Anticoagulation Therapy in Patients With Coronavirus Disease 2019: Results From a Multicenter International Prospective Registry (Health Outcome Predictive Evaluation for Corona Virus Disease 2019 [HOPE-COVID19])

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OBJECTIVES: No standard therapy, including anticoagulation regimens, is currently recommended for coronavirus disease 2019. Aim of this study was to evaluate the efficacy of anticoagulation in coronavirus disease 2019 hospitalized patients and its impact on survival.

DESIGN: Multicenter international prospective registry (Health Outcome Predictive Evaluation for Corona Virus Disease 2019).

SETTING: Hospitalized patients with coronavirus disease 2019.

PATIENTS: Five thousand eight hundred thirty-eight consecutive coronavirus disease 2019 patients.

INTERVENTIONS: Anticoagulation therapy, including prophylactic and therapeutic regimens, was obtained for each patient.

MEASUREMENTS AND MAIN RESULTS: Five thousand four hundred eighty patients (94%) did not receive any anticoagulation before hospitalization. Two-thousand six-hundred one patients (44%) during hospitalization received anticoagulation therapy and it was not associated with better survival rate (81% vs 81%; $p = 0.94$) but with higher risk of bleeding (2.7% vs 1.8%; $p = 0.03$). Among patients admitted with respiratory failure (49%, $n = 2,859$, including 391 and 583 patients requiring invasive and noninvasive ventilation, respectively), anticoagulation started during hospitalization was associated with lower mortality rates (32% vs 42%; $p < 0.01$) and nonsignificant higher risk of bleeding (3.4% vs 2.7%; $p = 0.3$). Anticoagulation therapy was associated with lower mortality rates in patients treated with invasive ventilation (53% vs 64%; $p = 0.05$) without increased rates of bleeding (9% vs 8%; $p = 0.88$) but not in those with noninvasive ventilation (35% vs 38%; $p = 0.40$). At multivariate Cox' analysis mortality relative risk with anticoagulation was 0.58 (95% CI, 0.49–0.67) in patients admitted with respiratory failure, 0.50 (95% CI, 0.49–0.67) in those requiring invasive ventilation, 0.72 (95% CI, 0.51–1.01) in noninvasive ventilation.

CONCLUSIONS: Anticoagulation therapy in general population with coronavirus disease 2019 was not associated with better survival rates but with higher bleeding risk. Better results were observed in patients admitted with respiratory failure and requiring invasive ventilation.

KEY WORDS: anticoagulation; coronavirus disease 2019; risk prediction

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Coronavirus disease 2019 (COVID-19) is an infectious disease caused by a newly discovered coronavirus, presenting mainly as a severe acute respiratory syndrome (1). First, reported in China in December 2019, it has quickly spread all over the world becoming pandemic in few months. Actually, there is no standard therapy and no clear consensus from scientific societies in the absence of solid clinical data. Recent data from registries and autopsies suggested a potential role for coagulopathy in influencing outcome of COVID-19 patients (2, 3). The prevalence of pulmonary embolism (PE) among COVID-19 patients in ICU is about 20% (4). Furthermore, Zhang et al (5) found in a cohort of 143 patients that 66 patients (46.1%) developed lower extremity deep vein thrombosis (DVT) (23 patients [34.8%] with proximal DVT and 43 [65.2%] with distal DVT). Patients with DVT were older and had a lower oxygenation index, a higher rate of cardiac injury and worse prognosis (mortality rate 23% vs 12%). However, ICU patients without COVID-19 have higher risk of DVT (about 12%) when compared with other hospitalized patients (6).

Among COVID-19 patients, mainly those presenting with respiratory insufficiency, a combination of low-grade disseminated intravascular coagulation (DIC) and localized pulmonary thrombotic microangiopathy may be present (7). Therefore, anticoagulation therapy could be theoretically useful in some COVID-19 patients. Aim of the study was therefore to evaluate the impact on survival through anticoagulation therapy in COVID-19 patients in an observational registry.

MATERIALS AND METHODS

Study Design and Population

We present data from a cohort study of 5,838 patients with COVID-19 infection enrolled in the multicenter international Health Outcome Predictive Evaluation for Corona Virus Disease 2019 (HOPE-COVID19) Registry (https://hopeprojectmd.com, NCT04334291).

The protocol was established through a consortium of physicians from Italy, Spain, Ecuador, and Germany. Patients were enrolled from seven countries (Spain, Italy, Ecuador, Cuba, Germany, China, and Canada).

Detailed information about participating countries and hospitals is reported on website of the Registry. All patients were diagnosed with COVID-19 according to World Health Organization (WHO) interim guidance through polymerase chain reaction (PCR) testing (8). In this analysis, hospital data and patients were included until May 5, 2020.

All patients discharged (deceased or alive) from any hospital center were included in the Registry.

The local ethics committee approved this study and was consistent with Helsinki declaration. All local principal investigators reviewed the draft and checked for the accuracy and veracity of data. A list of participating hospitals, investigators, collaborators, and the protocol are available in the **Supplementary Appendix** (http://links.lww.com/CCM/G283) and on the website of the project (https://hopeprojectmd.com).

Data Extraction

Epidemiological, clinical, and outcome data were manually extracted from electronic medical records and assessed by medical researchers.

The individual components of all definitions of clinical outcomes were recorded separately and checked by at least two persons in each hospital. Patient's data were confidentiality protected by assigning all the data in anonym form and the electronic data were stored and/or filled in an encrypted, password-protected computer/website.

Pharyngeal swab samples were obtained from all patients at admission and tested using real-time reverse transcriptase-PCR assays according to the WHO recommendation. Additionally, patient's data including blood test, coagulation, and biochemical tests and chest radiographs or CT were extracted. Comorbidities were evaluated at admission (hypertension, dyslipidemia, diabetes mellitus, obesity, current smoking, renal insufficiency, lung disease, cardiac disease, cerebrovascular disease, connective tissue disease, liver disease, cancer disease, and others). All drugs at admission and previous to hospitalization were recorded. All decisions and clinical procedures were performed by the attending physician team independently of this study following the local regular practice and protocols.

Anticoagulation Therapy

Patients were included in the anticoagulation group if they were treated during hospitalization with systemic or prophylactic anticoagulation including oral,

subcutaneous, or IV forms. Patients without information on anticoagulation ($n = 31$) were excluded from analysis.

Major bleeding was defined as 1) values of hemoglobin less than 7 g/dL with a drop of at least 2 g/L within 24 hours and any RBC transfusion, 2) at least two units of RBC transfusion within 48 hours, or 3) a diagnosis code for major bleeding including intracranial hemorrhage, hematemesis, melena, peptic ulcer with hemorrhage, colon, rectal, or anal hemorrhage, hematuria, ocular hemorrhage, and acute hemorrhagic gastritis.

Outcome and Endpoint

We considered as primary endpoint all-cause mortality during hospitalization. Other events were recorded as secondary endpoints, such as invasive mechanical ventilation, noninvasive mechanical ventilation, prone, respiratory insufficiency, heart failure, renal failure, upper respiratory tract involvement, pneumonia, sepsis, systemic inflammatory response syndrome, clinically relevant bleeding, hemoptysis, and embolic events. Events were allocated following local researchers' criteria upon HOPE COVID-19 registry definitions.

Statistical Analysis

Data are presented as means ± SD for continuous variables with a normal distribution and as frequency (%) for categorical variables. The Kolmogorov-Smirnov test was used to assess normal distribution. Student *t* test and the Mann-Whitney *U* test were used to compare continuous variables with normal and non-normal distributions, respectively. The chi-square test or Fisher exact test was used to compare categorical variables. Survival was plotted on Kaplan-Meier curves and assessed with log-rank test. Relative risk with 95% CIs was calculated. Factors with p value of less than 0.05 on univariate analysis were entered into Cox' multivariable regression analysis to define independent risk factors for the outcome.

Statistical analysis was performed with SPSS Statistics 24.0 (IBM, Armonk, NY). A p value of less than 0.05 was considered as statistically significant, all tests were two-sided.

RESULTS

Baseline Features

Five thousand eight hundred thirty-eight patients were enrolled in the study. Mean age of patients admitted was 65 ± 16 years, 58% were male. Nine percent of patients were admitted in ICU. During hospitalization, 13% of patients required noninvasive ventilation and 7% invasive ventilation. All demographic features are reported in **Table 1**. Mean follow-up was 15 ± 11 days.

During hospitalization, 2,601 patients (44%) received anticoagulation therapy, among these patients, 327 (12%) had history of anticoagulation treatment. Anticoagulation therapy in subjects not anticoagulated before admission was given for prophylaxis in 83% of cases, while 15% received full dose of low-molecular-weight heparin, 1% oral anticoagulation with vitamin K antagonists, and 1% direct oral anticoagulants (**Fig. 1**).

Three-hundred twenty-seven patients (5.7%) were taking anticoagulation therapy before hospitalization. Most of them ($n = 230$) were taking oral anticoagulation due to history of atrial fibrillation and remaining patients due to previous DVT and PE. In an additional analysis comparing subjects anticoagulated before admission, after admission and not anticoagulated, those anticoagulated before admission showed worse mortality rates (**Supplement Fig. 1**, http://links.lww.com/CCM/G283 [**legend**, http://links.lww.com/CCM/G285]; log-rank $p < 0.001$).

Anticoagulation in General Population

Patients who received anticoagulation therapy were older (66 ± 15 vs 63 ± 27 yr; $p = 0.01$), more frequently were male (60% vs 58%; $p = 0.02$), had diabetes (21% vs 17%; $p = 0.01$), obesity (24% vs 21%; $p = 0.01$), renal insufficiency (creatinine clearance < 30 mL/min) (7% vs 6%; $p = 0.01$), history of lung disease (21% vs 17%; $p = 0.01$), and heart disease (26% vs 21%; $p = 0.01$) (Table 1).

Among patients without previous anticoagulation therapy, anticoagulation was not associated with better survival rate (81% vs 81%; $p = 0.94$) but with higher risk of bleeding (2.7% vs 1.8%; $p = 0.03$) (**Fig. 2**). In this setting, lower mortality rates were associated with prophylactic parenteral anticoagulation when compared with therapeutic anticoagulation therapy including oral or IV administration (**Supplement Fig. 2**, http://links.lww.com/CCM/G284 [legend, http://links.lww.com/CCM/G285]; log-rank $p < 0.001$).

Respiratory Failure

Among patients admitted with respiratory failure (49%, 2,859 patients, including 391 and 583 patients

TABLE 1.

Baseline Clinical Features of Overall Coronavirus Disease 2019 Population and of Patients That Received Anticoagulation Therapy and Not

Variables	General Population	Anticoagulation Therapy, Mean ± SD	No Anticoagulation Therapy, Mean ± SD	*p*
Number of patients, *n* (	5,838	2,601 (44)	3,214 (56)	
Age, yr	65 ± 16	66 ± 15	63 ± 27	0.01
Male sex, %	59	60	58	0.02
Clinical baseline profile, %				
Hypertension	49	53	46	0.36
Diabetes	19	21	17	0.01
Obesity (body mass index > 30)	22	24	21	0.01
Renal insufficiency (creatinine clearance < 30 mL/min)	6	7	6	0.01
History of lung disease	19	21	17	0.01
History of heart disease	23	26	21	0.01
History of cancer	14	14	14	0.92
Clinical features at admission, %				
Asymptomatic	5	3	6	0.01
Hyposmia/anosmia	7	7	7	0.55
Dysgeusia	7	8	7	0,34
Diarrhea	19	20	19	0.76
Laboratory data				
Procalcitonin above normal values, %	22	22	22	0.08
Admission D-dimer levels > 3 normal values, %	62	72	59	0.01
Admission creatinine levels (mg/dL)	1.19 ± 0.59	1.22 ± 0.60	1.16 ± 0.57	0.65
Admission leucocytes count ($\times 10^9$/L)	7,148 ± 3,891	7,321 ± 3,825	7,001 ± 3,918	0.59
Admission lymphocyte ($\times 10^9$/L)	1,320 ± 1,811	1,210 ± 1,511	1,414 ± 2,030	0.01
Admission platelets count ($\times 10^9$/L)	213 ± 96	216 ± 93	211 ± 93	0.01

requiring invasive and nonventilation, respectively), anticoagulation started during hospitalization was associated with lower mortality rates (32% vs 42%; $p < 0.01$) (**Fig. 3*A***; log-rank $p < 0.001$) and not significant higher risk of bleeding (3.4% vs 2.7%; $p = 0.3$). In this subset of patients, 40% received prophylactic dose and 11% therapeutic dose (Fig. 1*B*).

Three-hundred ninety-one patients (14%) underwent invasive ventilation; of these, 154 received (39%) prophylactic dose anticoagulation and 110 (28%) therapeutic dose. Additional anticoagulation therapy was associated with lower mortality rates (53% vs 64%; $p = 0.05$) without increased rates of bleeding (9% vs 8%; $p = 0.88$) (**Fig. 3*B***; log-rank $p < 0.001$). Fourteen

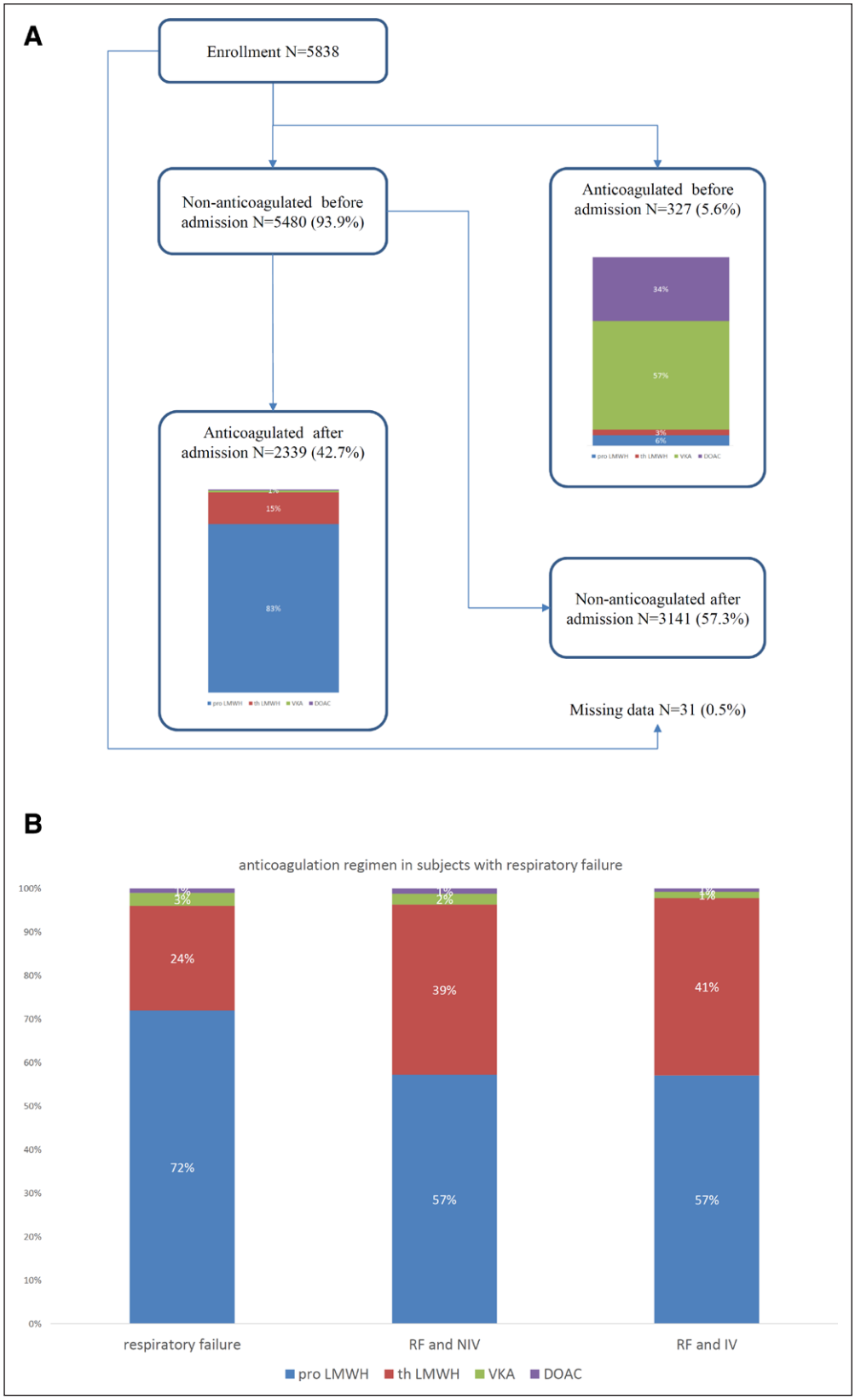

Figure 1. Anticoagulation regimens in general population (**A**), respiratory failure (RF) (**B**), RF treated with noninvasive ventilation (NIV) and invasive ventilation (IV). DOAC = direct oral anticoagulant, LMWH = low-molecular-weight heparin, Pro = prophylactic dose, th = therapeutic dose, VKA = vitamin K antagonist.

patients (3.4%) were on anticoagulation before hospitalization and two patients interrupted anticoagulation.

Five-hundred eighty-three patients (20%) underwent noninvasive ventilation; of these, 186 (32%) received prophylactic dose anticoagulation and 127 (22%) therapeutic dose. Additional anticoagulation therapy was not associated with lower mortality rates (35% vs 38%; $p = 0.40$), without increased rates of bleeding (4.4% vs 3.3%; $p = 0.55$). Thirty-eight patients (5%) were on anticoagulation therapy before hospitalization.

Multivariate Analysis

When evaluating patients admitted with respiratory failure (not anticoagulated before admission) in a multivariable Cox' regression analysis model including age, gender, prior history of heart, pulmonary or cancer disease, atrial fibrillation, admission to ICU, hypertension, diabetes, obesity, drug therapy during hospitalization with β-blockers, or angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers, anticoagulation was associated with lower mortality (risk ratio [RR], 0.58; 95% CI, 0.49–0.67; $p < 0.001$) (**Table 2**). In patients undergoing invasive ventilation the RR

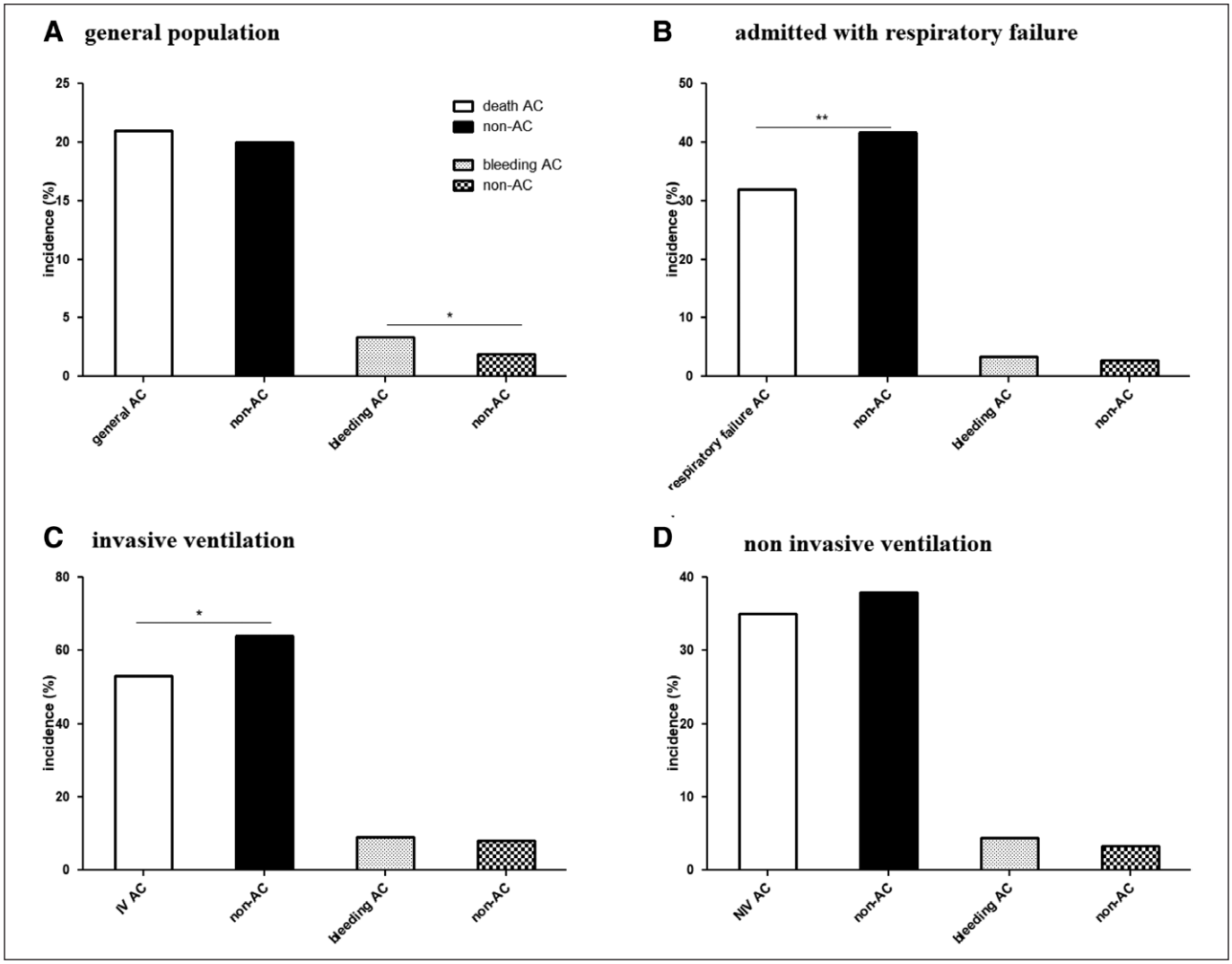

Figure 2. Rates of occurrence of death and bleeding in general population (**A**), naive subjects with respiratory failure (**B**), invasive ventilation (IV) (**C**), and noninvasive ventilation (NIV) (**D**), according to anticoagulant therapy during hospitalization. *Differences that are statistically different ($p < 0.05$). AC = anticoagulation.

with anticoagulation was 0.50 (95% CI, 0.37–0.70; $p < 0.001$), 0.72 (95% CI, 0.51–1.01; $p = 0.0575$) in noninvasive ventilation.

DISCUSSION

We report safety and efficacy of anticoagulation therapy from a large multicenter international registry on COVID-19. We found that anticoagulation therapy among general population with COVID-19 was not associated with better survival rates but with higher bleeding risk. Patients admitted with respiratory failure requiring invasive ventilation may benefit in terms of lower mortality through use of anticoagulation therapy.

COVID-19 is novel infectious disease that affects mainly respiratory system but also several organs. Indeed, severe acute respiratory syndrome coronavirus 2 enters human cells mainly by binding the ACE2, which is expressed in lung alveolar cells, vascular endothelial cells, cardiac myocytes, and other cells (9).

COVID-19 is featured by hemostatic abnormalities including mild thrombocytopenia and increased D-dimer levels. Recent literature showed that coagulopathy associated with COVID-19 is a combination of low-grade DIC and localized pulmonary thrombotic microangiopathy, which could have an impact among most severely affected patients (7).

Severe forms of COVID-19 are associated with increased concentrations of proinflammatory

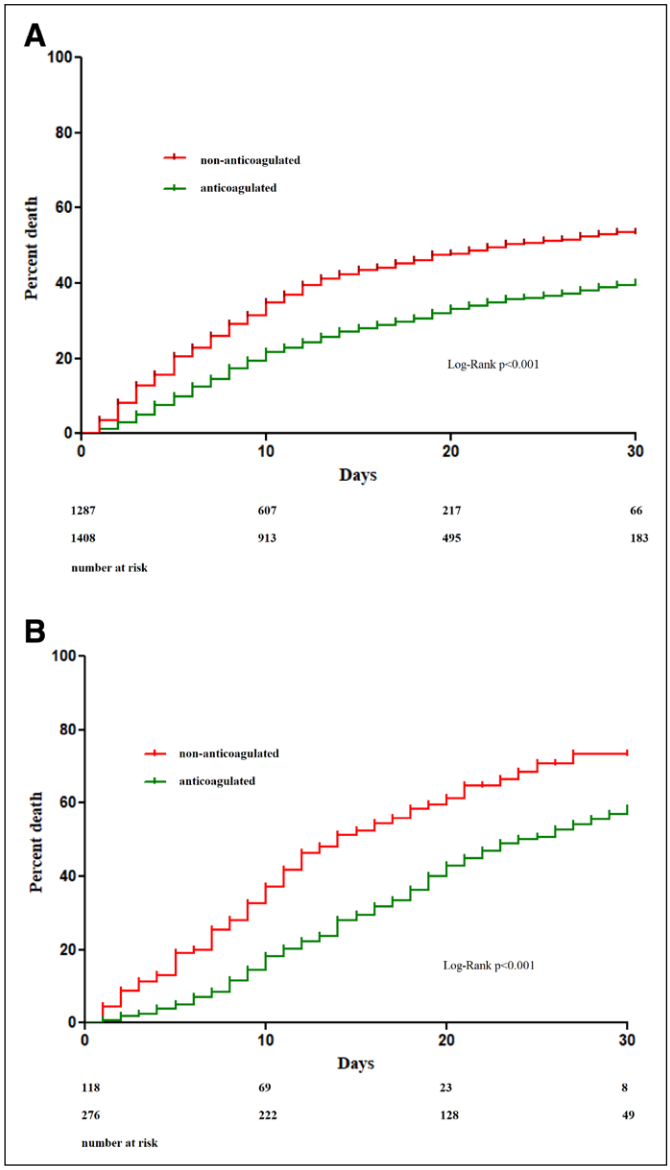

Figure 3. Cumulative death occurrence (**A**) in subjects not anticoagulated before admission and with respiratory failure according to anticoagulant therapy during hospitalization. Cumulative death occurrence (**B**) in subjects not anticoagulated before admission and with invasive ventilation according to anticoagulant therapy during hospitalization.

cytokines, such as tumor necrosis factor-α and interleukin (IL), including IL-1 and IL-6 (10). IL-6 can induce tissue factor expression on mononuclear cells, which subsequently initiates coagulation activation and thrombin generation.

Furthermore, a remarkable activation of the fibrinolytic system can be found in Coronavirus infections. Indeed, Plasma concentrations of tissue-type plasminogen activator were six times higher in patients infected with human severe acute respiratory syndrome coronavirus 1 than in patients with no infection (11).

Severe inflammatory response, critical illness, and underlying traditional comorbidities may predispose to thrombotic events, as previously found in severe acute respiratory syndrome (12). Hospitalized patients with acute medical illness, including infections such as pneumonia, are at increased risk of venous thromboembolism (VTE) (13). Therefore, especially in severe forms of COVID-19, there is a hypercoagulable state that could increase the risk of thromboembolic complications.

Most of the studies on the prevalence of thrombosis in COVID-19 have been performed in autopsies or in severe forms.

Autopsy studies showed various stages of diffuse alveolar damage in both lungs and thrombosis of small- and mid-sized pulmonary arteries in all patients associated with infarction in 72% of cases (14). Interestingly, all these patients were treated with prophylactic anticoagulation (11). Wichmann et al (2) found in an autopsy study DVT in seven out of 12 patients (58%) and PE was the direct cause of death in four patients.

Initial clinical series are supporting this finding, showing the common occurrence of VTE in patients with severe COVID-19 (3). The prevalence of PE among COVID-19 patients in ICU is about 20% (4) and 46% of patients may develop lower extremity DVT (5).

Klok et al (15) found an occurrence of PE among critically ill ICU patients of 35% and these patients had five times higher risk of death. Bompard et al (16), in a series of 135 patients, identified 24% (n = 32) of PE. Among these cases, 31% were proximal PE, 56% involved segmental pulmonary arteries, and 13% multiple subsegmental pulmonary arteries. Patients with PE required more frequently ICU stay and longer hospitalization.

Data on standard of care for anticoagulation therapy in COVID-19 are lacking and therapy is mainly based on operator choice. Some clinicians use prophylactic dosing and others intermediate- or full-dose (therapeutic) parenteral anticoagulation to prevent microvascular thrombosis.

Tang et al (17) evaluated a cohort of 449 patients with severe COVID-19; 22% of patients received heparin (mainly with low-molecular-weight heparin), and no differences were found in term of mortality according to anticoagulation therapy (30.3% vs 29.7%). Only patients with D-dimer levels six-fold higher than the upper limit of normal

TABLE 2.
Multivariable Cox' Regression Analysis in Subjects Admitted With Respiratory Failure (Nonanticoagulated Before Admission)

Variable	Risk Ratio (95% Lower–Upper)	*p*
Anticoagulant therapy	0.58 (0.49–0.67)	< 0.001
Age	1.05 (1.05–1.06)	< 0.001
Male	1.25 (1.06–1.48)	0.0075
ICU admission	0.93 (0.65–1.32)	0.6779
Hypertension	1.08 (0.87–1.34)	0.4881
Diabetes	1.06 (0.89–1.27)	0.4853
Obesity	1.30 (1.09–1.56)	0.0030
Renal failure	1.48 (1.19–1.83)	0.0004
Any lung disease	0.86 (0.71–1.03)	0.1062
Atrial fibrillation	1.45 (0.98–2.16)	0.0651
Any heart disease	1.26 (1.04–1.52)	0.0201
Any cancer	1.15 (0.94–1.40)	0.1736
Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers	0.97 (0.80–1.17)	0.7590
β-blockers	0.93 (0.76–1.14)	0.4909
Noninvasive ventilation	1.16 (0.96–1.40)	0.1216
Invasive ventilation	2.68 (1.88–3.83)	< 0.001

receiving heparin had lower mortality rate (32.8% vs 52.4%). Klok et al (15) found in critically ill ICU COVID-19 patients that chronic anticoagulation therapy at admission was associated with a lower risk of death (13).

In a large series from United States (2,773 patients), among patients who required mechanical ventilation (n = 395), anticoagulation was associated with lower in-hospital mortality (29.1% vs 62.7%) (18).

These data are in line with the present study where anticoagulation is associated with better outcome among patients with severe forms of COVID-19 admitted with respiratory failure. These patients, especially those requiring invasive ventilation, may benefit most from anticoagulation. This high-risk population might benefit from full doses of anticoagulation in order to prevent thromboembolic complication that are associated with worse outcome. However, in the present study, only 30% of patients with respiratory failure received full doses of anticoagulation therapy. On the other side, in general population, full doses of anticoagulation before and during admission were associated with higher mortality, probably because of underlying severe comorbidities in such patients.

Several multicenter, randomized, controlled trials (NCT04372589, NCT04367831, NCT04345848, and NCT04366960) are currently evaluating the use of anticoagulation and will provide additional insights.

LIMITATIONS

Some limitations have to be considered for the present investigation. The study is a large multicenter international prospective registry, and no patients were

randomized to different therapies. Anticoagulation therapy was based on operator choice. Timing of anticoagulation initiation during hospitalization was not prospectively collected, while anticoagulation dosage was not available in all patients. Most of the patients have 28 days follow-up, and no conclusion can be done for long-term outcome.

The lack of several clinical and individual variables does not allow a propensity score matching analysis.

CONCLUSIONS

Anticoagulation therapy in general population with COVID-19 was not associated with better survival rates but with higher bleeding risk. Better results in term of lower mortality through use of anticoagulation therapy were observed in patients admitted with respiratory failure requiring invasive ventilation.

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REFERENCES

1. Zhu N, Zhang D, Wang W, et al; China Novel Coronavirus Investigating and Research Team: A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med* 2020; 382:727–733
2. Wichmann D, Sperhake JP, Lütgehetmann M, et al: Autopsy findings and venous thromboembolism in patients with COVID-19. *Ann Intern Med* 2020; 173:1030
3. Dolhnikoff M, Duarte-Neto AN, de Almeida Monteiro RA, et al: Pathological evidence of pulmonary thrombotic phenomena in severe COVID-19. *J Thromb Haemost* 2020; 18:1517–1519
4. Poissy J, Goutay J, Caplan M, et al; Lille ICU Haemostasis COVID-19 Group: Pulmonary embolism in patients with COVID-19: Awareness of an increased prevalence. *Circulation* 2020; 142:184–186
5. Zhang L, Feng X, Zhang D, et al: Deep vein thrombosis in hospitalized patients with coronavirus disease 2019 (COVID-19) in Wuhan, China: Prevalence, risk factors, and outcome. *Circulation* 2020; 142:114–128
6. Malato A, Dentali F, Siragusa S, et al: The impact of deep vein thrombosis in critically ill patients: A meta-analysis of major clinical outcomes. *Blood Transfus* 2015; 13:559–568
7. Levi M, Thachil J, Iba T, et al: Coagulation abnormalities and thrombosis in patients with COVID-19. *Lancet Haematol* 2020; 7:e438–e440
8. Weissleder R, Lee H, Ko J, et al: COVID-19 diagnostics in context. *Sci Transl Med* 2020; 12:eabc1931
9. Zhang H, Penninger JM, Li Y, et al: Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: Molecular mechanisms and potential therapeutic target. *Intensive Care Med* 2020; 46:586–590

10. Huang C, Wang Y, Li X, et al: Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; 395:497–506
11. Liu ZH, Wei R, Wu YP, et al: Elevated plasma tissue-type plasminogen activator (t-PA) and soluble thrombomodulin in patients suffering from severe acute respiratory syndrome (SARS) as a possible index for prognosis and treatment strategy. *Biomed Environ Sci* 2005; 18:260–264
12. Lew TW, Kwek TK, Tai D, et al: Acute respiratory distress syndrome in critically ill patients with severe acute respiratory syndrome. *JAMA* 2003; 290:374–380
13. Rogers MA, Levine DA, Blumberg N, et al: Triggers of hospitalization for venous thromboembolism. *Circulation* 2012; 125:2092–2099
14. Lax SF, Skok K, Zechner P, et al: Pulmonary arterial thrombosis in COVID-19 with fatal outcome: Results from a prospective, single-center, clinicopathologic case series. *Ann Intern Med* 2020; 173:350–361
15. Klok FA, Kruip MJHA, van der Meer NJM, et al: Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: An updated analysis. *Thromb Res* 2020; 191:148–150
16. Bompard F, Monnier H, Saab I, et al: Pulmonary embolism in patients with Covid-19 pneumonia. *Eur Respir J* 2020; 56:2001365
17. Tang N, Bai H, Chen X, et al: Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost* 2020; 18:1094–1099
18. Paranjpe I, Fuster V, Lala A, et al: Association of treatment dose anticoagulation with in-hospital survival among hospitalized patients with COVID-19. *J Am Coll Cardiol* 2020; 76:122–124