

ORIGINAL ARTICLE

Thrombotic and hemorrhagic complications of COVID-19 in adults hospitalized in high-income countries compared with those in adults hospitalized in low- and middle-income countries in an international registry

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Abstract

Background: COVID-19 has been associated with a broad range of thromboembolic, ischemic, and hemorrhagic complications (coagulopathy complications). Most studies have focused on patients with severe disease from high-income countries (HICs).

Objectives: The main aims were to compare the frequency of coagulopathy complications in developing countries (low- and middle-income countries [LMICs]) with those in HICs, delineate the frequency across a range of treatment levels, and determine associations with in-hospital mortality.

Methods: Adult patients enrolled in an observational, multinational registry, the International Severe Acute Respiratory and Emerging Infections COVID-19 study, between January 1, 2020, and September 15, 2021, met inclusion criteria, including admission to a hospital for laboratory-confirmed, acute COVID-19 and data on complications and survival. The advanced-treatment cohort received care, such as admission to the intensive care unit, mechanical ventilation, or inotropes or vasopressors; the basic-treatment cohort did not receive any of these interventions.

Results: The study population included 495,682 patients from 52 countries, with 63% from LMICs and 85% in the basic treatment cohort. The frequency of coagulopathy complications was higher in HICs (0.76%-3.4%) than in LMICs (0.09%-1.22%). Complications were more frequent in the advanced-treatment cohort than in the basic-treatment cohort. Coagulopathy complications were associated with increased in-hospital mortality (odds ratio, 1.58; 95% CI, 1.52-1.64). The increased mortality associated with these complications was higher in LMICs (58.5%) than in HICs (35.4%). After controlling for coagulopathy complications, treatment intensity, and multiple

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other factors, the mortality was higher among patients in LMICs than among patients in HICs (odds ratio, 1.45; 95% CI, 1.39-1.51).

Conclusion: In a large, international registry of patients hospitalized for COVID-19, coagulopathy complications were more frequent in HICs than in LMICs (developing countries). Increased mortality associated with coagulopathy complications was of a greater magnitude among patients in LMICs. Additional research is needed regarding timely diagnosis of and intervention for coagulation derangements associated with COVID-19, particularly for limited-resource settings.

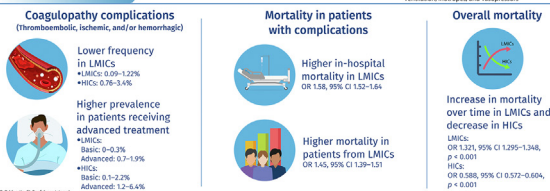
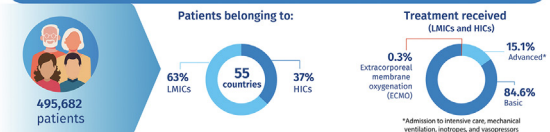
COVID-19 Coagulopathy Complications: Contrasting High-Income Countries and Developing Nations

Current studies on coagulopathy complications in COVID-19—which can adversely affect outcomes—originate mainly from high-income countries (HICs)



How do low- and middle-income countries (LMICs) compare to HICs with regard to coagulopathy complications of hospitalized patients with COVID-19?

Data from the International Severe Acute Respiratory and Emerging Infection (ISARIC) registry (January 1, 2020–September 15, 2021)



Although they show a lower frequency of coagulopathy complications, the mortality associated with these complications is higher for patients from LMICs with severe COVID-19

Thrombotic and hemorrhagic complications of COVID-19 for adults hospitalized in high-income countries compared to low- and middle-income countries in an international registry

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KEYWORDS

COVID-19, developing countries, disseminated intravascular coagulation, hemorrhage, ischemic stroke, SARS-CoV-2, thromboembolism, thrombosis

Essentials

- COVID-19 is associated with complications related to abnormal bleeding and clotting.
- We investigated bleeding and clotting complications in 495,682 adult patients.
- Bleeding and clotting complications were more frequent in high-income countries.
- The impact of complications on mortality was greater for patients in developing countries.

1 | INTRODUCTION

COVID-19 is associated with thrombotic, embolic, and hemorrhagic complications, which may lead to poor outcomes [1–3]. Because the viral binding target, angiotensin-converting enzyme 2 (ACE2), is present on endothelial cells, endothelial injury and inflammation may lead to thrombosis, thromboembolism, and disseminated intravascular coagulation [4]. Fatal cases of COVID-19 exhibited severe endothelial damage, including extensive pulmonary thrombosis, significantly more often than in cases of influenza [5,6]. ACE2 is also present on epithelial cells of the gastrointestinal tract, and gastrointestinal bleeding (GIB) is reported in 0.6% to 13% of patients hospitalized for COVID-19 [7]. Hypercoagulability and vascular inflammation caused by COVID-19 have been linked to markedly increased risks of ischemic stroke and myocardial infarction (MI) [8,9].

Early case series from Asia and Europe reported diagnosis of thromboembolic complications in 25% to 50% of patients with severe COVID-19 [10,11]. Similarly, a meta-analysis of studies with universal screening for venous thromboembolism revealed rates of pulmonary embolism (PE) and deep venous thrombosis (DVT) of 32% and 27%, respectively [12]. In contrast, other studies have reported substantially lower frequencies of thrombosis and bleeding among patients hospitalized for COVID-19 [13]. Clinical trials have shown that the optimal dosing of prophylactic anticoagulation varies based on disease severity, leading to consensus guideline recommendations from the International Society on Thrombosis and Hemostasis to incorporate an individualized assessment of the risk of thrombosis and bleeding into the prophylaxis strategy [14,15].

Most studies on thromboembolism, coagulopathy, and hemorrhage associated with COVID-19 are from high-income countries (HICs). Resource limitations in low- and middle-income countries

(LMICs) have had an impact on treatment options for patients with COVID-19, and the outcomes of severe COVID-19 have been worse in LMICs than in HICs [16–18]. More information is needed regarding the prevalence of coagulopathy complications of COVID-19 across a range of economic settings, including severe and non-severe disease presentations. This may be relevant as the pandemic transitions to endemic disease, and emerging variants may evade vaccine-mediated and post-infection immunity while continuing to enter tissues with ACE2 [19,20].

Our primary aims were to compare the frequency of coagulopathy complications in LMICs with those in HICs, with stratification by treatment intensity, and determine the association between coagulopathy complications and in-hospital mortality in LMICs and HICs. The secondary aims were to review trends over time for coagulopathy complications and mortality and identify independent risk factors for coagulopathy complications and mortality.

2 | METHODS

This was a prospective, observational study within the International Severe Acute Respiratory and Emerging Infection (ISARIC)—World Health Organization (WHO) Clinical Characterization Protocol for Severe Emerging Infections [21–23]. The study enrolled patients from LMICs (developing countries) and HICs hospitalized for COVID-19. Information on patient consent, the case report form, and the study protocol are available on the ISARIC website (<https://isaric.org> [22]). Investigators from 52 countries used data collection instruments, which have been adapted for a range of resource settings, to collect data using the ISARIC case report form, built using Research Electronic Data Capture (version 8.11.11) hosted by the University of Oxford [22,24]. The timing of data reporting was not controlled and depended on site resources and the medical information system structure. In some cases, data were entered into case report forms on a live basis—day by day throughout admission—whereas in other centers, data were completed by reviewing charts of patients hospitalized at a prior time. In addition, some collaborating investigators collected data using local systems and submitted these data to ISARIC for centralized mapping.

All investigators retain full rights to their data. The WHO Ethics Review Committee approved the ISARIC-WHO Clinical Characterisation Protocol (RPC571 and RPC572). In addition, local ethics approval was obtained for each participating country and site according to local requirements. The economic classification of countries was based on gross national income per capita using World Bank definitions (<https://data.worldbank.org/country>).

2.1 | Study population and measurements

The inclusion criteria were age ≥ 18 years, laboratory confirmation of SARS-CoV-2 infection, and admission to a hospital for acute illness due to COVID-19. Patients were excluded if they did not have a

country code or admission date. Sites were required to include all patients meeting the inclusion criteria (full recruitment) or, when full recruitment was not possible due to limited resources, select a strategy to reduce bias in patient selection (Supplementary File, “Procedure to Reduce Bias in Patient Selection”). We defined “coagulopathy complications” related to acute COVID-19 as any of the following 6 diagnoses using ISARIC definitions and clinical criteria for the diagnoses in the case report completion guide (<https://isaric.org/research/covid-19-clinical-research-resources/covid-19-crf/>, and Supplementary File, Case Definitions): PE, DVT, stroke, MI, GIB, or coagulation disorder/disseminated intravascular coagulation. The complications occurred during hospitalization. The 6 coagulopathy complications were selected based on clinical relevance and availability in the case report form. The following comorbidities were included: diabetes mellitus, chronic cardiac disease, chronic kidney disease, chronic pulmonary disease, chronic neurological disease, malignant neoplasm, chronic hematologic disease, chronic liver disease, smoking, and pregnancy. The complications and comorbidities are described in the case report form completion guide (available at <https://isaric.org/research/covid-19-clinical-research-resources/covid-19-crf/>). The collection of diagnoses included in “coagulopathy complications” is similar to those used in other COVID-19 studies [9,11,25]. Note that “coagulopathy complications” refers to the 6 complications described in Supplementary Material (ISARIC case report form completion guide), whereas “coagulation disorder/DIC” is one of the 6 complications.

Three cohorts of increasing treatment intensity were defined based on criteria used for a prior ISARIC analysis of patients with COVID-19 [26]. The most aggressively treated cohort received extracorporeal membrane oxygenation (ECMO). The advanced-treatment cohort received any of the following treatments: admission to the intensive care/high-dependency unit, invasive or noninvasive mechanical ventilation, high-flow nasal cannula oxygen, or inotropes or vasopressors. The basic-treatment cohort did not require ECMO or any of the treatments defining the advanced-treatment cohort. The main outcomes evaluated in this study were prevalence of coagulopathy complications and in-hospital mortality.

2.2 | Statistical analysis

The definitions of patient characteristics, complications, and outcomes are provided in Supplementary Material, “Case Report Form Completion Guide.” Clinically relevant variables were requested using the ISARIC data dictionary. The host repository at the University of Oxford converted data from contributing sites, which used a variety of local data systems, into Study Data Tabulation Model standards (version 1.7; Clinical Data Interchange Standards Consortium). The requested data fields for the data extraction period from January 1, 2020, to September 15, 2021, were sent to a secure server of the Study Design and Biostatistics Center at the University of Utah. Because the ISARIC collaboration process accommodates sites with a

wide range of data collection capabilities, the number of case reports, including clinical characteristics and complications, varied substantially [22]. For example, nearly all cases had sex and age included, but very few patients (<10%) had medications reported in the case report forms. Given this variation in the number of patients with variables of interest reported, the numbers of patients with the specified entry in the case report form are presented as denominators in tables. Patients with case report forms without complications were excluded from the evaluation of the prevalence of complications. Analysis was conducted using R, version 4.1.1.

Continuous variables were expressed as mean (SD), median (IQR), and range. Categorical variables were expressed as counts (percentages). To evaluate the association between demographic characteristics, economic stratification, and the presence of a coagulopathy complication, analysis of variance testing was used for continuous variables and chi-squared testing for categorical variables. A *P* value of <.05 was deemed statistically significant. When the clinical characteristics of patients with vs without coagulopathy were compared, a standardized mean difference (SMD) of >0.2 was considered as the minimum difference to suggest that the characteristic warranted consideration.

The trends in coagulopathy are represented graphically as monthly proportions calculated as the number of patients with reported coagulopathy complications divided by the number of patients enrolled. To answer the question “is there a significant linear trend over time in the rate of mortality?,” a logistic interaction model was constructed, with covariates of time and economic stratification as well as separate logistic models to determine the changes in mortality over the study period for each economic cohort. Results are presented as odds ratios (ORs) with 95% confidence limits.

Bar graphs are used to show the relationship between coagulopathy complications, income status, and treatment intensity. A 2-sample test of proportions was used to generate *P* values.

We fitted 2 multivariable logistic regression models. The first was to identify associations between clinically relevant patient characteristics and the outcome of any coagulopathy complication. Some characteristics were selected based on established risk factors for thromboembolism (such as cancer and smoking), and other characteristics were selected as indicators of high disease severity (such as treatment with mechanical ventilation or ECMO). The goal of the first model was to define potential clinical risk factors for coagulopathy complications, with adjustment for economic setting, treatment intensity, and increasing age. The goal of the second model was to quantify the association between coagulopathy complications and in-hospital mortality, with adjustment for treatment intensity, economic stratification, sex, increasing age, and clinically relevant comorbidities. ORs are presented using forest plots. Mortality designates in-hospital mortality, as specified in the final disposition section. Patients lacking a final disposition entry (*N* = 1013), located in the outcomes section of the case report form, were excluded from the evaluation of mortality for various cohorts and from the multivariable model of risk factors for mortality.

3 | RESULTS

A total of 495,682 patients from 52 countries met the inclusion criteria, including 312,033 (62.9%) patients from LMICs (developing countries), within the enrollment period of January 1, 2020, to September 15, 2021 (Figure 1). Eighty percent of patients in the registry were from the United Kingdom or South Africa (Supplementary Figure: patient numbers by country). In these countries, nation-wide protocols targeted full recruitment (all patients hospitalized for COVID-19). In addition, 84.6% (419,302/495,682) of the patients were classified as receiving basic treatment, 15.1% (74,907/495,682) as receiving advanced treatment, and 0.3% (1473/495,682) as receiving ECMO (Figure 1, Table 1); 6.5% (20,334/312,033) of the patients in LMICs received advanced treatment compared with 29.7% (54,573/183,649) of patients in HICs, and 91% (1344/1473) of the patients receiving ECMO were enrolled from HICs. Comparisons of demographics and comorbidities of patients in LMICs vs those of patients in HICs are presented in Table 1.

3.1 | Trends in coagulopathy complications and mortality over time

Over the 21 months of the study period, there were minor fluctuations in various coagulopathy complications, with a substantially lower frequency in LMICs than in HICs (Figure 2A, B). A plot of the cumulative prevalence of all coagulopathy complications and case counts showed steady accumulation over time (Figure 2C). For HICs, the mortality decreased over time, whereas for LMICs, the mortality increased over the study period (Figure 2D). Using a logistic interaction model, the OR for mortality over time was 0.588 (95% CI, 0.572-0.604; *P* < .001) in HICs; the OR for mortality over time was 1.321 (95% CI, 1.295-1.348; *P* < .001) in LMICs, indicating that there was a significant reduction in mortality over the study period in HICs but a significant increase in mortality over the study period in LMICs (Multimedia Content 4, Logistic Regression for Mortality over Time, Supplementary Tables for Figure 2D).

3.2 | Prevalence of coagulopathy complications

In LMICs, the prevalence of coagulopathy complications was <1% for stroke, coagulation disorder/disseminated intravascular coagulation (DIC), PE, and GIB and just >1% for MI and DVT (Table 2). In HICs, the complications with the highest prevalence were PE (3.4% [3608/105,987]) and coagulation disorder/DIC (3.4% [6004/177,695]). There was a significantly higher prevalence of 4 complication types in HICs: stroke, coagulation disorder/DIC, PE, and GIB (Table 2, *P* < .001 for each comparison). The prevalence of MI and DVT was higher in LMICs and was significantly higher for MI (*P* = .016) (Table 2). For both economic cohorts, the prevalence of coagulopathy complications was higher among patients receiving advanced treatment than the prevalence among patients receiving basic treatment (Figure 3A, B). The prevalence

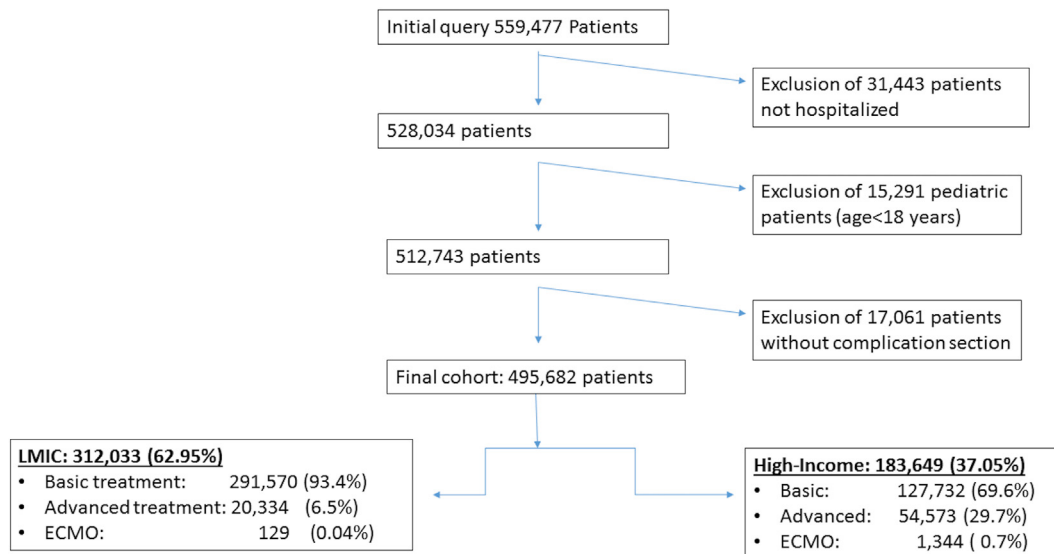


FIGURE 1 Patient Flow Diagram, showing exclusion steps and final cohorts by treatment intensity for LMIC and HIC.

of all complication types was higher among patients undergoing advanced treatment in HICs than the prevalence of complications among patients in the advanced-treatment cohort in LMICs, except for DVT. Notably, the ECMO cohort had a substantially increased prevalence of all complication types compared with the prevalence in both the advanced-treatment and basic-treatment cohorts.

3.3 | Characteristics of patients with vs without coagulopathy complications

The characteristics of patients with coagulopathy complications were compared with those of patients free from complications, without adjustment (Table 3). In addition, 61.9% of patients with coagulopathy complications were men. The comorbidities with a significantly higher prevalence in the cohort with coagulopathy complications were chronic cardiac disease and chronic kidney disease (each with an SMD of >0.2). Current smoking was reported for 26.9% (4009/14,888) of patients with complications compared with 10.2% (48,082/473,315) of patients without complications (SMD, 0.41). The average age of patients with coagulopathy complications was 67.2 years (SD, 16.3 years) compared with 58.9 years (SD, 18.2 years) in those without (SMD, 0.48).

3.4 | Mortality associated with coagulopathy complications

Patients with coagulopathy complications had higher in-hospital mortality than patients without coagulopathy complications (Figure 4A, $P < .001$). The mortality was almost identical across the economic stratification among patients without coagulopathy complications (24.0% [74,704/311,030] vs 24.1% [40,162/169,146]; $P = .952$), but the mortality among patients with coagulopathy complications in LMICs was 58.5% (583/1003) compared with 35.4%

(5110/14,503) among patients in HICs ($P < .001$). Across treatment intensity categories, coagulopathy complications were associated with increased mortality; the relative increase was greatest for the ECMO cohort (Figure 4B). When stratified by treatment intensity and economic classification, the mortality was higher in LMICs, both for those with and without coagulopathy complications (Figure 4C). The relative increase in mortality associated with coagulopathy complications in HICs was largest for the basic-treatment cohort (46%). For patients in LMICs, the largest relative increase in mortality associated with coagulopathy complications was for the advanced-treatment cohort (52%). When the mortality across economic strata and disease severity was compared, patients in LMICs without coagulopathy complications had significantly higher mortality in each severity category than patients in HICs ($P < .001$ for basic and advanced cohorts, $P = .02$ for the ECMO cohort; Figure 4D). In contrast, the mortality was significantly higher among patients in LMICs with coagulopathy complications only in the advanced-treatment cohort ($P < .001$ for advanced treatment, $P = .16$ for basic treatment, and $P = .12$ for ECMO) (Figure 4D). The mortality among patients in LMICs with advanced treatment and coagulopathy complications was similar to the mortality among patients in LMICs who received ECMO (64.9% [491/756] vs 66.7% [24/36], respectively) (Figure 4D).

3.5 | Risk factors for coagulopathy complications

Using multivariable logistic regression, selected risk factors for any coagulopathy complication were compared (Figure 5A). The covariates associated with the largest increased odds of coagulopathy complications were HIC economic classification (OR, 3.08; 95% CI, 2.84-3.35), advanced treatment (OR, 2.23; 95% CI, 2.15-2.32), and ECMO (OR, 10.49; 95% CI, 9.18-12). The comorbidities associated with an increased risk of coagulopathy complications were hematologic disease, chronic neurologic disease, cancer, and chronic cardiac disease.

TABLE 1 Demographics of high-income vs low- and middle-income patients.

| Characteristic | Category | High-income countries N = 183,649 (37.1%) | Low- and middle-income countries N = 312,033 (62.9%) | P value |
|-------------------------------|-------------------------------------|--|---|---------|
| Treatment intensity | Basic treatments | 127,732 (69.6%) | 291,570 (93.4%) | |
| Treatment intensity | Advanced treatments | 54,573 (29.7%) | 20,334 (6.5%) | |
| Treatment intensity | Extracorporeal membrane oxygenation | 1344 (0.7%) | 129 (0.04%) | |
| Age (y) | Mean (SD) | 67.7 (17.8) | 54.1 (16.4) | <.001 |
| | Median (IQR) | 71.0 (56.0-82.0) | 55.0 (42.0-66.0) | - |
| | Range | 18.0-107.0 | 18.0-109.0 | - |
| Body mass index | Mean (SD) | 29.8 (7.2) | 30.5 (8.8) | .001 |
| | Median (IQR) | 28.5 (25.2-33.0) | 28.9 (24.9-34.2) | - |
| Ethnicity | ABORIGINALFIRSTNATIONS | 104/150,548 (0.07%) | 0/195,354 (0%) | <.001 |
| | Arab | 1028/150,548 (0.68%) | 4/195,354 (0%) | - |
| | Black | 5842/150,548 (3.88%) | 127,234/195,354 (65.13%) | - |
| | East Asian | 1122/150,548 (0.75%) | 573/195,354 (0.29%) | - |
| | Latin American | 1358/150,548 (0.9%) | 1312/195,354 (0.67%) | - |
| | Mixed ethnicity | 1110/150,548 (0.74%) | 111/195,354 (0.06%) | - |
| | Other | 4618/150,548 (3.07%) | 15,361/195,354 (7.86%) | - |
| | South Asian | 10789/150,548 (7.17%) | 19,383/195,354 (9.92%) | - |
| | South East Asian | 59/150,548 (0.04%) | 3777/195,354 (1.93%) | - |
| | West Asian | 452/150,548 (0.3%) | 10/195,354 (0.01%) | - |
| | White | 124,066/150,548 (82.41%) | 27,589/195,354 (14.12%) | - |
| Sex | Female | 81,062/183,605 (44.15%) | 166,458/312,033 (53.35%) | <.001 |
| | Male | 102,334/183,605 (55.74%) | 145,525/312,033 (46.64%) | - |
| Pregnancy | Yes | 2116/183,649 (1.15%) | 8867/312,033 (2.84%) | <.001 |
| Diabetes | Yes | 52,849/180,870 (29.22%) | 63,632/311,735 (20.41%) | <.001 |
| Chronic cardiac disease | Yes | 69,992/154,485 (45.31%) | 93,459/311,498 (30%) | <.001 |
| Chronic kidney disease | Yes | 28,060/181,053 (15.5%) | 6183/311,734 (1.98%) | <.001 |
| Chronic pulmonary disease | Yes | 26,885/175,568 (15.31%) | 460/19,737 (2.33%) | <.001 |
| Chronic neurologic disease | Yes | 20,369/180,524 (11.28%) | 394/21,138 (1.86%) | <.001 |
| Malignant neoplasm | Yes | 17,275/180,539 (9.57%) | 168/21,138 (0.79%) | <.001 |
| Chronic hematologic disease | Yes | 7111/175,932 (4.04%) | 42/19,737 (0.21%) | <.001 |
| Chronic liver disease | Yes | 186/4593 (4.05%) | 19/1401 (1.36%) | <.001 |
| Oral steroid use on admission | Yes | 900/14,759 (6.1%) | 100/11,474 (0.9%) | <.001 |

Other risk factors included smoking and male sex. When other risk factors were controlled for, increasing age, chronic kidney disease, and chronic pulmonary disease were not associated with an increased risk of coagulopathy complications (Figure 5A).

advanced treatment, ECMO, multiple chronic diseases, male sex, and age, coagulopathy complications were associated with an increased risk of mortality (OR, 1.58; 95% CI, 1.52-1.64). Compared with patients in HICs, patients in LMICs had an increased risk of mortality (OR, 1.45; 95% CI, 1.39-1.51).

3.6 | Risk factors for in-hospital mortality

A multivariable analysis was performed to determine whether there was an independent association between coagulopathy complications and mortality (Figure 5B). After adjustment for economic cohort,

4 | DISCUSSION

In this multinational, prospective, observational study, we found that the frequency of coagulopathy complications associated with

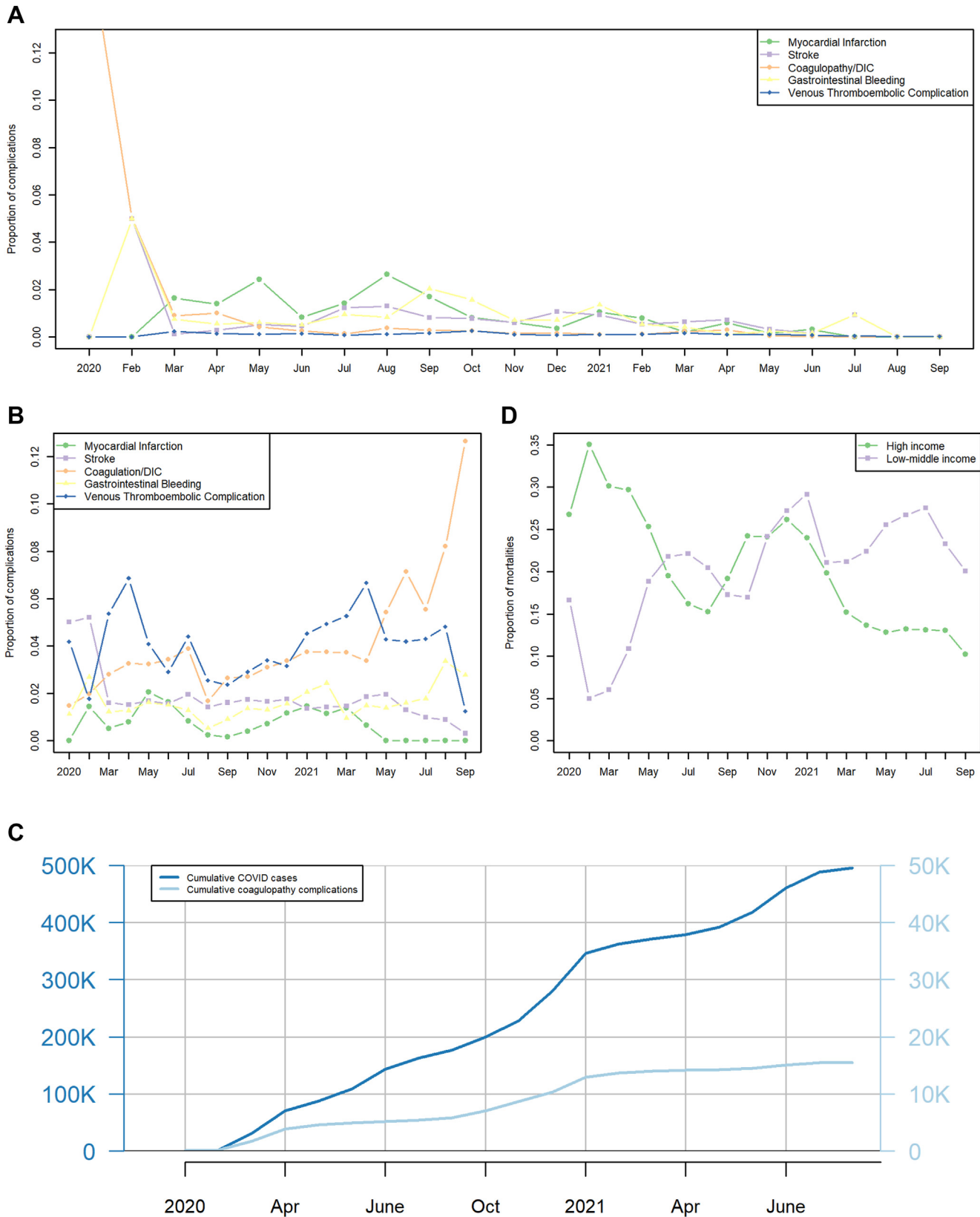


FIGURE 2 (A) Trends in coagulopathy complications over time for LMICs. Months specified along x-axis; "coagulation" stands for "coagulopathy/DIC"; "venous thromboembolic complication" is the combination of deep venous thrombosis and pulmonary embolism. (B) Trends in coagulopathy complications over time for HICs. Months specified along x-axis. "Coagulation/DIC" stands for "Coagulopathy/Disseminated intravascular coagulopathy"; Venous thromboembolic complication is the combination of both deep venous thrombosis and pulmonary embolism. (C) Cumulative Number of COVID-19 Cases and Complications: The x-axis displays the study period, dark blue line: cumulative number of COVID-cases in the registry over time; light blue line: cumulative number of coagulopathy complications over time. (D) Mortality over time by Income Cohort. The x-axis specifies month of study period, the monthly mortality rate is green for HICs and lavender for LMICs.

TABLE 2 Coagulopathy complications stratified by the economic classification of country.

| Coagulopathy complication | Low- and middle-income countries | High-income countries | P value |
|---|----------------------------------|-----------------------|---------|
| Myocardial infarction | 146/14,057 (1.04%) | 103/13,504 (0.76%) | .016 |
| Stroke | 113/19,932 (0.57%) | 2840/178,246 (1.59%) | <.001 |
| Coagulation disorder/disseminated intravascular coagulation | 467/310,529 (0.15%) | 6004/177,695 (3.38%) | <.001 |
| Pulmonary embolism | 262/303,156 (0.09%) | 3608/105,987 (3.4%) | <.001 |
| Gastrointestinal bleeding | 142/19,932 (0.71%) | 2686/177,716 (1.51%) | <.001 |
| Deep venous thrombosis | 13/1069 (1.22%) | 718/93,021 (0.77%) | .10 |

COVID-19 was lower than that reported in several smaller case series. Moreover, we found that coagulopathy complications were detected more frequently in HICs than in LMICs. Finally, we found that across all stages of treatment intensity (which would be expected to correlate with disease severity) and for both economic strata, the presence of coagulopathy complications was associated with increased mortality.

The frequency of venous thromboembolic complications (PE + DVT) in our study was substantially lower than the prevalence of venous thromboembolism in early reports from China (25%) and Europe (27%) but was comparable with the prevalence reported in 1 study from the United States (4.8%) [Table 2] [10,11,13].

The potential reasons for the low prevalence of these complications in our study include differences in the intensity of screening (ie, routine screening vs testing only for symptoms suggesting thromboembolism) and differences in anticoagulation practices as experience with treating COVID-19 evolved. The thrombotic complications reported in other studies included some outcomes, ie, central and arterial line thrombosis, clotting of dialysis circuits, and systemic arterial embolism, which were not included in the complication

questions of the ISARIC case report forms [11,13]. In the early stages of characterization of this new disease, laboratory and radiology assessments may have been performed exhaustively in institutions engaged in clinical research, leading to the detection of asymptomatic coagulopathy complications. Alternatively, early COVID-19 variants may in fact have had higher thrombogenicity than later variants. Further studies are needed to clarify these potential explanations.

There are many potential reasons for the higher frequency of coagulopathy complications observed in HICs, including more diagnostic resources such as computed tomography and laboratory tests of coagulation disorders, and resources for higher-intensity routine surveillance. In a survey of diagnostic resources available in LMICs, computed tomography was one of the most limited resources [27]. A markedly lower incidence of venous thromboembolism in LMICs than that in HICs has been reported in other international studies [28]. Early in the pandemic, intensive surveillance, including universal screening for thromboembolic disease in well-funded hospitals, may have led to reports that a majority of patients with COVID-19 had manifestations of a hypercoagulable state, leading to a working hypothesis that thromboembolic complications were central to the

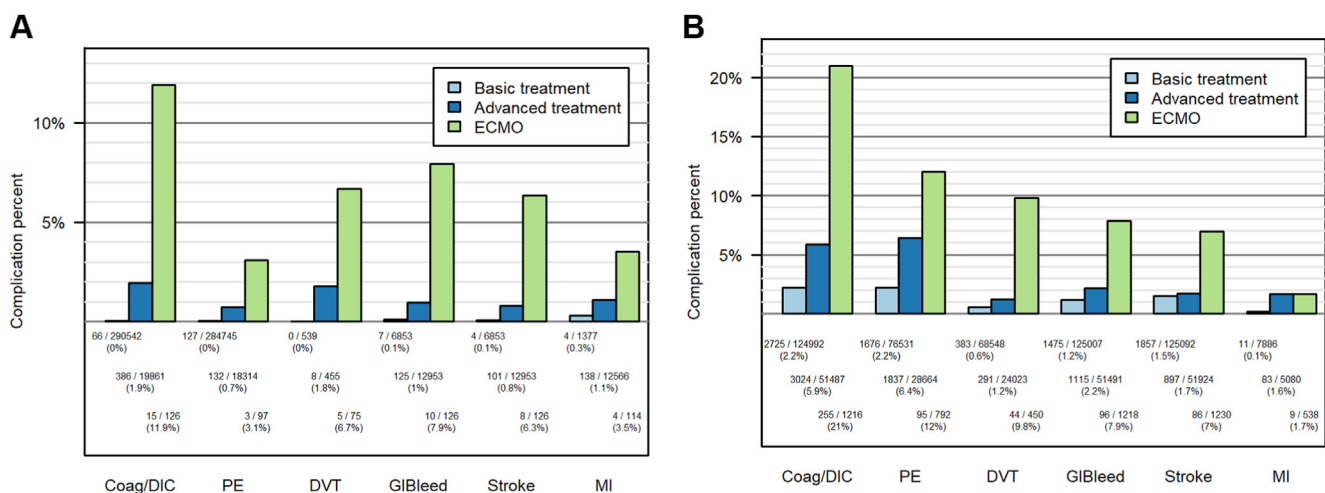


FIGURE 3 (A) Frequency of complications in low- and middle-income countries. Light blue bars: patients receiving basic treatment, dark blue bars: patients receiving advanced treatments; green bars: patients treated with extracorporeal membrane oxygenation. (B) Frequency of complications in high-income countries. Light blue bars: patients receiving basic treatment, dark blue bars: patients receiving advanced treatments; green bars: patients treated with extracorporeal membrane oxygenation. Coag/DIC, coagulopathy/disseminated intravascular coagulation; DVT, deep venous thrombosis; ECMO, extracorporeal membrane oxygenation; GI, gastrointestinal; MI, myocardial infarction; PE, pulmonary embolism.

TABLE 3 Comparison of demographics and comorbidities of patients with vs without coagulopathy complications.

| Characteristic | No coagulopathy complication N = 480,176 (96.9%) | Coagulopathy complication present N = 15,506 (3.1%) | Standardized mean difference (absolute value) | P value |
|-------------------------------|---|--|---|---------|
| Age (y), mean (SD) | 58.89 (18.15) | 67.22 (16.25) | 0.48 | <.001 |
| Median (IQR) | 59 (46-73) | 69 (56-80) | | |
| Female | 241,627/480,133 (50.3%) | 5893/15,505 (38%) | 0.25 | <.001 |
| Male | 238,256/480,133 (49.6%) | 9603/15,505 (61.9%) | 0.25 | |
| Pregnant patients | 10,904/480,176 (2.3%) | 79/15,506 (0.5%) | 0.15 | <.001 |
| Diabetes | 112,038/477,447 (23.5%) | 4443/15,158 (29.3%) | 0.13 | <.001 |
| Chronic cardiac disease | 156,611/452,250 (34.6%) | 6831/13,733 (49.7%) | 0.31 | <.001 |
| Chronic kidney disease | 31,839/477,613 (6.7%) | 2404/15,174 (15.8%) | 0.29 | <.001 |
| Chronic pulmonary disease | 25,234/180,473 (14%) | 2111/14,832 (14.2%) | 0.02 | <.001 |
| Chronic neurologic disease | 18,908/186,797 (10.1%) | 1855/14,865 (12.5%) | 0.07 | <.001 |
| Malignant neoplasm | 15,877/186,811 (8.5%) | 1566/14,866 (10.5%) | 0.07 | <.001 |
| Chronic hematologic disease | 6311/180,802 (3.5%) | 842/14,867 (5.7%) | 0.10 | <.001 |
| Smoking | 48,082/473,315 (10.2%) | 4009/14,888 (26.9%) | 0.41 | <.001 |
| Oral steroid use on admission | 893/24,636 (3.6%) | 107/1597 (6.7%) | 0.14 | <.001 |

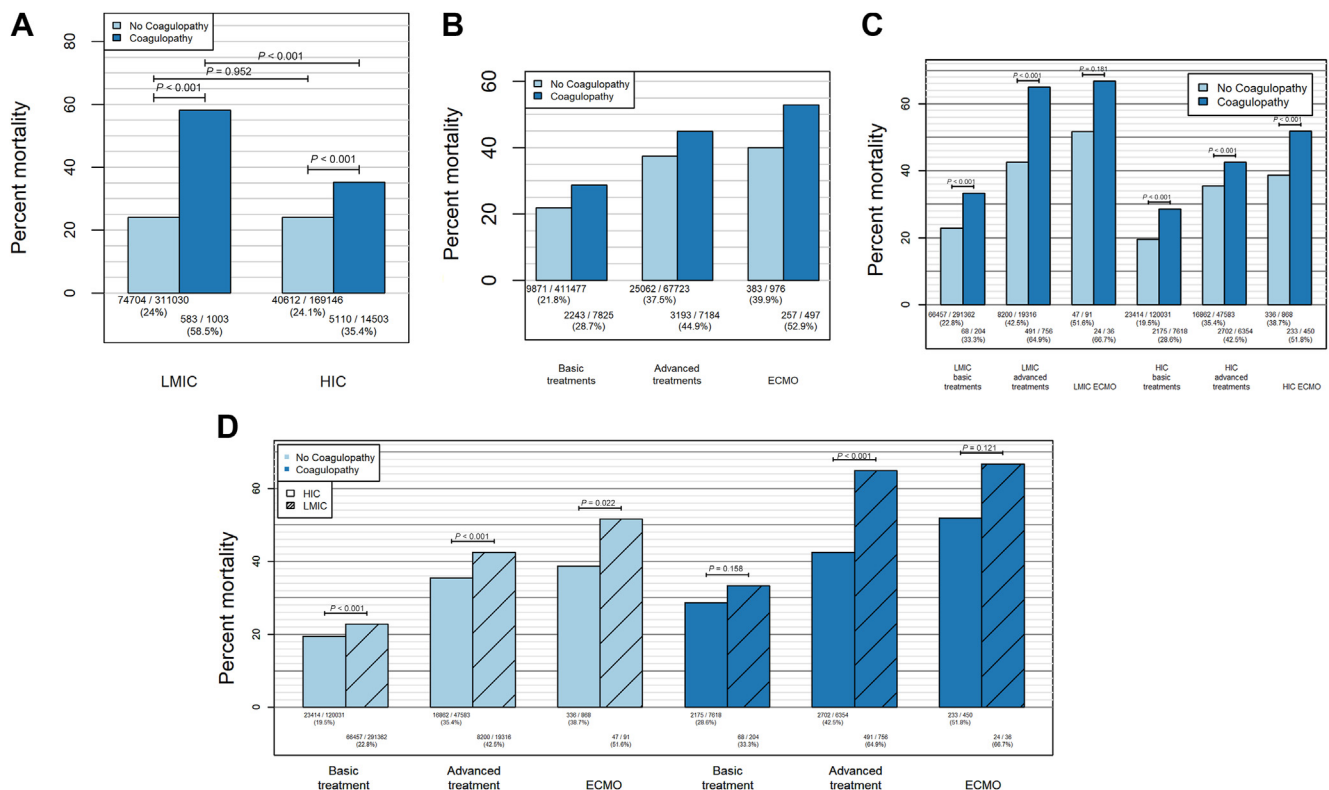


FIGURE 4 In-hospital mortality by the presence of coagulopathy complications (dark blue) vs no such complications (light blue), for low- and middle-income countries (LMICs) and high-income countries (HICs). (B) Mortality by treatment intensity, light blue for cohorts without coagulopathy complications, dark blue for cohorts with coagulopathy complications, patient fractions specified along x-axis. (C) Mortality by income category (LMIC on left and HIC on right), coagulopathy free (light blue), coagulopathy complications (dark blue). (D) Mortality by treatment intensity, economic stratification (HIC, open rectangles; LMIC, cross-hatched rectangles), and treatment intensity.

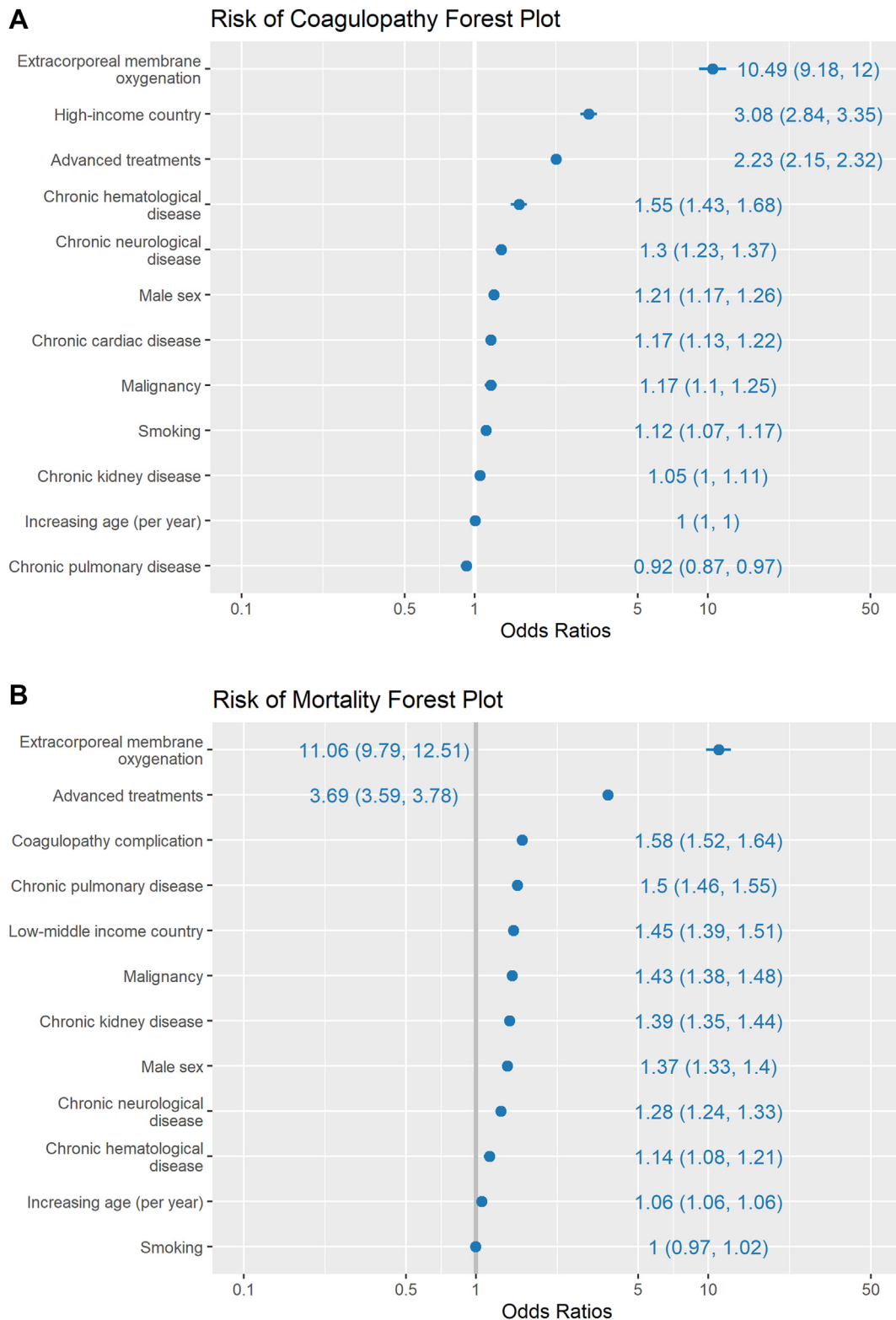


FIGURE 5 (A) Multivariable analysis of risk factors for coagulopathy complications. Odds ratios and 95% CIs are indicated along the margin. (B) Multivariable analysis of risk factors for mortality. Odds ratios and 95% CIs are indicated along the margin.

pathophysiology of many fatal cases. Based on this perspective, many clinicians rapidly adopted a practice of routinely using full or partial anticoagulation (rather than standard-dose prophylactic anticoagulation) for hospitalized patients. Subsequently, randomized

controlled trials demonstrated that full anticoagulation of patients with COVID-19 did not improve outcomes across the severity spectrum [29–31]. Extensive use of imaging and laboratory testing was mainly a feature of HICs, based on the depth and breadth of diagnostic

resources not available in LMICs. We thus hypothesize that the availability of diagnostic resources to learn about a new disease in HICs is the most likely explanation for a higher frequency of coagulopathy complications of COVID-19 in HICs than that in LMICs. Many of these diagnoses in HICs may have been mild or asymptomatic disorders, which would not be expected to lead to increased mortality.

The increased mortality among those with coagulopathy complications was substantial in not only the advanced-treatment cohort but also the basic treatment cohort: an absolute mortality difference of 10.5% among patients in LMICs receiving basic treatment and 9.1% among the patients in HICs receiving basic treatment. This contradicts the concept that inflammation, coagulopathy, and the severity of COVID-19 pulmonary disease could be modeled as a pyramid of increasing illness, with parallel increases in cardiopulmonary failure and coagulopathy [32]. An alternative paradigm is that a distinct subset of patients with COVID-19 who are free from severe respiratory failure or shock and thus do not require advanced treatment may still have significant coagulopathy derangements, with clinical consequences that may be life threatening. This illustrates the importance of taking an individualized approach to coagulopathy risk stratification and prophylaxis [33].

For patients with coagulopathy complications, the difference in mortality between LMIC and HIC cohorts was significant in the advanced-treatment cohort (Figure 4D). The potential explanations for the high mortality in this LMIC cohort (64.9%) are that many diagnoses may have been made when the complication was clinically severe or at an advanced stage when treatment was not likely to be effective.

In the multivariable analysis, both coagulopathy complications and living in a LMIC were independently associated with increased mortality after adjustment for treatment intensity and multiple comorbidities (Figure 5B). The mortality was higher across the spectrum of treatment intensity among patients in LMICs, and the increase in mortality associated with coagulopathy complications was greater among patients in LMICs than among patients in HICs. The potential reasons for this include delayed presentation to the hospital for patients in rural settings and lack of resources for escalating care for patients not improving with basic care. Limited resources for advanced care are a potential explanation for the observation that only 6.5% of patients in LMICs received advanced care compared with 29.7% of patients in HICs. A finding that calls for additional investigation is that mortality improved over the study period for HICs but worsened for LMICs. This finding highlights the profound need for distributing specific antiviral therapies (such as vaccines and novel antiviral medications) to developing countries during a pandemic.

Although COVID-19 is no longer classified as a global public health crisis, this study has important implications for future novel diseases. Multicenter registries are important for gathering information representative of a broad sample of clinical presentations, which may differ substantially from initial reports from single centers. Another key insight is that case report forms for new diseases should contain a wide variety of symptoms and complications; this will make it more likely that unexpected manifestations of the disease can be

captured earlier and in a larger number of patients than if case report forms must be modified. Finally, this work highlights the imperative to develop evaluation and intervention strategies that can be used in low-resource settings to narrow the stark disparities in outcomes in LMICs vs HICs during the conditions of a pandemic crisis.

4.1 | Limitations

This study has some limitations and strengths that are important to acknowledge. Each site participated in the registry voluntarily, which constitutes selection bias, resulting in unknown external validity of the observations. There were no protocols specifying the criteria for testing patients for coagulopathy complications; testing was based on clinical judgment or local policies for managing patients with COVID-19. In addition, the advanced-treatment cohort was based on treatments such as mechanical ventilation, administration of vasoactive medications, and admission to intensive care, with treatment decisions at the discretion of attending medical staff. While a similar method of defining a cohort with advanced care needs, as a surrogate for severe COVID-19, has been used in another ISARIC study, we cannot determine to what extent resource limitations and variability of treatment thresholds, eg, criteria for admission to the intensive care unit across sites, might lead to important differences in the treatment intensity cohorts between LMICs and HICs. Unfortunately, information such as blood gas values was missing in too many patients to use more objective criteria for disease severity [26]. Another important limitation to consider is that the type of laboratory assay to confirm SARS-CoV-2 infection was not specified in the case report form instrument; thus, it is not possible to determine, for example, the number of tests based on polymerase chain reaction vs based on antigen detection using colorimetry. Data collection was performed across a wide range of resource settings and during periods of surges, necessitating the accommodation of centers with limited data sets, and patients without data on complications had to be excluded. This resulted in the largest limitation of the study: the number of patients in LMICs with case report forms including the complications MI, stroke, GIB, and DVT was relatively small. This subset of patients in LMICs with details regarding complications may have differed in important ways from patients who did not have complication data available for analysis. The insight that coagulopathy and thrombosis were the hallmarks of severe COVID-19 led to addition of specific fields for DVT and PE to the complications section of case report forms after the initial enrollment period. Because of missing data, medication use, including the use of anticoagulants and steroids, as well as coagulation laboratory values could not be incorporated into the analysis. At the time of data extraction, vaccination status was not included in the registry; a future study is focused on this important aspect. The strengths of the study include the number of patients involved and inclusion of patients who received both advanced and basic treatments as well as recruitment from both HICs and LMICs. Additionally, 80% of the patients were enrolled in countries with full national recruitment of patients hospitalized for COVID-19, and all sites were required to adhere to a strategy to prevent selection bias (Supplementary File).

5 | CONCLUSIONS

In this large, international registry, we found that the prevalence of coagulopathy complications (defined as any of the following 6 outcomes: PE, DVT, stroke/cerebrovascular accident, MI, GIB, and coagulation disorder/DIC) in adult patients hospitalized for COVID-19 was substantially lower than that reported in smaller case series, particularly from reports published early during the pandemic. Coagulopathy complications were more frequently observed in HICs than in LMICs, and the prevalence was higher among patients who received advanced treatment. In-hospital mortality was higher among patients with coagulopathy complications, and the increase in mortality associated with coagulopathy complications was greater in LMICs than in HICs, particularly for patients in the advanced-treatment cohort. Coagulopathy complications were associated with increased mortality across economic settings and among patients receiving both basic and advanced treatment; therefore, future efforts should be directed toward early diagnosis and intervention, particularly in lower-resource settings.

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ETHICS STATEMENT

Ethics approval and informed consent were obtained at each site by the site investigators, according to local regulations, which included a waiver of consent to collect de-identified data at several sites due to the burden on front-line workers and the data protection framework in place. The WHO-ISARIC Clinical Characterization Protocol was approved by the WHO Ethics Committee (RPC571 and RPC572) (Reference [22], pages 2-3).

AUTHOR CONTRIBUTIONS

M.J.G. was involved in study conception and design, acquisition of data, analysis and interpretation, drafting and revision of the article, as well as conception and revision of figures. P.T.B., S.-M.C., and L.F.R. were involved in study design, analysis and interpretation of data, revision of the article. D.P.E. was involved in statistical analysis, data cleaning, analysis of data, composition and formatting of figures, and drafting of the manuscript. D.R. was involved in study conception and design, analysis and interpretation of data, and manuscript drafting and revising. L.M. was involved in study design, data acquisition, interpretation of results, revision of data analysis, and proofreading. B.W.C. was involved in study design, data acquisition, and revision of the manuscript. J.F. and P.M.A.A. were involved in study design and interpretation of results. J.F. was involved in concept and design of database and contribution of data. H.D. was involved in concept and design of the study. All authors read and approved the final version of the paper.

RELATIONSHIP DISCLOSURE

There are no competing interests to disclose.

DATA AVAILABILITY

The data that underpin this analysis are highly detailed clinical data on individuals hospitalized for COVID-19. Due to the sensitive nature of these data and the associated privacy concerns, they are available via a governed data access mechanism following review of a data access committee. Data can be requested via the Infectious Disease Data Observatory COVID-19 Data Sharing Platform (<http://www.iddo.org/covid-19>). The Data Access Application, Terms of Access, and details of the Data Access Committee are available on the website. Briefly, the requirements for access are a request from a qualified researcher working with a legal entity who has a health and/or research remit; a scientifically valid reason for data access that adheres to appropriate ethical principles. The full terms are at <https://www.iddo.org/document/covid-19-data-access-guidelines>. A small subset of sites that contributed data to this analysis have not agreed to pooled data sharing as above. In the case of requiring access to these data, please contact the corresponding author in the first instance, who will look to facilitate access.

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SUPPLEMENTARY MATERIAL

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APPENDIX

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Henriquez-Trujillo; Maxime Hentzien; Diana Hernandez; Jaime Hernandez-Montfort; Andrew Hershey; Liv Hesstvedt; Eibhlin Higgins; Dawn Higgins; Rupert Higgins; Rita Hinchion; Samuel Hinton; Hiroaki Hiraiwa; Hikombo Hitoto; Antonia Ho; Yi Bin Ho; Alexandre Hochtin; Isabelle Hoffmann; Wei Han Hoh; Oscar Hoiting; Rebecca Holt; Jan Cato Holter; Peter Horby; Juan Pablo Horcajada; Koji Hoshino; Ikram Houas; Catherine L. Hough; Stuart Houltham; Jimmy Ming-Yang Hsu; Jean-Sébastien Hulot; Abby Hurd; Samreen Ijaz; M. Arfan Ikram; Hajnal-Gabriela Illes; Patrick Imbert; Hugo Inácio; Carmen Infante Dominguez; Yun Sii Ing; Elias Iosifidis; Mariachiara Ippolito; Sarah Isgett; Tiago Isidoro; Nadiah Ismail; Margaux Isnard; Junji Itai; Daniel Ivulich; Danielle Jaafar; Salma Jaafoura; Julien Jabot; Clare Jackson; Victoria Janes; Pierre Jaquet; Waasila Jassat; Coline Jaud-Fischer; Stéphane Jaureguierry; Denise Jaworsky; Florence Jego; Anilawati Mat Jelani; Synne Jenum; Ruth Jimbo-Sotomayor; Ong Yiau Joe; Ruth N. Jorge García; Cédric Joseph; Mark Joseph; Mercé Jourdain; Philippe Jouvét; Anna Jung; Hanna Jung; Dafsah Juzar; Oufiyya Kaff; Florentia Kaguelidou; Neerusha Kaisbain; Thavamany Kaleesvran; Sabina Kali; Smaragdi Kalomoiri; Muhammad Aisar Ayadi Kamaluddin; Zul Amali Che Kamaruddin; Nadiah Kamarudin; Darshana Hewa Kandamby; Chris Kandel; Kong Yeow Kang; Pratap Karpayah; Christiana Kartsonaki; Daisuke Kasugai; Anant Kataria; Kevin Katz; Aasmine Kaur; Christy Kay; Lamees Kayyali; Hannah Keane; Seán Keating; Claire Kelly; Yvelynne Kelly; Andrea Kelly; Niamh Kelly; Aoife Kelly; Sadie Kelly; Maeve Kelsey; Ryan Kennedy; Kalynn Kennon; Maeve Kernan; Younes Kerroumi; Sharma Keshav; Imrana Khalid; Antoine Khalil; Coralie Khan; Irfan Khan; Michelle E Kho; Saye Khoo; Ryan Khoo; Denisa Khoo; Khor How Kiat; Yuri Kida; Peter Kiiza; Beathe Kiland Granerud; Anders Benjamin Kildal; Antoine Kimmoun; Detlef Kindgen-Milles; Alexander King; Nobuya Kitamura; Paul Klenerman; Rob Klont; Gry Kloumann Bekken; Stephen R Knight; Malte Kohns Vasconcelos; Mamoru Komatsu; Caroline Kosgei; Arsène Kpangon; Karolina Krawczyk; Sudhir Krishnan; Vinothini Krishnan; Oksana Kruglova; Deepali Kumar; Ganesh Kumar; Pavan Kumar Vecham; Dinesh Kuriakose; Ethan Kurtzman; Demetrios Kutsogiannis; Galyna Kutsyna; Konstantinos Kyriakoulis; Marie Lachatre; Marie Lacoste; John G. Laffey; Nadhem Lafhej; Marie Lagrange; Fabrice Laine; Olivier Lairez; Antonio Lalueza; Marc Lambert; François Lamontagne; Marie Langelot-Richard; Vincent Langlois; Eka Yudha Lantang; Marina Lanza; Cédric Laouéan; Samira Laribi; Delphine Lariviere; Stéphane Lasry; Odile Launay; Didier Laureillard; Yoan Lavie-Badie; Andy Law; Teresa Lawrence; Cassie Lawrence; Minh Le; Clément Le Bihan; Cyril Le Bris; Georges Le Falher; Lucie Le Fevre; Quentin Le Hingrat; Marion Le Maréchal; Soizic Le Mestre; Gwenaél Le Moal; Vincent Le Moing; Hervé Le Nagard; Paul LeTurnier; Ema Leal; Marta Leal Santos; Todd C. Lee; Su Hwan Lee; James Lee; Jennifer Lee; Heng Gee Lee; Biing Horng Lee; Yi Lin Lee; Gary Leeming; Bénédicte Lefebvre; Laurent Lefebvre; Benjamin Lefèvre; Sylvie LeGac; Jean-Daniel Lelievre; François Lellouche; Adrien Lemaigen; Véronique Lemeé; Anthony Lemeur; Gretchen Lemmink; Ha Sha Lene; Jenny Lennon; Rafael León; Marc Leone; Michela Leone; Quentin Lepiller; François-Xavier Lescure; Olivier Lesens; Mathieu Lesouhaitier; Amy Lester-Grant; Sophie Letrou; Bruno Levy; Yves Levy;

Claire Levy-Marchal; Katarzyna Lewandowska; Erwan L'Her; Gianluigi Li Bassi; Geoffrey Liegeon; Wei Shen Lim; Kah Chuan Lim; Chantre Lima; Bruno Lina; Lim Lina; Andreas Lind; Guillaume Lingas; Sylvie Lion-Daolio; Samantha Lissauer; Keibun Liu; Marine Livrozet; Patricia Lizotte; Navy Lolong; Leong Chee Loon; Diogo Lopes; Dalia Lopez-Colon; Anthony L. Loschner; Paul Loubet; Bouchra Loufti; Guillame Louis; Silvia Lourenco; Lee Lee Low; Marije Lowik; Jia Shyi Loy; Jean-Christophe Lucet; Carlos Lumbreras Bermejo; Carlos M. Luna; Olguta Lungu; Liem Luong; Nestor Luque; Dominique Luton; Nilar Lwin; Ruth Lyons; Olavi Maasikas; Oryane Mabilia; Moise Machado; Sara Machado; Gabriel Macheda; Hashmi Madiha; Guillermo Maestro de la Calle; Rafael Mahieu; Sophie Mahy; Ana Raquel Maia; Lars S. Maier; Mylène Maillet; Thomas Maitre; Maximilian Malferttheiner; Nadia Malik; Paddy Mallon; Fernando Maltez; Denis Malvy; Victoria Manda; Laurent Mandelbrot; Frank Manetta; Julie Mankikian; Edmund Manning; Aldric Manuel; Ceila Maria Sant'Ana Malaque; Flávio Marino; Samuel Markowicz; Ana Marques; Catherine Marquis; Brian Marsh; Laura Marsh; Megan Marshal; John Marshall; Celina Turchi Martelli; Emily Martin; Guillaume Martin-Blondel; F. Eduardo Martinez; Ignacio Martin-Loeches; Martin Martinot; João Martins; Ana Martins; Nuno Martins; Caroline Martins Rego; Gennaro Martucci; Olga Martynenko; Eva Miranda Marwali; Marsilla Marzukie; David Maslove; Sabina Mason; Mohd Basri Mat Nor; Moshe Matan; Daniel Mathieu; Mathieu Mattei; Laurence Maulin; Michael Maxwell; Javier Maynar; Thierry Mazzoni; Lisa Mc Sweeney; Colin McArthur; Peter McCanny; Anne McCarthy; Aine McCarthy; Colin McCloskey; Rachael McConnochie; Sherry McDermott; Sarah E. McDonald; Aine McElroy; Samuel McElwee; Victoria McEneaney; Natalie McEvoy; Allison McGeer; Chris McKay; Johnny McKeown; Kenneth A. McLean; Paul McNally; Bairbre McNicholas; Elaine McPartlan; Edel Meaney; Cécile Mear-Passard; Maggie Mechlin; Omar Mehkri; Ferruccio Mele; Luis Melo; Joao Joao Mendes; Kusum Menon; France Mentré; Alexander J. Mentzer; Emmanuelle Mercier; Noémie Mercier; Antoine Merckx; Mayka Mergeay-Fabre; Blake Mergler; Laura Merson; António Mesquita; Osama Metwally; Agnès Meybeck; Dan Meyer; Alison M. Meynert; Vanina Meysonnier; Amina Meziane; Mehdi Mezidi; Céline Michelanglei; Isabelle Michelet; Efstathia Mihelis; Vladislav Mihnovit; Jennene Miller; Hugo Miranda-Maldonado; Nor Arisah Misnan; Tahira Jamal Mohamed; Nik Nur Eliza Mohamed; Asma Moin; Elena Molinos; Brenda Molloy; Sinead Monahan; Mary Mone; Agostinho Monteiro; Claudia Montes; Giorgia Montrucchio; Shona C. Moore; Sarah Moore; Lina Morales Cely; Lucia Moro; Ben Morton; Catherine Motherway; Ana Motos; Hugo Mouquet; Clara Mouton Perrot; Julien Moyet; Caroline Mudara; Ng Yong Muh; Dzawani Muhamad; Jimmy Mullaert; Fredrik Müller; Karl Erik Müller; Aisling Murphy; Lorna Murphy; Patrick Murray; Marlène Murriss; Srinivas Murthy; Himed Musaab; Gugapriyaa Muyandy; Dimitra Melia Myrodi; Dave Nagpal; Alex Nagrebetsky; Mangala Narasimhan; Nageswaran Narayanan; Alasdair Nazerali-Maitland; Nadège Neant; Holger Neb; Raul Neto; Emily Neumann; Pauline Yeung Ng; Wing Yiu Ng; Anthony Nghi; Duc Nguyen; Orna Ni Choileain; Niamh Ni Leathlobhair; Alistair D Nichol; Prompak Nitayavardhana; Stephanie Nonas; Nurul Amani Mohd Noordin; Marion Noret; Nurul Faten Izzati Norharizam; Lisa Norman;

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