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Is Atrial Fibrillation a Risk Factor for Worse Outcomes in Severe COVID-19 Patients: A Single Center Retrospective Cohort

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Abstract

Introduction: New onset atrial fibrillation leads to worse outcomes in patients with sepsis. The association between new onset atrial fibrillation (AF) in COVID19 patients with COVID19 outcomes are lacking. This study aims to determine whether new onset atrial fibrillation in COVID19 patients admitted in the ICU is a risk factor for death or requirement of mechanical ventilation (MV).

Methods: This is a retrospective study conducted in a cohort of COVID-19 patients admitted to Bahrain Defence Force COVID19 Field ICU between April 2020 to November 2020. Data were extracted from the electronic medical records. The patients who developed new onset AF during admission were compared to patients who remained in sinus rhythm. Multivariate logistic regression models were used to control for confounders and estimate the effect of AF on the outcomes of these patients.

Results: Our study included a total of 492 patients out of which 30 were diagnosed with new onset AF. In the AF group, the primary outcome occurred in 66.7% of patients (n = 20). In the control group, 17.1% (n = 79) developed the primary outcome.

Upon adjusting for the confounders in the multivariate regression model, AF had an odds ratio of 3.96 (95% CI: 1.05 – 14.98; p = 0.042) for the primary outcome.

Conclusion: Our results indicate that new onset AF is a risk factor for worse outcomes in patients admitted with COVID19 in the ICU.

Keywords: Atrial fibrillation, arrhythmia, atrial arrhythmia, COVID-19, Sars-CoV2, Corona virus, ICU, Critical Care, Bahrain

Introduction

SARS-CoV2 continues to spread rampantly since its emergence in Wuhan, China in December 2019. To date, this novel virus has infected more than 175 million people and resulted in more than 3.7 million deaths worldwide [1]. People with history of cardiovascular disease are considered at a high risk for severe COVID19 [2]. Severe COVID19 have been associated with an

increase in Troponin-I levels which suggests a myocardial injury and is associated with poor outcomes [2]. Severe COVID-19 disease is also known to cause a spectrum of cardiovascular complications such as acute coronary syndromes, myocarditis, heart failure and arrhythmias [3].

In a study conducted in New York on 393 patients with COVID19, atrial arrhythmias were more prevalent among patients requiring mechanical ventilation [4].

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Similarly Colon et al reported that new onset atrial tachyarrhythmias were only seen in COVID19 patients admitted in the ICU and none in the general medical services [5].

AF has been associated with worse clinical outcomes in patients with sepsis [6].

With atrial fibrillation (AF) being the most common arrhythmia in the severely ill COVID19 patients, this suggests that it is possible that people who develop atrial fibrillation during their COVID19 illness are at an increased risk of poor outcomes [7].

Studies that examine the effect of Atrial fibrillation on COVID-19 outcomes are a few and it is predicted that these patients might have unfavorable outcomes with high rates of morbidity and mortality.

This study aims to determine if Atrial fibrillation is a risk factor for the primary outcome (death or requirement of mechanical ventilation) in severe COVID-19 cases.

Objectives

Compare the odds ratio of mechanical ventilation or death in COVID19 patients with atrial fibrillation to non-atrial fibrillation patients.

Methods

Study design and setting

This is a retrospective study conducted in a cohort of COVID-19 patients admitted to Bahrain Defence Force COVID19 Field ICU between April 2020 to November 2020. The BDF-FICU is a field hospital, transformed from a multistorey parking lot into a fully equipped hospital with an ICU setting. Only male patients with severe COVID 19 disease were admitted to the BDF-FICU [8].

Outcomes

The primary endpoint are the requirement of mechanical ventilation or death. The outcome was compared between patients who developed new onset AF with COVID19 to patients with COVID19 in sinus rhythm.

Data sources and variables assessed

All COVID-19 patients admitted to the Field Hospital (BDF-FICU) in the study period were included and their data extracted from the electronic medical records. The data gathered included patients' demographic details, vital signs, peak

laboratory test results, past medical history, ECG findings, echocardiographic finding and outcomes.

Diagnosis

The following methods were used to diagnose COVID-19

COVID-19

All patients were confirmed to be infected by SARS-CoV-2 using a PCR test of a nasopharyngeal sample. The PCR test was conducted using Thermo Fisher Scientific (Waltham, MA) TaqPath 1-Step RT-qPCR Master Mix, CG on the Applied Biosystems (Foster City, CA) 7500 Fast Dx RealTime PCR Instrument. The assay used and targeted the E gene. If the E gene was detected, the sample was then confirmed by RdRP and N genes. The E gene Ct value was reported and used in this study. Ct values > 40 were considered negative. Positive and negative controls were included for quality control purposes.

Exposure assessment

Atrial fibrillation

All admitted patients ECGs and their medical records were examined for the presence of Atrial fibrillation Any patient who developed atrial fibrillation (paroxysmal or continuous) during the course of admission was added to the atrial fibrillation group. Cases who developed atrial fibrillation after the onset of mechanical ventilation were considered as controls (non-atrial fibrillation). Cases with known history of atrial fibrillation were excluded from this study.

Statistical analysis

The distribution of groups were summarized. Bivariate associations were analyzed using Chi-squared (χ^2) tests for categorical variables and t-test for continuous variables. We assessed endpoints and their associations with both groups.

Multivariable logistic regression model was used to estimate the relationship between atrial fibrillation and death. Given that 99 cases developed the outcome, and in order to prevent model over fitting, 9 variables at most were allowed in the model building. In order to choose the adjusted factors in the multivariate model, a univariate analysis between other variables and the outcome was conducted. Variables without group differences were excluded from the univariate analysis. A p value of 0.2 was used to screen

the other variables. Colinear variables were excluded from the multivariate model. The included covariates were selected based on each variable association with the outcome and the predictor in a univariate analysis. Post estimation testing, AUC and Adjusted R-Square were used to compare regression models and select the final model.

A two sides p value of 0.05 was considered statistically significant. The STATA software, version 15.1, was used to execute the statistical analyses, (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC.) [9].

Ethical approval

The protocol and manuscript for this study were reviewed and approved by the National COVID-19 Research Committee in Bahrain. All methods and retrospective analysis of data was approved by the National COVID-19 Research and Ethics Committee, and carried out in accordance with the local guideline and ethical guidelines of the Declaration of Helsinki 1975. All data used in this study was collected as part of normal medical procedures.

Informed consent was waived by the National COVID-19 Research and Ethics Committee for this study due to its retrospective and observational nature and the absence of any patient identifying information.

Results

492 cases with severe COVID19 were included. Of which a total of 30 patients were diagnosed with new onset AF. Table 1 summarizes the baseline characteristics of both groups. The mean age of the AF group was 70.0 years in comparison to 52.3 years in the control group. 96.4% (n = 27) of the atrial fibrillation

group were Bahraini nationals, compared to 69.6% (n = 312) of the non-atrial fibrillation group.

Diabetes, hypertension, coronary artery disease and heart failure were more common in the AF group. 46.7% were diabetic 56.7% were hypertensive, 33.3% had coronary artery disease and 10% had heart failure. Significant differences at the 0.05 level between the two groups were only seen in coronary artery disease and heart failure. The prevalence of diabetes and hypertension were not significantly different across the studied groups.

The biochemical markers showed significant differences between the study and control groups. The mean CKMB (IU/L) level was 91.4 (± 110.5) in the Atrial fibrillation group compared to 55.3 (± 87.0) in the control group (p = 0.03). Mean eGFR (ml/min/1.7 m²) was 43.6 (± 18.0) in the Atrial fibrillation group compared to 55.4 (± 12.2) in the control group (p < 0.001). BNP (pg/ml) was significantly elevated in Atrial fibrillation, mean level 4814.4 (± 10606.7) compared to 715.9 (± 4155.3). Ddimer (ug/ml) was also significantly elevated in Atrial fibrillation group, mean DDimer was 7 (± 7) in the Atrial fibrillation group compared to 3.4 (± 5.7) in the control group. Fig. 1 shows the mean level of biochemical markers stratified by AF status. Peak troponin level were not significantly different between the two groups. The AF group had significantly lower systolic BP, higher blood urea and serum creatinine and had more patients requiring inotropic.

The characteristics of the studied sample and the in hospital investigations and management are summarized in Tables 1 and 2.

Disease outcomes

In the Atrial fibrillation group, the primary outcome of mechanical ventilation or death

Table 1. Baseline characteristics.

Factor	Level	Non-Atrial fibrillation	Atrial fibrillation	p-value
N		462	30	
Age, mean (SD)		52.3 (15.7)	70.0 (11.8)	<0.001
Bahraini National		312 (69.6%)	27 (96.4%)	0.002
Alcohol		10 (2.2%)	0 (0.0%)	0.42
Diabetes		166 (35.9%)	14 (46.7%)	0.24
Hypertension		181 (39.2%)	17 (56.7%)	0.058
Coronary artery disease		49 (10.6%)	10 (33.3%)	<0.001
Heart failure		6 (1.3%)	3 (10.0%)	<0.001
Pulmonary Embolism		1 (0.2%)	0 (0.0%)	0.80
LVEF, mean (SD)		51.2 (12.3)	48.6 (11.7)	0.37
Smoking	None	392 (84.8%)	24 (80.0%)	0.64
	Current smokers	27 (5.8%)	3 (10.0%)	
	Ex smokers	43 (9.3%)	3 (10.0%)	

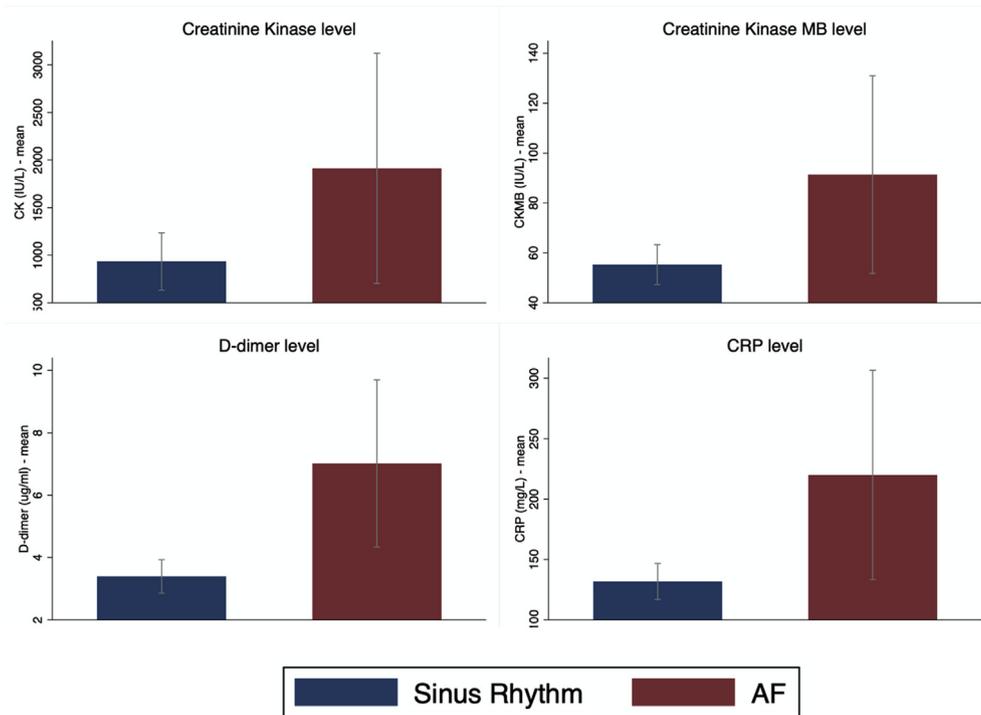


Fig. 1. Mean level and 95% Confidence interval of biochemical markers (CK, CKMB, CRP D-dimer) stratified by AF status.

occurred in 66.7% of patients (n = 20) as compared to 17.1% (n = 79) in the control group.

In the AF group, 16 patients (53.3%) required mechanical ventilation and 17 (56.7%) deaths

occurred. In the control group, 62 patients required mechanical ventilation (13.4%) and 64 (13.7%) deaths occurred. These difference were highly significant in all the aforementioned cases (p < 0.001).

Table 2. In hospital investigations and management.

Factor	Reference range	Non-Atrial Fibrillation	Atrial Fibrillation	p-value
N		462	30	
Vital signs^a				
Systolic Blood Pressure, mmHg, mean (SD)	≤120	126.8 (20.5)	111.8 (21.6)	<0.001
Diastolic Blood Pressure, mmHg, mean (SD)	≤80	73.1 (33.8)	62.7 (12.9)	0.095
Heart Rate, bpm, mean (SD)	60-100	83.0 (16.4)	87.4 (23.2)	0.16
Laboratory results^b				
Troponin I (Peak), ug/L, mean (SD)	<0.04	1.8 (11.4)	0.8 (1.9)	0.65
CK, IU/L, mean (SD)	55-170	934.6 (3270.1)	1912.0 (3314.3)	0.12
CKMB, IU/L, mean (SD)	≤25	55.3 (87.0)	91.4 (110.5)	0.031
CRP, mg/L, mean (SD)	<5	131.8 (161.8)	220.0 (233.1)	0.007
Urea, mmol/L, mean (SD)	1.8 – 7.1	9.2 (8.2)	18.1 (11.1)	<0.001
Creatinine, umol/L, mean (SD)	60-100	95.9 (87.7)	157.4 (124.9)	<0.001
Estimated Glomerular filtration rate, ml/min/ 1.7 m ² , mean (SD)	>60	55.4 (±12.2)	43.6 (±18.0)	<0.001
BNP, pg/ml, mean (SD)	<125	715.9 (4180.0)	4814.4 (10606.7)	<0.001
D-dimer, ug/ml, mean (SD)	<0.4	3.4 (5.7)	7.0 (7.1)	0.002
INR, mean (SD)	≤1.1	1.6 (6.5)	1.6 (0.6)	0.99
Anticoagulation				
Type of anticoagulant		462 (100%)	30 (100%)	–
	Heparin	448 (97.0%)	20 (66.7%)	<0.001
	Warfarin	0 (0.0%)	4 (13.3%)	
	NOAC	14 (3.0%)	6 (20.0%)	
Inotropes				
		45 (9.8%)	13 (44.8%)	<0.001

^a Vital signs were measured on admission.

^b Laboratory values are the peak levels prior to the development of the primary outcome.

Table 3. Disease outcome.

Factor	Non-Atrial Fibrillation	Atrial Fibrillation	p-value
N	462	30	
Primary Outcome	79 (17.1%)	20 (66.7%)	<0.001
Ventilation	62 (13.4%)	16 (53.3%)	<0.001
Death	64 (13.9%)	17 (56.7%)	<0.001

The unadjusted odds ratio for Atrial fibrillation patients developing the outcome was 9.70 (95% CI: 4.37 – 21.51; $p < 0.001$). Upon adjusting for confounders in the multivariate model, we found the odds ratio to be 3.96 (95% CI: 1.05 – 14.98; $p = 0.042$). Tables 3 and 4 summarizes results

Additional details on the statistical models are available in the Appendix.

Discussion

COVID 19 has been associated with increase in mortality and morbidity among ICU admitted patients since December 2019 when it was first reported in China [2,10]. In this study, we looked at AF as a parameter that may contribute to outcomes in severe COVID 19 patients admitted in the ICU. Atrial fibrillation was significantly associated with an increase odds in the requirement for mechanical ventilation and/or in hospital death in hospitalized COVID-19 patients in the ICU.

There was several differences between the studied groups. The AF group were older, had more prevalent comorbidities and had a higher incidence of the studied outcome.

Atrial Fibrillation is the most common arrhythmia seen in elderly, with a reported disease burden of more than 33 million world wide [11,12]. Moreover, AF can be triggered by systemic infection [13]. Hence, the elderly population were at a greater risk to develop AF. The relationship between age and atrial fibrillation explains the difference in the mean age observed between the two groups. Age has a significant association with worse disease progression in COVID19 [7,14], especially in patients above 60 years of age [15]. In a study conducted on 72314 COVID19 cases in China, increasing age was

strongly associated with COVID-19-related death, with people aged 80 or over having a more than 20-fold-increased risk compared to 50–59-year-olds [16].

The prevalence of baseline comorbidities, namely diabetes, hypertension, coronary artery disease and heart failure, were more common in the AF group. Multiple reasons explain the observed difference. These comorbidities are known risk factors for AF. In the Framingham heart study, age adjusted risk factors for the development of AF were diabetes mellitus, hypertension, coronary artery disease and smoking [17]. Furthermore, many of these comorbidities are considered age related comorbidities and hence are expected with the higher mean age observed in our study [14]. The higher prevalence of these comorbidities coupled with the increased mean age can explain the difference observed in the studied groups. Moreover these are also important risk factors for worse disease outcomes and hence are significant confounders. Similar findings were reported in a study by Peltzer et al, who observed increased comorbidities and higher mean age in hospitalized COVID19 patients with AF [18].

The differences observed in nationality is of interest. Upon further examining the data, more than 80% of the non-Bahraini nationals were from Asian countries and are expatriate workers. This population is generally of a much younger age as they represent majority of the working force in labor jobs. Younger patients have lower prevalence of AF [14]. In our sample, the non-Bahraini population were the younger sample, and hence populated the non-AF group given their lower risk for AF. This could have led to the observed differences in nationality. A study by Mallah et al which described the demographics of 83,811 COVID19 cases in Bahrain reported similar findings in regards to nationality [19]. This findings has also been discussed in another study published from Bahrain which studied 63 thousand COVID19 cases [20]. It is also plausible that the difference in nationality carries different risk factors for the development of disease and having a worse COVID19 outcomes. South Asian were at a higher risk than white ethnicity for

Table 4. Primary outcome analysis.

Analysis	Value	P value
Number of events/number of participants at risk (%) in the total sample	99/492 (20.1%)	-
Number of events/number of participants at risk (%) in the Atrial fibrillation group	20/30 (66.7%)	-
Number of events/number of participants at risk (%) in the Non-Atrial fibrillation group	79/462 (17.1%)	-
Crude analysis – Odds ratio (95% CI)	9.70 (95% CI: 4.37 – 21.51)	$P < 0.001$
Multivariate analysis* – Odds ratio (95% CI)	3.96 (95% CI: 1.05 – 14.98)	$P = 0.043$

*Adjusted for: Age, DM, HTN, CAD, GFR, Nationality, CRP, DDimer

COVID19 related death in a study conducted in the USA [21].

Atrial fibrillation is associated with worse outcomes in COVID 19

Atrial fibrillation has been shown to be an independent risk factor of mortality in patients admitted with septic shock. Furthermore, AF is an independent mortality predictor for patients presenting with myocardial infarction and heart failure [22,23].

Systemic inflammatory response as well as sepsis are both entities which are associated with multi-organ involvement. The onset of Atrial fibrillation in these patients carries a worse prognosis [6]. This was linked to the direct effect of septic mediators as well as to their effect on the myocytes [24].

The presence of comorbidities (including diabetes, heart failure, coronary artery disease and hypertension) are associated with poorer outcomes in any patient with AF; also making these patients more prone to thromboembolic events [25,26].

The AF group had a significantly higher rise in biochemical parameters (CK, D-Dimer, CRP) as well as higher percentage of inotrope use (44.8% compared to 9.8%. $P < 0.001$). These have been shown to be markers severe inflammatory response in severe COVID disease and probably new onset of AF may also be the result of cytokine release syndrome in severe COVID19 [18].

In our study newly detected Atrial fibrillation in COVID 19 positive patients was associated with worse clinical outcomes (death and/or ventilator support), despite the higher baseline risk in the AF group. There was an increase in mortality and the requirement of invasive ventilation in the atrial fibrillation group compared to patients in sinus rhythm. The effect was significant after adjusting for confounding factors, which included age, nationality, comorbidities and laboratory biomarkers. There was 56.7% death in the AF group compared to 13.9% in the non-AF group ($P < 0.001$) and mechanical ventilation requirement in 53.3% in AF vs 13.4% in control ($p < 0.001$). This indicates that the development of new onset atrial fibrillation in COVID19 patients in the ICU negatively impacts the clinical course of the diseases and carries worse outcomes.

These findings are reinforced by similar results that were reported by Zaniar Ghazizadeh et al, who reported that patients with COVID19 and with Atrial fibrillation or flutter had significant lower odds of ICU survival (OR 0.22; 0.08 to 0.59; $p = 0.002$) and increased risk of death (OR 2.47 [1.35-4.53], $p = 0.004$) [27]

Sans et al also reported a higher incidence of all cause mortality in COVID19 patients with new onset atrial fibrillation [28].

Peltzer et al studied the effect of atrial arrhythmias in patients hospitalized with COVID-19 and concluded that atrial arrhythmias are independently associated with increased mortality [18].

AF in COVID 19 patient is not necessarily a result of direct myocardial injury

It is unclear yet if the AF onset is a direct consequence of COVID19 infection on the myocyte or as a systemic response to the inflammatory process in the body or both.

Some COVID19 patients may have substrate for AF and the COVID19 infection acted as trigger for precipitating AF while other studies have suggested that SARS-CoV2 virus may directly involve cardiac tissue inflammation through multiple mediators modulating the activities of the atrial myocytes [3,13,29–31]

In our study, the peak troponin level were not significantly different between cases who developed AF and those who did not. Those who developed atrial fibrillation had lower mean peak troponin level (mean: 0.844; SE: 0.35 95%; CI: 0.13 to 1.56) compared to the non-atrial fibrillation group (mean: 1.80; SE 0.53 95%; CI: 0.75 to 2.84).

This probably supports the theory that AF onset is secondary to systemic illness rather a direct COVID 19 effect on myocyte. Also these findings are in concordance with what Colon et al and Bhatla et al have reported [5,32].

Treatment protocol for the Atrial fibrillation COVID 19 patients

Most patients with AF were treated with a rate-controlled strategy. Trans-esophageal echocardiograms and cardioversions were discouraged due to exposure risk [33].

The patients admitted with pneumonia are at increased risk of venous thromboembolism [34]. All patients in the study were anti-coagulated with either low molecular weight heparin, heparin or novel oral anticoagulant. The dosage used included full anticoagulation doses. This use stemmed from the guidance by the British thoracic society which categorized high risk patients to have an increased risk of venous thromboembolism, as well as other studies and local protocol which supported anticoagulation at that time [35–39]. Early treatment with anticoagulation has shown to speed up the recovery in severe

COVID19, where as delay in the initiation may end with bad prognostic response [40].

The use of anticoagulation across the health system evolved rapidly during the study period. All patient in this study receive standard COVID treatment protocol and a form of anticoagulant as shown in Table 2 [39].

Strengths

Restriction of the sample to a single center allowed controlling for confounding caused by treatment regimens, available services and center differences. Moreover, the manual revision of the electronic medical records ensured high quality data collection. The use of regression models allowed adequate control of measured confounding variables. The study was conducted on a large sample of critically ill patients and represent the only study in the region to study such association.

Limitations

The study conducted was a retrospective observational study and most of the limitations stem from the design of the conducted study. Some variables were undocumented and hence not analyzed, leaving room for potential bias, like obesity. The fact that all cases were critically ill males, limits the generalizability of the results observed.

Conclusion

New onset atrial fibrillation is a risk for worse outcomes in patients admitted with severe COVID19 in the ICU. New onset atrial fibrillation in COVID19 increases risk of mechanical ventilation requirement and mortality. Further studies are required to further understand this association.

Author contributions

Data collection: Safraz Nawaz, Fawaz Bardooli. Analysis and interpretation of data: Abdulkarim Abdulrahman, Abdulrahman Almadani. Drafting of manuscript: Abdulkarim Abdulrahman, Fawaz Bardooli. Revising and editing the manuscript critically for important intellectual contents: Shereen AlShaikh, Abdulrahman Almadani, Tajammul Hussain.

Conflict of interest

The authors have declared that no conflict of interest exists.

Ethics approval

The study was approved by the National COVID-19 Research and Ethics Committee.

Funding

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We would like to express our gratitude towards our colleagues in the BDF FICU who played an essential role in pandemic. We thank all the participants of the study and hope they will lead a long healthy life. We extend our condolences to the families of the lives lost due to COVID-19.

Appendix. Multivariate logistics regression model.

Primary outcome	Coef.	St.Err.	t-value	p-value	[95% Confidence Interval]	Sig
AFib	3.964	2.689	2.03	0.042	1.048 14.983	**
Age	1.061	0.019	3.23	0.001	1.023 1.099	***
Diabetes	2.627	1.189	2.13	0.033	1.081 6.380	**
Hypertension	1.049	0.515	0.10	0.922	0.401 2.745	
Coronary artery disease	1.115	0.636	0.19	0.849	0.364 3.413	
Glomerular filtration rate	0.913	0.014	-6.08	0.000	0.887 0.940	***
Bahraini Nationality	0.212	0.126	-2.60	0.009	0.066 0.682	***
CRP	1.002	0.001	2.62	0.009	1.001 1.004	***
Ddimer	1.223	0.041	6.08	0.000	1.146 1.305	***
Constant	0.326	0.397	-0.92	0.357	0.030 3.542	
Mean dependent var	0.197	SD dependent var	0.398			
Pseudo r-squared	0.602	Number of obs	437.000			
Chi-square	261.005	Prob > chi2	0.000			
Akaike crit. (AIC)	192.437	Bayesian crit. (BIC)	233.236			
Hosmer-Lemeshow chi2	13.75	area under ROC curve	0.9586			
Hosmer-Lemeshow p value	0.089					

*** $p < 0.01$, ** $p < 0.05$, * $p < 0.1$

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