (1.348, 9.293)	
Comorbidities	None	30	13 (43.3)	.846	-	-
	Yes	66	30 (45.5)			
Duration of Sx prior to admission	≤ 5 days	32	15 (46.9)	.409	-	-
	> 5 days	58	22 (37.9)			

Had a risk factor of thrombosis	No	76	33 (43.4)	.599	-	-
	Yes	20	10 (50)			
Prior H/O thrombosis	No	78	35 (44.9)	.974	-	-
	Yes	18	8 (44.4)			
Bedbound	No	92	40 (43.5)	.322†	-	-
	Yes	4	3 (75)			
D dimer	≤ 1	18	4 (22.2)	.035*	Ref.	.020*
	> 1	68	34 (50)		4.97 (1.281, 19.308)	
PT	≤ 15	68	25 (36.8)	.030*	Ref.	.111
	> 15	26	16 (64)		1.949 (0.858, 4.427)	
APTT	≤ 45	74	32 (43.2)	.888	-	-
	> 45	20	9 (45)			
Plt	< 150	11	6 (54.5)	.529†	-	-
	≥ 150	84	36 (42.9)			
Diagnosis	Before	21	10 (47.6)	.768	-	-
	After	75	33 (44)			
Anticoagulation Status	Therapeutic	91	39 (42.9)	.170†	-	-
	Prophylactic	5	4 (80)			
Vaccination Status	Unvaccinated	67	31 (46.3)	.667	-	-
	1 dose	17	6 (35.3)			
	2 doses	12	6 (50)			
Completed two doses	No	84	37 (44)	.698	-	-
	Yes	12	6 (50)			

* Significant at the 0.05 level;** Significant at the 0.01 level;† Chi-square test assumptions were violated, so Fisher's Exact test was used instead.

As seen above, 50% of patients with a D-dimer >1 expired {OR 4.97 (1.281, 19.308 95% CI)}, statistically significant at P-value 0.020, whereas only 22.2% of patients with D dimer <1 expired. 64% of patients with PT>15 expired compared to 36.8% with PT≤15 {OR 1.949 (0.858, 4.427 95% CI)}, still proving a link though not as statistically significant as elevated D-dimer. Previous studies have also established this.[11, 19, 25, 28-29] Mortality rate was noted to increase with increasing age.

Overall mortality rate in COVID-19 patients with thrombotic events was 44.8% (43 patients out of 96). This was similar to the data published in a study of 3334 patients, where all-cause mortality was 43.2% in patients with thrombotic events.[30] 37 out of the 43 patients (86%) were not fully vaccinated, suggesting higher incidence of all-cause mortality in unvaccinated individuals in patients with thrombotic events in COVID-19 patients.

Out of the 43 patients, 19 patients (44.2%) cause of death was determined as solely secondary to the thrombotic event. 15 out of 19 patients (79%) were not fully vaccinated, again suggesting higher incidence of mortality solely secondary to thrombotic event in unvaccinated individuals.

Table 3: Mortality rates for each age group

Age Groups	N	Mortality	P-value
30-45	18	4 (22.2%)	0.033*
46-60	30	11 (36.7%)	
61-75	38	21 (55.3%)	
>75	10	7 (70%)	

Table 4: Age analyzed as a continuous variable (using t-test)

	Mortality	N	Mean	Std. Deviation	P-value	Mean Difference	95% CI for mean difference
Age	Expired	43	63.93	14.340	0.002**	9.251	3.635, 14.867

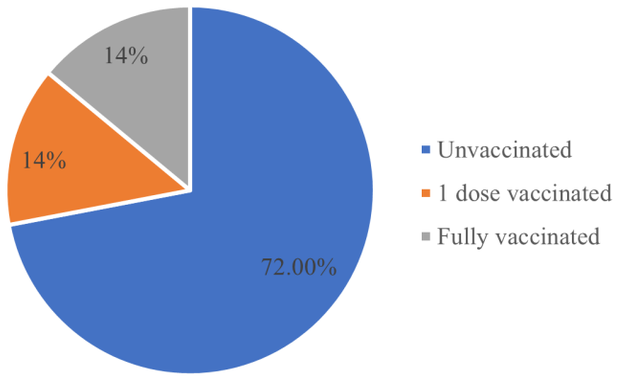

Figure 4: All-cause mortality depending on vaccination status

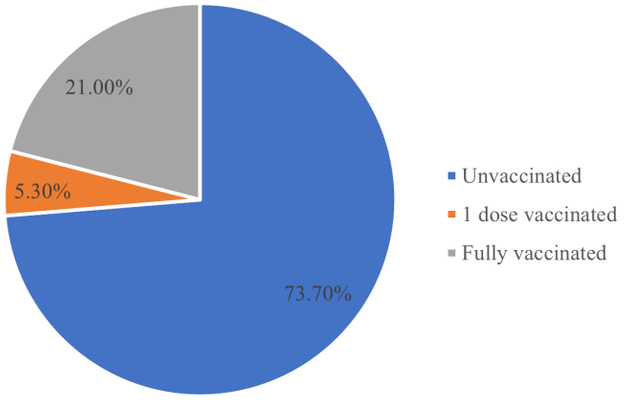

Figure 5: Mortality secondary to thrombotic event depending on vaccination status

Discussion

Till date, to our knowledge, a vaccination link to thrombosis in COVID-19 has never been studied. One of the strengths of our study is that we studied this link and established the association between vaccination and thrombotic events in COVID-19 and mortality rate in vaccinated *vs* unvaccinated COVID-19 patients who developed thrombosis. This makes our study pathbreaking.

Several studies have been published on coagulation parameters and anticoagulation management in COVID-19 rather than on their influence on thrombotic risk or on the thrombotic events themselves, which we have attempted to do in our paper.

Most VTEs are asymptomatic and whether they are the cause of death or only concurrent events remains controversial.[19] We have tried to explore this association.

Perhaps the greatest limitation is that this being a retrospective study, we could only use data available to us, some information was missing or not collected. Additionally, the data collection ceased upon either discharge / transfer / death. Thrombotic events that happened after the above remain unknown hence the incidence underestimated, leading to a somewhat immortal time bias. An option to combat this would be to follow up the discharged or transferred patients for 6-12 months post-COVID and note how many were diagnosed with a thrombotic event at a later stage. Additionally, only male patients requiring ICU admission were included in this study.

The incidence of thrombotic events in our patient population of 6.5% is similar to that reported by previous studies based in the USA.[31-33] Other studies have reported incidences ranging as low as 5% to as high as 42%[12, 14-15, 31, 34-35], however, some had a smaller sample size, included only VTEs, included only ward or only ICU patients, had more lenient diagnostic criteria which included thrombotic events based on clinical suspicion only. Perhaps a limitation is that we only included objectively diagnosed thrombotic events and not clinically suspected ones.

A diagnostic challenge arises among patients with COVID-19, as imaging studies may not be pursued due to logistic reasons: unavailability of radiological resources within facilities particularly temporary make-shift ones, inability to shift patients for imaging due to hemodynamic instability and risk of transmitting infection to other patients and healthcare workers. Imaging studies may also be challenging in patients who are hypoxemic requiring invasive or non-invasive ventilation or those required to be in prone position. This is a limitation to confirm diagnosis of PE, stroke, and bowel ischemia. Though clinically probable, these are underdiagnosed since other differential diagnoses for the clinical picture are also possible (e.g. hypoxia and ARDS, hypoxic encephalopathy, other co-existing intra-abdominal pathology respectively). Alternatively, if based on clinical suspicion only, one may overestimate the incidence, given that all of the above differential diagnoses are also possible.

ACS, though, is diagnosed based on clinical symptoms, elevated troponin I and ECG changes. But if the patient is unable to communicate or is asymptomatic cardiac wise with a mildly elevated troponin I and borderline ECG, other differentials such as myocarditis and sepsis may exist. In our study, we only included patients in whom ECG and cardiac markers were significant, diagnosis of ACS was agreed by Cardiologist and no other diagnosis was more likely. Recent data showed that approximately 40% of patients with COVID-19 and STEMI did not present with culprit lesions at coronary angiography.[36] Possible pathogenetic mechanisms of this are acute myocarditis, type 2 myocardial infarction due to mismatch between oxygen demand and supply or Takotsubo-like myocardiopathy.[37]

It is possible that thrombotic events may remain under or overestimated depending on which patients are included and on what diagnostic criteria; there can be variations based on physician suspicion and on diagnostic availability and feasibility.

Another vital observation was that the risk of thrombotic events despite anticoagulation was extremely high. This suggests that provision of adequate prophylaxis without subjecting the patient to a significantly higher risk of bleeding, a lower threshold for suspecting thrombotic events and a lower threshold for diagnostic imaging (perhaps earlier on in the disease when the patient is more stable) should be implemented. Moreover, any other factor that could contribute to the risk be eliminated or controlled where possible, since it is possible that the procoagulant state of COVID-19 does not respond to or exists despite regular anticoagulation.

Conclusion

In this study with a sample size of 1597 patients over 6 months, 6% of patients were found to have objectively diagnosed VTE or ATE with a cumulative incidence of 6.5% thrombotic events. PE and ACS were the two most common thrombotic events diagnosed. Prior risk factors for thrombosis did not seem to play a huge role as majority of patients had no underlying risk factors. It was apparent and statistically significant that an elevated D dimer >1 was associated with an increased risk of thrombosis and an increased risk of mortality. It was proven that despite adequate anticoagulation, risk of thrombotic event was still very significant. Increasing age was proven to be associated with increased mortality. The most pathbreaking aspect of our study was the link established between vaccination status, thrombotic events and mortality. Unvaccinated individuals were at significantly higher risk of developing thrombotic events. Additionally, all-cause mortality in COVID-19 patients complicated with thrombosis and mortality solely secondary to thrombotic event were both significantly higher in unvaccinated individuals.

This knowledge enables physicians to be prompt in their review of patient characteristics and lab parameters, start adequate anticoagulation after assessing bleeding risk and lower threshold of diagnosing thrombotic events early on in the disease when it may be more logistically possible even if asymptomatic. More studies to further evaluate vaccination status and its association to thrombotic events in COVID-19 and mortality are necessary as this can be pathbreaking, as it is a variable that can be controlled.

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Conflict of Interest

The Authors declare that there is no conflict of interest.

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