Rev Esp Cardiol. 2021;74(7):608–615

Original article

Atrial fibrillation in patients with COVID-19. Usefulness of the CHA_2DS_2-VASc score: an analysis of the international HOPE COVID-19 registry

Aitor Uribarri,[a,*] Iván J. Núñez-Gil,[b] Álvaro Aparisi,[a] Ramón Arroyo-Espliguero,[c] Charbel Maroun Eid,[d] Rodolfo Romero,[e] Víctor M. Becerra-Muñoz,[f] Gisela Feltes,[g] María Molina,[h] Marcos García-Aguado,[i] Enrico Cerrato,[j] Thamar Capel-Astrua,[k] Emilio Alfonso-Rodríguez,[l] Alex F. Castro-Mejía,[m] Sergio Raposeiras-Roubín,[n] Carolina Espejo,[o] Nerea Pérez-Solé,[p] Alfredo Bardají,[q] Francisco Marín,[r] Óscar Fabregat-Andrés,[s] Fabrizio D'ascenzo,[t] Francesco Santoro,[u] Ibrahim Akin,[v] Vicente Estrada,[b] Antonio Fernández-Ortiz,[b] and Carlos Macaya[b], on behalf of HOPE COVID-19 investigators

[a] *Servicio de Cardiología, Hospital Clinico Universitario de Valladolid, Valladolid, Spain*
[b] *Servicio de Cardiología, Hospital Clínico San Carlos, Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (IdISSC), Madrid, Spain*
[c] *Servicio de Cardiología, Hospital Universitario Guadalajara, Guadalajara, Spain*
[d] *Servicio de Urgencias, Hospital Universitario La Paz, Instituto de Investigación Hospital Universitario La Paz (IdiPAZ), Madrid, Spain*
[e] *Servicio de Urgencias, Hospital Universitario de Getafe, Getafe, Madrid, Spain*
[f] *Servicio de Cardiología, Hospital Clinico Universitario Virgen de la Victoria, Málaga, Spain*
[g] *Servicio de Cardiología, Hospital Nuestra Señora de América, Madrid, Spain*
[h] *Servicio de Cardiología, Hospital Universitario Severo Ochoa, Madrid, Spain*
[i] *Servicio de Cardiología, Hospital Puerta de Hierro de Majadahonda, Majadahonda, Madrid, Spain*
[j] *Servizio di Cardiologia, San Luigi Gonzaga University Hospital, Orbassano, Turin, Italy*
[k] *Servicio de Medicina Interna, Hospital Virgen del Mar, Madrid, Spain*
[l] *Servicio de Cardiología, Instituto de Cardiología y Cirugía Cardiovascular, La Habana, Cuba*
[m] *Servicio de Cardiología, Hospital General del Norte de Guayaquil IESS Los Ceibos, Guayaquil, Ecuador*
[n] *Servicio de Cardiología, Hospital Álvaro Cunqueiro, Vigo, Pontevedra, Spain*
[o] *Servicio de Cardiología, Hospital Universitario Príncipe de Asturias, Alcalá de Henares, Madrid, Spain*
[p] *Servicio de Cardiología, Hospital Clínico Universitario, Universidad de Valencia, Valencia, Spain*
[q] *Servicio de Cardiología, Hospital Universitario Joan XXIII, Tarragona, Spain*
[r] *Servicio de Cardiología, Hospital de la Arrixaca, El Palmar, Murcia, Spain*
[s] *Servicio de Cardiología, Hospital IMED Valencia, Valencia, Spain*
[t] *Servizio di cardiologia, San Giovanni Battista Hospital, Turin, Italy*
[u] *Department of Medical and Surgery Sciences, University of Foggia, Foggia, Italy*
[v] *Sektion Interventionelle Kardiologie, University Mannheim, Mannheim, Germany*

Article history:
Received 15 September 2020
Accepted 18 December 2020
Available online 13 January 2021

Keywords:
COVID-19
SARS-CoV-2
Mortality
Registry
Prognosis
Atrial fibrillation
CHA_2DS_2-VASc
Bleeding

ABSTRACT

Introduction and objectives: Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2. Atrial fibrillation (AF) is common in acute situations, where it is associated with more complications and higher mortality.

Methods: Analysis of the international HOPE registry (NCT04334291). The objective was to assess the prognostic information of AF in COVID-19 patients. A multivariate analysis and propensity score matching were performed to assess the relationship between AF and mortality. We also evaluated the impact on mortality and embolic events of the CHA_2DS_2-VASc score in these patients.

Results: Among 6217 patients enrolled in the HOPE registry, 250 had AF (4.5%). AF patients had a higher prevalence of cardiovascular risk factors and comorbidities. After propensity score matching, these differences were attenuated. Despite this, patients with AF had a higher incidence of in-hospital complications such as heart failure (19.3% vs 11.6%, $P = .021$) and respiratory insufficiency (75.9% vs 62.3%, $P = .002$), as well as a higher 60-day mortality rate (43.4% vs 30.9%, $P = .005$). On multivariate analysis, AF was independently associated with higher 60-day mortality (hazard ratio, 1.234; 95%CI, 1.003-1.519). CHA_2DS_2-VASc score acceptably predicts 60-day mortality in COVID-19 patients (area ROC, 0.748; 95%CI, 0.733-0.764), but not its embolic risk (area ROC, 0.411; 95%CI, 0.147-0.675).

Conclusions: AF in COVID-19 patients is associated with a higher number of complications and 60-day mortality. The CHA_2DS_2-VASc score may be a good risk marker in COVID patients but does not predict their embolic risk.

* Corresponding author: Instituto de Ciencias del Corazón (ICICOR), Hospital Clínico Universitario de Valladolid, Ramón y Cajal 3, 47005 Valladolid, Spain.
E-mail address: auribarrig@gmail.com (A. Uribarri).

https://doi.org/10.1016/j.rec.2020.12.009
1885-5857/

Fibrilación auricular en pacientes con COVID-19. Utilidad de la puntuación CHA_2DS_2-VASc: un análisis del registro internacional HOPE COVID-19

Palabras clave:
COVID-19
SARS-CoV-2
Mortalidad
Registro
Pronóstico
Fibrilación auricular
CHA_2DS_2-VASc
Hemorragia

RESUMEN

Introducción y objetivos: La enfermedad por coronavirus de 2019 (COVID-19) está causada por el segundo coronavirus del síndrome respiratorio agudo y grave. La fibrilación auricular (FA) es común en situaciones agudas, en las que conlleva más complicaciones y mortalidad.

Métodos: Análisis del Registro internacional HOPE (NCT04334291); el objetivo es evaluar la información pronóstica de FA en pacientes con COVID-19. Se realizó un análisis multivariable y un emparejamiento por puntuación de propensión para evaluar la relación entre FA y mortalidad. Además, se evaluó en estos pacientes el impacto en la mortalidad y los eventos embólicos de la puntuación CHA_2DS_2-VASc.

Resultados: Entre los 6.217 pacientes inscritos en el registro HOPE, 250 tenían FA (4,5%). Los pacientes con FA tenían una mayor prevalencia de factores de riesgo cardiovascular y comorbilidades. Después del emparejamiento por puntuación de propensión, estas diferencias se atenuaron. A pesar de ello, los pacientes con FA tuvieron una mayor incidencia de complicaciones hospitalarias como insuficiencia cardiaca (el 19,3 frente al 11,6%; p = 0,021) e insuficiencia respiratoria (el 75,9 frente al 62,3%; p = 0,002), así como una mayor tasa de mortalidad a los 60 días (el 43,4 frente al 30,9%; p = 0,005). En el análisis multivariado, la FA se asoció de manera independiente con una mayor mortalidad a los 60 días (*hazard ratio* = 1,234; IC95%, 1,003-1,519). La puntuación CHA_2DS_2-VASC predice de manera aceptable la mortalidad a los 60 días de los pacientes con COVID-19 (área ROC = 0,748; IC95%, 0,733-0,764), pero no su riesgo embólico (área ROC = 0,411; IC95%, 0,147-0,675).

Conclusiones: La FA en pacientes con COVID-19 se asocia con más complicaciones y mayor mortalidad a los 60 días. La puntuación CHA_2DS_2-VASc puede ser un buen marcador de riesgo en pacientes con COVID-19, pero no predice su riesgo embólico.

Abbreviations

AF: atrial fibrillation
PSM: propensity score matching

INTRODUCTION

In January, 2020, a novel virus, known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was identified as the sole causative agent for a cluster of pneumonia cases initially detected in Wuhan City, Hubei province, China.[1] SARS-CoV-2, which causes the disease now named coronavirus disease 2019 (COVID-19), has spread from China to the rest of the world.[2,3]

Currently the percentage of asymptomatic infected carriers is unknown, but several studies indicate that it could be very high.[4] In symptomatic patients, the clinical spectrum of SARS-CoV-2 infection appears to be wide, encompassing mild upper respiratory tract illness, and severe viral pneumonia with respiratory failure and even death.[5] Most fatal cases occurred in patients with advanced age or underlying medical comorbidities such us cardiovascular disease, hypertension, diabetes mellitus, chronic lung disease, and chronic kidney disease.[6,7]

Atrial fibrillation (AF) is the most frequent arrythmia worldwide, and its prevalence is higher in patients with cardiovascular risk factors and other comorbidities.[8] This arrythmia is common in the context of acute situations such as myocardial infarction, cardiac surgery or infections, where it is linked with a higher risk of complications and mortality.[9] However, there is no work specifically addressing the impact of AF on the prognosis of COVID-19. Here, we present details of an international registry of patients discharged from a hospital with laboratory-confirmed or high suspicion SARS-CoV-2 infection and definite clinical outcomes. We aimed to describe the clinical features and prognosis of COVID-19 patients with AF and to evaluate the impact of this arrythmia on the short-term prognosis of the disease. Additionally, we also aimed to investigate the impact of the CHA_2DS_2-VASc score and anticoagulation treatment during admission for the prognosis in this population. The CHA_2DS_2-VASc score is a simple stroke risk stratification schema, based on a risk factor approach (congestive heart failure/left ventricular dysfunction, hypertension, age, diabetes mellitus, stroke, vascular disease, and sex), and offers good predictive value for embolic events in patients with AF.[8,10]

METHODS

Study design and population

This is a subanalysis of the Health Outcome Predictive Evaluation (HOPE) COVID-19 registry, with an overall study sample of 6217 patients with a definitive diagnosis or high suspicion of SARS-CoV-2 infection.[11] In brief, the HOPE registry is a retrospective cohort registry (ie, a "real-world" all comers type, with voluntary participation and with no financial compensation. All patients discharged (deceased or alive) after hospital admissions for COVID-19 were suitable for the study. There were no exclusion criteria, except for patients' explicit refusal to participate. From March 23, 2020 to June 1, 2020 all patients fulfilling the inclusion criteria from 24 centers in Spain were assessed in the present study. Clinical and demographic data were collected at inclusion and during hospitalization. The study was performed according to the ethical principles of the Declaration of Helsinki and Good Clinical Practice Guidelines and was approved by the local Ethics Research Committee of the Hospital Clínico San Carlos (Madrid, Spain) (20/241-E). Written informed consent was waived because of the characteristics of the anonymized registry and the severity of the situation. However, at least verbal authorization from the patient (or familiar or caregiver when unavailable) was required. A list of participating hospitals, investigators, collaborators and the protocol are available in the appendix of the supplementary data.

Definitions and study outcomes

Enrolled patients were divided into 2 groups according to AF history. Study definitions are available elsewhere on the registry's

website.[12] The primary endpoint was all-cause mortality at 60-days in either cohort. We evaluated whether the use of the CHA_2DS_2-VASc risk score was useful to assess the risk of death or embolism in patients with COVID-19. The CHA_2DS_2-VASc score was not recorded in the original dataset, but was obtained retrospectively for this research study. Enrolled patients were divided into 3 groups according to their CHA_2DS_2-VASc score (group 1: CHA_2DS_2-VASc = 0 in men and ≤ 1 in women; group 2: CHA_2DS_2-VASc = 1 in men or 2 in women; and group 3: CHA_2DS_2-VASc > 1 in men or > 2 in women). Other clinically relevant events were recorded as secondary endpoints: invasive mechanical ventilation, noninvasive mechanical ventilation, respiratory insufficiency, heart failure, renal failure, sepsis, systemic inflammatory response syndrome, clinically relevant bleeding, and embolic events. Events were classified following local researchers' criteria according to the definitions of the HOPE COVID-19 registry. The vital status at 60 days of the patients discharged alive was confirmed by telephone interview.

Statistical analysis

Data are presented as mean ± standard deviation for continuous variables with a normal distribution, median (interquartile range [IQR]) for continuous variables with a nonnormal distribution, and as frequency (%) for categorical variables. The student *t* test and the Mann-Whitney *U* test were used to compare continuous variables with normal and nonnormal distributions, when needed. The chi-square test or Fisher exact test was used to compare categorical variables. Univariate analysis was performed for qualitative variables and reported as odds ratios with 95% confidence interval (95%CI). Given the multiplicity of variables, only factors associated with all-cause mortality

Table 1
Features of COVID-19 patients and comparative analysis according to atrial fibrillation

	Before PSM				After PSM			
	Overall N = 6217	AF n = 250	No AF n = 5967	*P*	Overall n = 466	AF n = 233	No AF n = 233	*P*
Demographic								
Male, %	3579 (57.6)	171 (68.4)	3408 (57.1)	<.001	268 (57.5)	134 (57.5)	134 (57.5)	1
Age, y	65.7 ± 16.8	79.9 ± 9.9	65.1 ± 16.7	<.001	79.4 ± 10.7	79.7 ± 9.7	79.1 ± 11.5	.538
BMI, kg/m²	28.8 ± 5.2	28.8 ± 4.4	28.8 ± 5.2	.229	28.5 ± 4.2	28.5 ± 4.2	28.6 ± 4.4	.858
Comorbidities								
Hypertension	3020 (50.3)	203 (81.2)	2817 (49.0)	<.001	378 (81.1)	189 (81.1)	189 (81.1)	1
Diabetes mellitus	1237 (19.9)	77 (30.8)	1160 (19.4)	<.001	138 (29.6)	69 (29.6)	69 (29.6)	1
Hypercholesterolemia	2237 (37.5)	140 (56.7)	2097 (36.7)	<.001	262 (56.2)	132 (56.7)	130 (55.8)	.852
Smoker	271 (5.1)	10 (4.1)	261 (5.1)	.478	23 (4.9)	10 (4.3)	13 (6.3)	.354
Lung disease	1243 (30.5)	87 (47.3)	1156 (29.7)	<.001	159 (34.1)	81 (34.8)	78 (33.5)	.769
Chronic kidney disease	416 (7.1)	370 (88.9)	46 (18.8)	<.001	82 (17.6)	41 (17.6)	41 (17.6)	1
Obesity	1174 (24.5)	59 (27.7)	1115 (24.3)	.263	103 (27.2)	56 (28.1)	47 (26.1)	.657
Heart failure	265 (4.2)	15 (6.0)	250 (4.2)	.234	176 (37.8)	110 (47.2)	66 (28.3)	<.001
Ischemic heart disease	396 (6.4)	9 (3.6)	387 (6.5)	.067	35 (7.5)	9 (3.9)	26 (11.2)	.003
Cardiomyopathy	127 (2.0)	6 (2.4)	121 (2.0)	.684	19 (4.1)	6 (2.6)	13 (5.6)	.101
Cerebrovascular disease	479 (8.1)	33 (13.4)	446 (7.9)	.002	68 (14.6)	31 (13.3)	37 (15.9)	.431
Any cancer	861 (14.6)	51 (20.7)	810 (14.3)	.005	94 (20.2)	47 /20.2)	47 (20.2)	1
Concomitant treatment								
Beta-blockers	933 (15.7)	123 (49.6)	810 (14.2)	<.001	179 (38.6)	120 (51.7)	59 (25.4)	<.001
ACEi/ARBs	2214 (37.1)	2090 (36.6)	124 (49.8)	<.001	261 (56.3)	118 (50.9)	143 (61.6)	.019
Antiplatelet therapy	901 (15.2)	23 (9.2)	878 (15.4)	.008	85 (18.4)	22 (9.5)	63 (27.3)	<.001
Oral anticoagulation therapy	651 (10.9)	214 (85.6)	437 (7.6)	<.001	230 (49.3)	198 (85.0)	32 (13.8)	<.001
Vitamin K antagonists	535 (82.2)	145 (67.8)	390 (89.2)		163 (70.9)	137 (69.2)	26 (81.3)	
Direct-acting oral anticoagulants	116 (17.8)	69 (32.2)	47 (10.8)		67 (29.1)	61 (30.8)	6 (18.7)	
Laboratory parameters								
Creatinine, mg/dL	1.1 ± 1.7	1.5 ± 1.3	1.1 ± 1.6	.035	1.4 ± 1.2	1.3 ± 1.0	1.5 ± 1.4	.071
Hemoglobin, g/dL	13.5 ± 1.9	12.7 ± 2.4	13.6 ± 1.9	<.001	12.9 ± 2.3	13.1 ± 2.2	12.8 ± 2.4	.146
Platelet count, x 10^9/L	213 ± 95	192 ± 90	213 ± 85	.513	203 ± 95	231 ± 99	192 ± 89	.017
Lymphocytes, g/dL	1229 ± 1715	1276 ± 3279	1228 ± 161	.015	1318 ± 3063	1330 ± 2726	1305 ± 3377	.930
Elevated D-dimer	3633 (69.7)	151 (71.2)	3482 (69.6)	.619	292 (75.1)	140 (71.4)	152 (78.8)	.095
Elevated procalcitonin	832 (13.4)	41 (30.1)	791 (21.6)	.018	87 (30.5)	40 (31.3)	47 (29.9)	.811
Elevated C-reactive protein	5249 (90.0)	217 (90.0)	5032 (90.0)	.990	408 (90.5)	202 (90.2)	206 (90.7)	.837
Elevated troponins	382 (14.1)	28 (31.5)	354 (13.5)	<.001	50 (25.8)	26 (31.3)	24 (21.6)	.126
Elevated transaminases	2304 (41.9)	73 (31.1)	2231 (42.4)	.001	150 (34.6)	69 (31.5)	81 (37.9)	.165
Elevated ferritin	2018 (64.0)	70 (65.4)	1948 (63.9)	.753	140 (63.1)	67 (67.0)	73 (59.8)	.271
Elevated LDH	4155 (77.0)	175 (77.4)	3980 (77.0)	.879	327 (78.2)	164 (77.7)	163 (78.7)	.801

ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; LDH, lactate dehydrogenase; PSM, propensity score matching.
The data are presented as No. (%) or mean ± standard deviation.

with $P < .01$ on univariate analysis (age, sex, hypertension, dyslipidemia, diabetes mellitus, smoke, chronic kidney failure, ischemic heart disease, heart failure, lung disease, cerebrovascular disease, cancer, renin-angiotensin-aldosterone system inhibitor treatment, AF, aspirin treatment, anticoagulation treatment, saturation $O_2 < 92\%$ on admission, D-dimer elevation, C-reactive protein elevation, lactate dehydrogenase elevation) were entered into the Cox multivariate regression analysis to define independent risk factors for the main outcome in the matched population. The assumption of proportionality of risks was verified by analyzing Schoenfeld residuals. The C-index and Gronesby Borgan test were calculated to determine discrimination and calibration, respectively. Kaplan-Meier curves were used to estimate survival function and compare subgroups with the log-rank test. Possible collinearity and interactions were evaluated with the introduction of multiplicative terms calculating the tolerance and the variance inflation factor. Propensity score matching (PSM) was estimated with AF as the dependent variable and the main clinical profiles at admission (PSM 1:1; 0.01 tolerance, without replacement, nearest neighbor) to obtain balanced pairs. The MatchIt package (Ho, Imai, King, & Stuart, 2007) was used. Variables included in the PSM were age, dyslipidemia, smoking, cerebrovascular disease, lung disease and were exactly added (sex, hypertension, diabetes, chronic kidney failure, and any type of cancer). Quality adjustment generated by the PSM model is shown in the figure 1 of the supplementary data. The area under the receiver operating characteristic curve (ROC curve) was used to measure how well the models discriminated the CHA_2DS_2-VASc score for 60-day all-cause mortality and risk of in-hospital embolic event. All tests were 2-sided. The statistical analysis was performed with the IBM SPSS 24.0 software package, STATA software, version 15 and R Core Team (2020).

RESULTS

Of the 6217 patients consecutively enrolled in the HOPE COVID-19 registry, 250 had history of AF (4.2%) and 1687 patients were men (60.3%). After matching for the main baseline confounding factors, 233 patients with AF and 233 without AF were selected for the definitive analysis.

Baseline characteristics

The percentage of patients testing positive patients for SARS-CoV-2 infection by nasopharyngeal PCR was 89%. The baseline characteristics of COVID-19 patients are shown in table 1. Mean age was 66 ± 17 years, 57.6% of patient were male and the median interval from disease onset to admission was 6 [IQR 5] days. Of the total reported patients, 3020 (50.3%) had hypertension, 2237 (37.5%) dyslipidemia, 1237 (19.9%) diabetes mellitus, 1243 (30.5%) previous pulmonary disease, 265 (4.2%) heart failure, and 416 (7.1%) chronic kidney failure.

Patients were categorized in 2 groups according to history of AF. When we compared these groups, we observed that patients with AF were older and had a greater number of comorbidities. Furthermore, this group had more frequently received prior treatment with antiplatelets, anticoagulants, and renin-angiotensin-aldosterone system inhibitors. These differences were controlled after statistical matching (table 1).

Treatment and outcomes during admission

Management is depicted in table 2. The specific COVID-19 drugs most frequently used were hydroxychloroquine (86.1%), followed by antibiotics (77.9%) and lopinavir/ritonavir (54.4%). Corticoids were prescribed in approximately 31% of the patients. For respiratory support, prone positioning was used in 7%, and noninvasive mechanical ventilation in 10%. An invasive mechanical ventilation approach was required in more than 6%. When we compared these groups according to AF, antiviral drugs and tocilizumab were more frequently used in non-AF patients; in contrast, corticoids and antibiotics were more frequently used in AF patients. After PSM these differences were attenuated (table 2).

In-hospital events are shown in figure 1. The most common was bilateral pneumonia (75%) with concomitant respiratory insufficiency in 52.3% of all patients. In the overall COVID-19 population, acute renal injury, sepsis and systemic inflammatory response syndrome were reported in roughly 20% of the patients. Systemic inflammatory response syndrome, heart failure and respiratory failure were more frequent in the AF group. In parallel, we observed a higher incidence of hemorrhagic complications in the AF group (9.8% vs 2.6%; OR, 4.03; 95%CI, 2.56-6.33), but with comparable outcomes in embolic events between the 2 groups. Despite the statistical matching, the AF group continued to show a higher incidence of all these complications (table 2).

In-hospital anticoagulation management

During hospitalization, close to 80% of all patients received some type of anticoagulation therapy, with 62.7% of them receiving a prophylactic dose, while 17.1% received the full anticoagulant dose. In particular, in the AF group, only 135 (57%) patients received anticoagulation at an appropriate dose [102 (75.6%) of them using intravenous/subcutaneous anticoagulation with heparin/enoxaparin, 18 (13.3%) with acenocumarol and 15 (11.1%) with a direct-acting anticoagulant], 61 (25.7%) received a prophylactic dose, and 41 (17.3%) did not receive anticoagulant treatment. We did not observe differences in age (79.4 vs 81.5; $P = .248$) or in the CHA_2DS_2-VASc score (3.8 vs 3.8, $P = .277$) between patients who had received some dose of anticoagulant treatment and those who had not. Despite this low percentage of patients treated with appropriate doses of anticoagulant treatment, the incidence of relevant bleeding complications during admission was higher in the AF group (9.8% vs 2.6%; OR, 4.03; 95%CI, 2.56-6.33). When we compared the entire cohort of patients, we observed that those who received full anticoagulant doses had a higher risk of bleeding than those who received only a prophylactic dose or did not receive any (OR full dose vs prophylactic dose 4.17; 95%CI, 2.90-6.00; and OR full dose vs any dose 3.32; 95%CI, 2.05-5.35). However, these differences were not observed when we analyzed only the group of patients with AF (OR full dose vs prophylactic dose 1.42, 95%CI, 0.49-4.11; and OR full dose vs any dose 1.57, 95%CI, 0.43-5.72). When we analyzed embolic events, we observed no differences between the groups based on the type of anticoagulant (2 [6.1%] in nonvitamin K antagonist oral anticoagulant group vs 4 [6.6%] in vitamin K antagonist group vs 33 [5.1%] in unfractionated heparin group vs 115 [3.9%] in low-molecular-weight-heparin group; $P = .298$) and dose received (40 [4.7%] in the full-dose anticoagulation group vs 99 [3.2%] prophylaxis group vs 15 [1.5%] group without anticoagulation; $P = .231$).

Prognostic impact of atrial fibrillation on COVID-19

Univariable analysis of 60-day all-cause mortality from COVID-19 showed a linear relation between AF development and mortality (mortality in patients with AF 43.6% vs mortality in patients without AF 18%; OR, 3.51; 95%CI, 2.71-4.55). In the multivariate analysis (C-Index and 95% Jackknife CI, 0.750 (0.71-0.788), Groennesby and Borgan test $P = .782$) (table 3), the presence of AF was independently associated with 60-day all-cause mortality in these patients (HR, 1.234; 95%CI, 1.003-1.519) together with other variables such as age, lactate dehydrogenase elevated on admission, saturation on admission $< 92\%$, and chronic kidney disease. In addition, we observed high mortality in patients who were on anticoagulant treatment before

Table 2
Adverse events during hospitalization in patients with COVID-19 and comparative analysis according to atrial fibrillation

	Before PSM				After PSM			
	Overall N = 6217	AF n = 250	No AF n = 5967	*P*	Overall N = 466	AF n = 233	No AF n = 233	*P*
Acute renal injury	1047 (17.8)	95 (38.6)	952 (16.8)	< .001	156 (33.5)	87 (37.3)	69 (29.6)	.077
Heart failure	406 (6.9)	49 (20.0)	357 (6.3)	< .001	72 (15.5)	45 (19.3)	27 (11.6)	.021
Sepsis	1351 (23.2)	27 (10.9)	589 (10.5)	.842	57 (12.4)	27 (11.6)	30 (13.2)	.608
Systemic inflammatory response syndrome	1351 (23.2)	74 (30.1)	1277 (22.9)	.009	126 (27.5)	69 (29.7)	57 (25.1)	.266
Relevant bleeding	169 (2.9)	24 (9.8)	145 (2.6)	< .001	27 (5.9)	20 (8.7)	7 (3.1)	.012
Embolic event	154 (2.6)	5 (2.0)	149 (2.7)	.544	8 (1.7)	5 (2.2)	3 (1.3)	.487
Respiratory insufficiency	3100 (52.3)	190 (76.3)	2910 (51.2)	< .001	320 (69.1)	176 (75.9)	144 (62.3)	.002
High flow nasal cannula	994 (17.1)	22 (9.1)	972 (17.4)	.001	76 (16.8)	18 (7.9)	58 (25.7)	< .001
Noninvasive mechanical ventilation	589 (10.0)	10 (4.0)	579 (10.3)	.001	34 (7.4)	8 (3.4)	26 (11.4)	.001
Invasive mechanical ventilation	350 (6.0)	7 (2.8)	343 (6.1)	.033	13 (2.8)	7 (3.0)	6 (2.6)	.797
Use of corticoids	1819 (31.2)	106 (42.6)	1713 (30.7)	< .001	166 (36.5)	98 (42.2)	68 (30.5)	.009
Use of hydroxychloroquine	5094 (86.1)	207 (83.1)	4887 (86.2)	.166	374 (81.1)	191 (82.3)	183 (79.9)	.508
Use of antiviral drugs	3204 (54.4)	97 (39.3)	3107 (55.1)	< .001	190 (41.8)	91 (39.6)	99 (44.0)	.038
Use of interferon or similar	659 (11.4)	21 (8.5)	638 (11.5)	.142	46 (10.2)	19 (8.2)	27 (12.2)	.165
Use of tocilizumab or similar	540 (9.3)	8 (3.3)	532 (9.5)	.001	19 (4.2)	8 (3.5)	11 (4.9)	.452
Use of antibiotics	4323 (77.9)	199 (84.3)	4124 (77.6)	.015	345 (79.7)	184 (83.3)	161 (75.9)	.059
Anticoagulation				< .001				< .001
No	990 (20.2)	41 (17.3)	949 (20.4)		116 (25.3)	38 (16.7)	78 (33.9)	
Prophylactic dose	3068 (62.7)	61 (25.7)	3007 (64.6)		179 (39.1)	58 (25.4)	121 (52.6)	
Complete dose	837 (17.1)	135 (57.0)	702 (15.0)		163 (35.6)	132 (57.9)	31 (13.5)	

AF, atrial fibrillation; PSM, propensity score matching.
The data are presented as No. (%).

admission (41.9% vs 16.9%; OR 3.55; 95%CI, 2.99-4.28), specifically, 43.9% within the AF group. The 60-day Kaplan-Meier survival analysis after PSM confirmed the higher mortality among AF patients (figure 2).

A total of 1185 patients died during the 60-day follow-up. The main causes of mortality in our registry were respiratory failure (59.2%), combined cause (19.9%), infectious etiology (6.2%), and systemic inflammatory response (5.0%). Cardiovascular cause was the main cause of death in 1.4% of the patients. In addition, a total of 154 embolic events were recorded during hospital admission, with no differences between the groups (table 2).

CHA_2DS_2-VASc score and mortality risk assessment

Kaplan-Meier survival landmark analysis according to the CHA_2DS_2-VASc score is shown in figure 3. CHA_2DS_2-VASc score had a modest ability to predict 60-day all-cause mortality in the entire cohort (area ROC, 0.748; 95%CI, 0.733-0.764); however, it had a poor performance when the group of patients with AF was specifically evaluated (area ROC, 0.618; 95%CI, 0.546-0.689). Furthermore, CHA_2DS_2-VASc score was also unable to predict the incidence of embolism during admission in the overall cohort

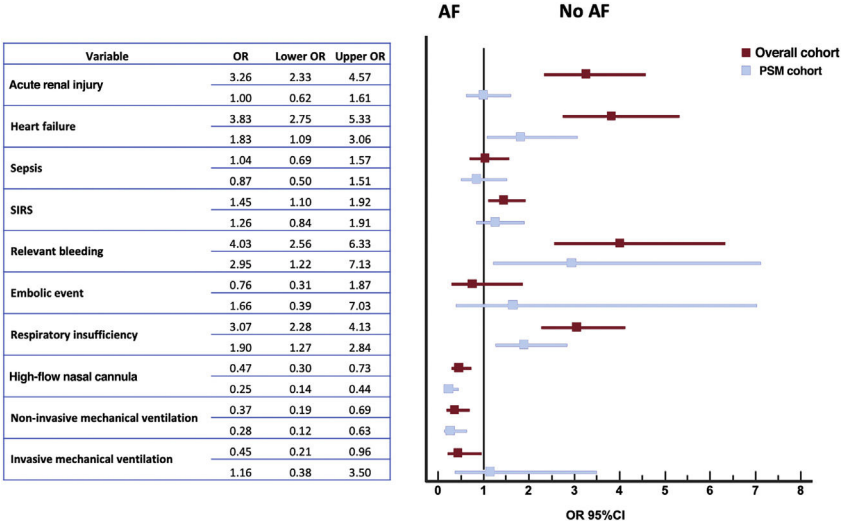

Figure 1. Adverse events during hospitalization in patients with COVID-19 and comparative analysis according to atrial fibrillation. 95%CI, 95% confidence interval; AF, atrial fibrillation; OR, odds ratio; PSM, propensity score matching; SIRS, systemic inflammatory response syndrome.

Table 3
Multivariate Cox regression analysis for evaluating the risk of 60-day all-cause mortality

	HR (95%CI)	*P*
Age (per year)	1.04 (1.02-1.06)	<.001
Saturation on admission <92%	3.84 (2.65-5.58)	<.001
Elevated LDH on admission	1.65 (1.06 -1.58)	.027
Chronic kidney disease	1.78 (1.29-2.58)	.002
Atrial fibrillation	1.57 (1.12-2.20)	.009

95%CI, 95% confidence interval; HR, hazard ratio; LDH, lactate dehydrogenase. Adjustment variables included in the full model: age, sex, hypertension, dyslipidemia, diabetes mellitus, smoking, chronic kidney failure, ischemic heart disease, heart failure, lung disease, cerebrovascular disease, cancer, renin-angiotensin-aldosterone system inhibitors treatment, atrial fibrillation, aspirin treatment, anticoagulation treatment, saturation O_2 <92% on admission, D-dimer elevation, C-reactive protein elevation, lactate dehydrogenase elevation.

(area ROC, 0.519; 95%CI, 0.471-0.568) and AF group (area ROC, 0.411; 95%CI, 0.147-0.675).

DISCUSSION

COVID-19 patients with underlying cardiovascular disease have an increased risk of morbidity and mortality from complicated myocardial injury, myocarditis, congestive heart failure, thromboembolism, and arrhythmias.[13] Interestingly, AF is the most common arrhythmia seen in tertiary care and critically ill patients.[14] In fact, cardiac arrhythmias are among the most common comorbidities in COVID-19 patients and have been identified in almost all fatal cases.[15] However, to date there is no evidence on whether AF contributes somehow to COVID-19 prognosis and we therefore report the first work specifically addressing the influence and prognostic role of AF on COVID-19. The main findings are: *a)* 4% of patients with COVID-19 had a prior history of AF before hospitalization; *b)* patients with COVID-19 and AF had higher 60-day all-cause mortality; *c)* AF is an independent predictor of mortality; *d)* patients with a high CHA_2DS_2-VASc score had higher 60-day all-cause mortality; *e)* CHA_2DS_2-VASc score is not useful for predicting the incidence of embolic events during SARS-CoV-2 infection; *f)* full-dose anticoagulant therapy may increase bleeding complications.

AF is the most common arrhythmia worldwide, and it is known that its prevalence is higher among the elderly and patients with conditions such as hypertension, diabetes mellitus, chronic kidney disease, and heart disease.[16] Our data confirm a higher burden of cardiovascular risk factors in this group of patients, but in the multivariate analysis, the presence of AF was independently associated with COVID-19 prognosis. Therefore, the following question arises: is AF in COVID-19 a simple bystander or a marker of increased risk? Several theories have been postulated to try to explain why patients with AF may be at higher risk from SARS-CoV-2 infection, but they are probably based on both inflammatory status and the mechanisms of cellular entry of the virus.[17] It has been previously demonstrated that high AF burden is associated with higher activity levels of angiotensin-converting enzyme 2, the peptide through which the virus binds to human cells.[18] Up-regulation of angiotensin-converting enzyme 2 can potentially increase susceptibility to COVID-19.[18] Interestingly, angiotensin-converting enzyme

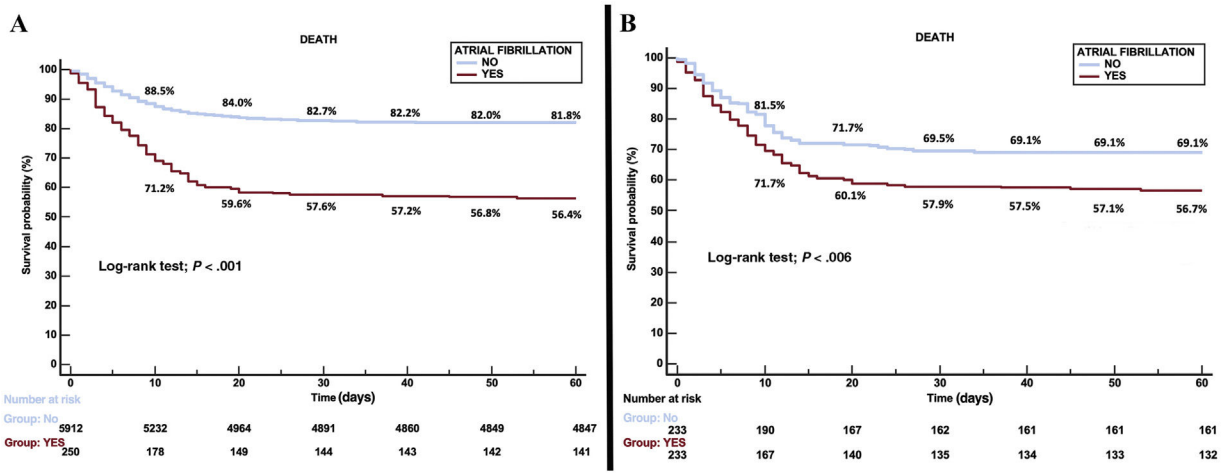

Figure 2. Kaplan-Meier survival landmark analysis according to atrial fibrillation history. A: before propensity score matching. B: after propensity score matching.

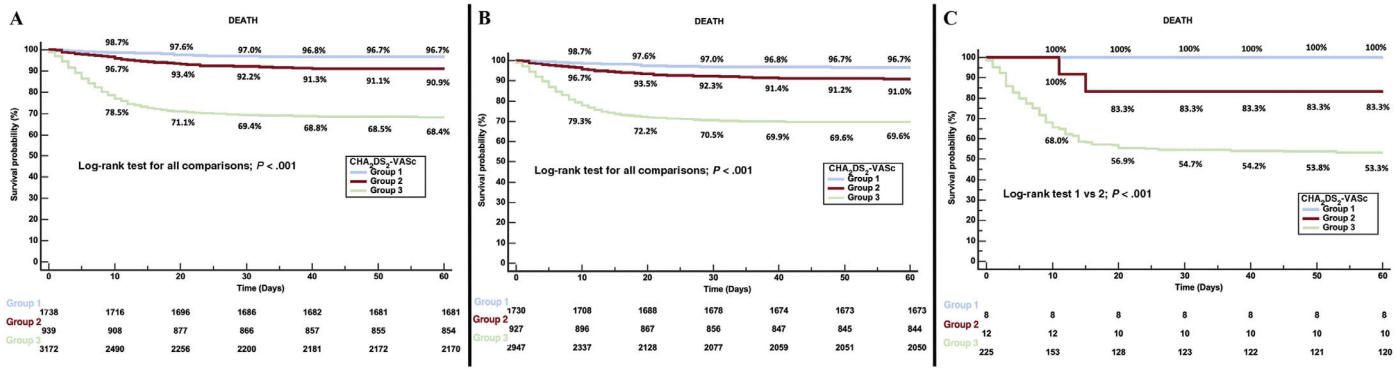

Figure 3. Kaplan-Meier survival landmark analysis according to the CHA_2DS_2-VASc score. Group 1: CHA_2DS_2-VASc = 0 in men and ≤ 1 in women; Group 2: CHA_2DS_2-VASc = 1 in men or 2 in women; and Group 3: CHA_2DS_2-VASc > 1 in men or > 2 in women. A: entire cohort. B: patients without AF. C: patients with AF.

2 levels also correlate with structural and functional remodeling of the left atrium, which are in turn substrates for a greater susceptibility to AF.[19] In addition, one of the key pathways of COVID-19 is represented by the abnormal inflammatory response of the host. Importantly, systemic inflammation precedes and predicts AF in the community. From this perspective, AF may reflect the existence of an increased inflammatory substrate that favors worse outcomes, amplified when coupled with COVID-19. The presence of AF itself is a poor prognostic factor in multiple clinical contexts; likewise, new onset AF worsens the prognosis of patients admitted for serious diseases.[20] In the context of infections, this worse prognosis is accentuated and is prolonged during the mid-term follow-up.[21] In addition, it is known that AF increases mortality both in patients with and without previous cardiovascular disease.[22,23].

It is important to note that most patients with AF require anticoagulation to prevent the risk of embolism, but in some cases, this treatment is related to hemorrhagic complications. Both complications can be accentuated in patients with SARS-CoV-2 infection. COVID-19 frequently induces hypercoagulability with inflammation driving increased levels of procoagulant clotting factors and disruption of the normal homeostasis of vascular endothelial cells, which results in microangiopathy, local thrombus formation, and a systemic coagulation defect leading to large vessel thrombosis and hence major thromboembolic complications.[24] Whether anticoagulation alone is sufficient to prevent these thrombotic events, especially those driven by endothelial dysfunction, is unknown, although it is recommended that all admitted patients should receive prophylaxis for deep vein thrombosis.[25] However, the prevalence of drug-drug interactions from anticoagulation was reported to be as high as 26.3% in the AF population. Such interactions increased the risk of bleeding up to 7-fold and it is expected to be higher in COVID-19 patients. Although the guiding principles for anticoagulation in COVID-19 patients with AF are the same as in patients without SARS-CoV-2 infection, little is known about potential complications with COVID-19. Our data show that patients receiving full dose anticoagulation have a higher incidence of bleeding complications. In contrast, they do not have a higher incidence of embolic complications. In addition, the CHA_2DS_2-VASc score is not capable of predicting in-hospital embolic risk in this population. Therefore, its use to assess the need for in-hospital anticoagulation should not be justified by this scale alone and should be individualized; it could be considered that in patients with AF who are admitted because of COVID-19, only treatment with prophylactic anticoagulation regimens might be considered during admission.

Limitations

The design of this study entails some constraints. Some incident events in the participating centers may not have been diagnosed and/or reported. The calculation of the incidence of the events is not precise since recruitment was performed in participating centers without other sampling procedures other than the broad inclusion criteria (hospital discharge). Regarding the management applied, at all times it was decided by the attending medical team, as well as in the comparison group.

Other considerations to take into account are that we did not have information on the type of AF (paroxysmal/permanent) so we cannot know if this classification influenced the prognosis or management of these patients; although we performed a PSM, some variables such as heart failure and ischemic heart disease were not balanced; although we attempted to adjust for many confounders, other unmeasured or unknown confounders might have played a role; we tried to report all the treatments used during admission, but the protocols differed between the centers, which may influence the results. In addition, we were not able to record possible in-hospital AF events, because the health situation experienced in some hospitals included in the registry did not allow electrocardiographic monitoring or daily electrocardiograms to be performed in many patients. The variable "previous anticoagulation" was not included in the matching process; therefore, we cannot rule out that this variable could have modified our results. Despite this, we did include this variable in the multivariate analysis and it was not predictive of a worse prognosis. Furthermore, our registry only included in-hospital complications (except for mortality) and, therefore, we cannot exclude the possibility that some of the patients may have had an embolic or hemorrhagic event at discharge. The precise impact of AF on COVID-19 warrant further investigation.

CONCLUSIONS

Our findings show that AF in patients with COVID-19 is associated with a high 60-day all-cause mortality rate. CHA_2DS_2-VASc score may be a good risk marker in COVID patients, but it does not predict their embolic risk. More studies are needed to confirm these findings.

FUNDING

Unconditioned grant (*Fundación Interhospitalaria para la Investigación Cardiovascular* [FIC] Madrid, Spain). This nonprofit institution had no role in the study design; in the collection, analysis, interpretation of data; in the writing of the report; nor in the decision to submit the paper for publication.

CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

ACKNOWLEDGEMENTS

Cardiovascular Excellence SL, for their essential support in the database and HOPE webpage. All HOPE researchers.

WHAT IS KNOWN ABOUT THE TOPIC?

- COVID-19 ranges from asymptomatic to critical forms, and several prognostic factors have been described, however, there is no work addressing the specific impact of atrial fibrillation.

WHAT DOES THIS STUDY ADD?

- AF in COVID-19 patients is associated with a higher number of complications and 60-day mortality. The CHA_2DS_2-VASc score may be a good risk marker in COVID patients, but it does not predict their embolic risk. Clinicians should systematically assess CHA_2DS_2-VASc in patients with COVID-19 and atrial fibrillation at the time of hospital admission in order to optimize risk stratification and improve resource allocation. However, its use to assess the need for in-hospital anticoagulation should not be justified by this scale alone and should be individualized.

APPENDIX. SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.1016/j.rec.2020.12.009

REFERENCES

1. Word Health Organization. Novel coronavirus – China. 2020. Available at: http://www.who.int/csr/don/12-january-2020-novel-coronavirus-china/en/. Accessed 14 Dec 2020.
2. Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU). COVID-19 Dashboard. 2020. Available at: https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6. Accessed 12 Dec 2020
3. Chan JF, Yuan S, Kok KH, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet.* 2020;395:514–523.
4. Pollán M, Pérez-Gómez B, Pastor-Barriuso R, et al. Prevalence of SARS-CoV-2 in Spain (ENE-COVID): a nationwide, population-based seroepidemiological study. *Lancet.* 2020;396535–396544.
5. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet.* 2020;395:1054–1062.
6. Petrilli CM, Jones SA, Yang J, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. *BMJ.* 2020;369:m1966.
7. Uribarri A, Núñez Gil IJ, Aparisi A, et al. Impact of renal function on admission in COVID-19 patients: an analysis of the international HOPE COVID-19 (Health Outcome Predictive Evaluation for COVID 19) Registry. *J Nephrol.* 2020;33:737–745.
8. Hindricks G, Potpara T, Dagres N, et al.2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). *Eur Heart J.* 2020. http://dx.doi.org/10.1093/eurheartj/ehaa612.
9. Steinberg BA, Zhao Y, He X, et al. Management of postoperative atrial fibrillation and subsequent outcomes in contemporary patients undergoing cardiac surgery: insights from the Society of Thoracic Surgeons CAPS-Care Atrial Fibrillation Registry. *Clin Cardiol.* 2014;37:7–13.
10. Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns HJGM. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest.* 2010;137:263–272.
11. ClinicalTrials.gov. International COVID19 Clinical Evaluation Registry, (HOPE COVID 19) Available at: https://clinicaltrials.gov/ct2/show/NCT04334291. Accessed 12 Dec 2020.
12. HOPE registry website. Available at: https://hopeprojectmd.com. Accessed 14 Dec 2020.
13. Driggin E, Madhavan MV, Bikdeli B, et al. Cardiovascular Considerations for Patients, Health Care Workers, and Health Systems During the COVID-19 Pandemic. *J Am Coll Cardiol.* 2020;75:2352–2371.
14. Bosch NA, Cimini J, Walkey AJ. Atrial Fibrillation in the ICU. *Chest.* 2018;154:1424–1434.
15. Sanchis-Gomar F, Perez-Quilis C, Lavie CJ. Should atrial fibrillation be considered a cardiovascular risk factor for a worse prognosis in COVID-19 patients? *Eur Heart J.* 2020;41:3092–3093.
16. Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation.* 2014;129:837–847.
17. Inciardi RM, Adamo M, Lupi L, Metra M. Atrial fibrillation in the COVID-19 era: simple bystander or marker of increased risk? *Eur Heart J.* 2020;41:3094.
18. Tomasoni D, Italia L, Adamo M, et al. COVID-19 and heart failure: from infection to inflammation and angiotensin II stimulation. *Searching for evidence from a new disease Eur J Heart Fail.* 2020;22:957–966.
19. Walters TE, Kalman JM, Patel SK, Mearns M, Velkoska E, Burrell LM. Angiotensin converting enzyme 2 activity and human atrial fibrillation: increased plasma angiotensin converting enzyme 2 activity is associated with atrial fibrillation and more advanced left atrial structural remodelling. *Europace.* 2017;19:1280–1287.
20. Moss TJ, Calland JF, Enfield KB, et al. New-Onset Atrial Fibrillation in the Critically Ill. *Crit Care Med.* 2017;45:790–797.
21. Gundlund A, Olesen JB, Butt JH, et al. One-year outcomes in atrial fibrillation presenting during infections: a nationwide registry-based study. *Eur Heart J.* 2020;41:1112–1119.
22. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation.* 1998;98:946–952.
23. Pedersen OD, Bagger H, Køber L, Torp-Pedersen C; The occurrence and prognostic significance of atrial fibrillation/-flutter following acute myocardial infarction. TRACE Study group. TRAndolapril Cardiac Evalution. *Eur Heart J.* 1999;20:748–754.
24. Iba T, Levy JH, Levi M, Connors JM, Thachil J. Coagulopathy of Coronavirus Disease 2019. *Crit Care Med.* 2020;48:1358–1364.
25. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost.* 2020;18:1094–1099.