

Heparin in COVID-19 Patients Is Associated with Reduced In-Hospital Mortality: The Multicenter Italian CORIST Study*

Augusto Di Castelnuovo^{1,**} Simona Costanzo^{2,**}  Andrea Antinori³ Nausicaa Berselli⁴
 Lorenzo Blandi⁵ Marialaura Bonaccio² Roberto Cauda^{6,7} Giovanni Guaraldi⁸ Lorenzo Menicanti⁹
 Marco Mennuni¹⁰ Giustino Parruti¹¹ Giuseppe Patti¹⁰ Francesca Santilli¹² Carlo Signorelli¹³
 Alessandra Vergori¹⁴ Pasquale Abete¹⁵ Walter Ageno¹⁶ Antonella Agodi¹⁷
 Piergiuseppe Agostoni^{18,19} Luca Aiello²⁰ Samir Al Moghazi²¹ Rosa Arboretti²² Marinella Astuto²³
 Filippo Aucella²⁴ Greta Barbieri²⁵ Alessandro Bartoloni²⁶ Paolo Bonfanti^{27,28}
 Francesco Cacciatore¹⁵ Lucia Caiano¹⁶ Laura Carrozzi²⁹ Antonio Cascio³⁰ Arturo Ciccullo⁶
 Antonella Cingolani^{6,7} Francesco Cipollone¹² Claudia Colomba³⁰ Crizia Colombo¹⁰
 Francesca Crosta¹¹ Gian Battista Danzi³¹ Damiano D'Ardes¹² Katleen de Gaetano Donati⁶
 Francesco Di Gennaro³² Giuseppe Di Tano³¹ Gianpiero D'Offizi³³ Massimo Fantoni^{6,7}
 Francesco Maria Fusco³⁴ Ivan Gentile³⁵ Francesco Gianfagna^{1,16} Elvira Grandone²⁴
 Emauele Graziani³⁶ Leonardo Grisafi¹⁰ Gabriella Guarnieri³⁷ Giovanni Larizza³⁸ Armando Leone³⁹
 Gloria Maccagni³¹ Ferruccio Madaro³⁸ Stefano Maitan²⁰ Sandro Mancarella⁴⁰
 Massimo Mapelli^{18,19} Riccardo Maragna^{18,19} Rossella Marcucci²⁶ Giulio Maresca⁴¹
 Silvia Marongiu⁴² Claudia Marotta³² Lorenzo Marra³⁹ Franco Mastroianni³⁸ Maria Mazzitelli⁴³
 Alessandro Mengozzi⁴⁴ Francesco Menichetti⁴⁴ Marianna Meschiari⁸ Jovana Milic⁸
 Filippo Minutolo⁴⁵ Beatrice Molena³⁷ Arturo Montineri⁴⁶ Cristina Mussini⁸ Maria Musso⁴⁷
 Daniela Niola¹² Anna Odone⁵ Marco Olivieri⁴⁸ Antonella Palimodde⁴² Roberta Parisi²
 Emanuela Pasi³⁶ Raffaele Pesavento⁴⁹ Francesco Petri²⁷ Biagio Pinchera³⁵ Venerino Poletti^{50,51}
 Claudia Ravaglia⁵⁰ Andrea Rognoni¹⁰ Marco Rossato⁴⁹ Marianna Rossi²⁷ Vincenzo Sangiovanni³⁴
 Carlo Sanrocco¹¹ Laura Scorzoloni⁵² Raffaella Sgariglia⁴⁰ Paola Giustina Simeone¹¹
 Eleonora Taddei⁶ Carlo Torti⁴³ Roberto Vettor⁴⁹ Andrea Vianello³⁷ Marco Vinceti^{4,53}
 Alexandra Virano¹⁶ Laura Vocciante⁴¹ Raffaele De Caterina²⁹ Licia Iacoviello^{2,16}

Thromb Haemost 2021;121:1054–1065.

Address for correspondence Licia Iacoviello, MD, PhD, Department of Epidemiology and Prevention, IRCCS Neuromed, Via dell'Elettronica, 86077 Pozzilli, Isernia, Italy (e-mail: licia.iacoviello@moli-sani.org).

¹ Mediterranea Cardiocentro, Napoli, Italy

² Department of Epidemiology and Prevention, IRCCS Neuromed, Pozzilli, Isernia, Italy

³ UOC Immunodeficienze Virali, National Institute for Infectious Diseases "L. Spallanzani," IRCCS, Rome, Italy

⁴ Section of Public Health, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy

⁵ Università di Pavia, Pavia, Italy

⁶ Fondazione Policlinico Universitario A, Gemelli IRCCS, Rome, Italy

⁷ Dipartimento di Sicurezza e Bioetica Sede di Roma, Università Cattolica del Sacro Cuore, Rome, Italy

⁸ Infectious Disease Unit, Department of Surgical, Medical, Dental and Morphological Sciences, University of Modena and Reggio Emilia, Modena, Italy

* *THE COVID-19 RISK and Treatments (CORIST) collaboration.*

** *These authors contributed equally to this work.*

received

December 14, 2020

accepted after revision

January 6, 2021

published online

January 7, 2021

© 2021. Thieme. All rights reserved.

Georg Thieme Verlag KG,

Rüdigerstraße 14,

70469 Stuttgart, Germany

DOI <https://doi.org/10.1055/a-1347-6070>.

ISSN 0340-6245.

- ⁹IRCCS Policlinico San Donato, San Donato, Milanese (MI), Italy
- ¹⁰University of Eastern Piedmont, Maggiore della Carità Hospital, Novara, Italy
- ¹¹Department of Infectious Disease, Azienda Sanitaria Locale (ASUL) di Pescara, Pescara, Italy
- ¹²Department of Medicine and Aging, Clinica Medica, "SS. Annunziata" Hospital and University of Chieti, Chieti, Italy
- ¹³School of Medicine, Vita-Salute San Raffaele University, Milan, Italy
- ¹⁴Department of HIV/AIDS, National Institute for Infectious Diseases "Lazzaro Spallanzani"-IRCCS, Rome, Italy
- ¹⁵Dipartimento di Scienze Mediche Traslazionali, Università degli studi di Napoli "Federico II," Napoli, Italy
- ¹⁶Department of Medicine and Surgery, University of Insubria, Varese, Italy
- ¹⁷Department of Medical and Surgical Sciences and Advanced Technologies "G.F. Ingrassia," University of Catania; AOU Policlinico "G. Rodolico - San Marco," Catania, Italy
- ¹⁸Centro Cardiologico Monzino IRCCS, Milan, Italy
- ¹⁹Section of Cardiovascular, Department of Clinical Sciences and Community Health, University of Milano, Milan, Italy
- ²⁰UOC, Anestesia e Rianimazione, Dipartimento di Chirurgia Generale Ospedale Morgagni-Pierantoni, Forli, Italy
- ²¹UOC Infezioni Sistemiche dell'Immunodepresso, National Institute for Infectious Diseases L. Spallanzani, IRCCS, Rome, Italy
- ²²Department of Civil Environmental and Architectural Engineering, University of Padova, Padova, Italy
- ²³Department of General Surgery and Medical-Surgical Specialties, University of Catania, U.O. Anestesia, Rianimazione 1. P.O. "G. Rodolico," AOU Policlinico "G. Rodolico - San Marco," Catania, Italy
- ²⁴Fondazione I.R.C.C.S "Casa Sollievo della Sofferenza," San Giovanni Rotondo, Foggia, Italy
- ²⁵Department of Surgical, Medical and Molecular Medicine and Critical Care, Azienda Ospedaliera Universitaria Pisana, University of Pisa, Pisa, Italy
- ²⁶Department of Experimental and Clinical Medicine, University of Florence and Azienda Ospedaliero-Universitaria Careggi, Firenze, Italy
- ²⁷UOC Malattie Infettive, Ospedale San Gerardo, ASST Monza, Monza, Italy
- ²⁸School of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy
- ²⁹Cardiovascular and Thoracic Department, Azienda Ospedaliero-Universitaria Pisana and University of Pisa, Pisa, Italy
- ³⁰Infectious and Tropical Diseases Unit, Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties (PROMISE), University of Palermo, Palermo, Italy
- ³¹Department of Cardiology, Ospedale di Cremona, Cremona, Italy
- ³²Medical Direction, IRCCS Neuromed, Pozzilli, Isernia, Italy
- ³³UOC Malattie Infettive-Epatologia, National Institute for Infectious Diseases L. Spallanzani, IRCCS, Roma, Italy
- ³⁴UOC Infezioni Sistemiche e dell'Immunodepresso, Azienda Ospedaliera dei Colli, Ospedale Cotugno, Napoli, Italy
- ³⁵Department of Clinical Medicine and Surgery, University of Naples Federico II, Napoli, Italy
- ³⁶Medicina Interna, Ospedale di Ravenna, AUSL della Romagna, Ravenna, Italy
- ³⁷Division of Respiratory Pathophysiology, Department of Cardiologic, Thoracic and Vascular Sciences, University of Padova, Padova, Italy
- ³⁸COVID-19 Unit, EE Ospedale Regionale F. Miulli, Acquaviva delle Fonti, Bari, Italy
- ³⁹UOC di Pneumologia, P.O. San Giuseppe Moscati, Taranto, Italy
- ⁴⁰ASST Milano Nord, Ospedale Edoardo Bassini Cinisello Balsamo, Milan, Italy
- ⁴¹UOC di Medicina - Presidio Ospedaliero S. Maria di Loreto Nuovo. ASL Napoli 1 Centro. Napoli. Italy
- ⁴²P.O. Santissima Trinità di Cagliari, Cagliari, Italy
- ⁴³Infectious and Tropical Diseases Unit, Department of Medical and Surgical Sciences "Magna Graecia" University, Catanzaro, Italy
- ⁴⁴Department of Clinical and Experimental Medicine, Azienda Ospedaliera Universitaria Pisana, University of Pisa, Pisa, Italy
- ⁴⁵Dipartimento di Farmacia, Università di Pisa, Pisa, Italy
- ⁴⁶U.O. C. Malattie Infettive e Tropicali, P.O. "San Marco." AOU Policlinico "G. Rodolico - San Marco," Catania, Italy
- ⁴⁷UOC Malattie Infettive-Apparato Respiratorio, National Institute for Infectious Diseases "L. Spallanzani," IRCCS, Rome, Italy
- ⁴⁸Computer Service, University of Molise, Campobasso, Italy
- ⁴⁹Clinica Medica 3, Department of Medicine – DIMED, University hospital of Padova, Padova, Italy
- ⁵⁰UOC Pneumologia, Dipartimento di Malattie Apparato Respiratorio e Torace, Ospedale Morgagni-Pierantoni, Forli, Italy
- ⁵¹Department of Respiratory Diseases and Allergy, Aarhus University Hospital, Aarhus, Denmark
- ⁵²UOC Malattie Infettive ad Alta Intensità di Cura, National Institute for Infectious Diseases "L. Spallanzani," IRCCS, Rome, Italy
- ⁵³Department of Epidemiology, Boston University School of Public Health, Boston, Massachusetts, United States

Abstract

Introduction A hypercoagulable condition was described in patients with coronavirus disease 2019 (COVID-19) and proposed as a possible pathogenic mechanism contributing to disease progression and lethality.

Aim We evaluated if in-hospital administration of heparin improved survival in a large cohort of Italian COVID-19 patients.

Methods In a retrospective observational study, 2,574 unselected patients hospitalized in 30 clinical centers in Italy from February 19, 2020 to June 5, 2020 with laboratory-confirmed severe acute respiratory syndrome coronavirus-2 infection were analyzed. The primary endpoint in a time-to event analysis was in-hospital death, comparing patients who received heparin (low-molecular-weight heparin [LMWH] or unfractionated heparin [UFH]) with patients who did not. We used multivariable Cox proportional-hazards regression models with inverse probability for treatment weighting by propensity scores.

Keywords

- ▶ COVID-19
- ▶ coronavirus
- ▶ heparin
- ▶ coagulation activation
- ▶ treatments
- ▶ mortality

Results Out of 2,574 COVID-19 patients, 70.1% received heparin. LMWH was largely the most used formulation (99.5%). Death rates for patients receiving heparin or not were 7.4 and 14.0 per 1,000 person-days, respectively. After adjustment for propensity scores, we found a 40% lower risk of death in patients receiving heparin (hazard ratio = 0.60; 95% confidence interval: 0.49–0.74; E-value = 2.04). This association was particularly evident in patients with a higher severity of disease or strong coagulation activation.

Conclusion In-hospital heparin treatment was associated with a lower mortality, particularly in severely ill COVID-19 patients and in those with strong coagulation activation. The results from randomized clinical trials are eagerly awaited to provide clear-cut recommendations.

Introduction

Coronavirus disease 2019 (COVID-19), provoked by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection, has afflicted millions of people globally with an impressive cost in death and disabilities that is still rapidly rising around the world. Awaiting for the development of effective and safe vaccines and specific antiviral therapies, researchers are struggling to better understand the disease and optimize supportive treatment. A hypercoagulable condition, associated with the presence of microvascular thrombosis, has been described in patients with COVID-19^{1–5} and proposed as a possible pathogenic mechanism contributing to disease progression and lethality. Therefore, the possibility to improve clinical outcomes of COVID-19 patients by commonly used and inexpensive antithrombotic drugs has become attractive, although data on the risk–benefit profile of anticoagulant (AC) therapy in COVID-19 have been sparse and contradictory.

Recent data show that treatment by low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) at prophylactic doses is associated with reduced 28-day mortality in severe COVID-19 patients featuring a high level of activation of the coagulation system.⁶ Moreover, in a large cohort of COVID-19-hospitalized patients, treatment doses of AC have been reported to be associated with improved outcomes.⁷ Other studies, however, have been unable to find any efficacy of prediagnosis anticoagulation among either hospitalized or ambulatory patients with COVID-19 infection.⁸ It is still not clear if pulmonary vessel occlusions observed in COVID-19 patients derive from embolism from peripheral vein thrombosis⁹ or from locally generated thrombi.^{10–12} The pathogenic substrate of pulmonary occlusions implies different AC therapeutic approaches, with either therapeutic or prophylactic doses of heparin or the use of other antithrombotic therapies,¹³ an issue still unsolved by available studies. Differing recommendations by guidelines on thromboprophylaxis and AC therapy in COVID-19 have thus been issued.^{14–20} The World Health Organization, the U.S. Center for Disease Control and Prevention and the Department of Defense have recommended the use of prophylactic doses of heparin or LMWH for prevention of venous thromboembolism (VTE) in hospitalized adults

and adolescents with severe COVID-19 disease, unless contraindicated.^{14–16} The Italian Society on Thrombosis and Haemostasis¹⁷ and a recent position paper endorsed by several international societies^{18,19} have suggested a VTE risk stratification for all individuals with COVID-19 and extended post-discharge thromboprophylaxis in patients at a higher risk of VTE, recognizing insufficient evidence to recommend the empiric use of therapeutic doses of UFH or LMWH. Other agencies have suggested intermediate or therapeutic doses of LMWH for hospitalized patients and extended VTE prophylaxis for up to 45 days postdischarge.¹⁸ Recently, the VAS-European Independent Foundation in Angiology/Vascular Medicine drew attention to patients with vascular disease and COVID-19, recommending LMWH (weight-adjusted intermediate doses, unless contraindicated) as the drug of choice over UFH or direct oral ACs for the treatment of VTE or hypercoagulability.²⁰ Hard data on the efficacy of heparin treatment either at therapeutic or at prophylactic doses are not conclusive.

We therefore evaluated the association between in-hospital administration of heparin and survival in a large cohort of patients with COVID-19 hospitalized in 30 centers all over Italy.

Methods**Setting**

This national retrospective observational study was conceived, coordinated, and analyzed within the CORIST project (ClinicalTrials.gov ID: NCT04318418).^{21–23} The study was approved by the institutional ethics board of the Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Neuromed, Pozzilli, and of all recruiting centers. Each hospital provided data from hospitalized patients who had a positive test result for the SARS-CoV-2 virus at any time during their hospitalization from February 19 to June 5, 2020. The follow-up continued through June 30, 2020.

The acquisition of retrospective information about in-hospital heparin use started in April 2020, and 30 centers (listed in the ▶ **Supplementary Material**, available in the online version) provided data. The acceptance to participate in the project or to provide data for the present analysis was not related to the use of heparin.

Data Sources

In the framework of the CORIST study, we developed a cohort comprising 4,312 patients with laboratory-confirmed SARS-CoV-2 infection in an in-patient setting. The SARS-CoV-2 status was declared based on laboratory results (polymerase chain reaction on a nasopharyngeal swab) from each participating hospital. Clinical data were abstracted at one-time point from electronic medical records or charts, and collected using either a centrally designed electronic worksheet or a centralized web-based database. Collected data included patients' demographics, laboratory test results, medication administration, historical and current medication lists, historical and current diagnoses, and clinical notes. In addition, specific information on the most severe manifestations of COVID-19 occurred during hospitalization was retrospectively captured. Following the World Health Organization criteria, the maximum clinical severity observed was classified as mild pneumonia (pneumonia and no signs of severe pneumonia); or severe pneumonia (fever or suspected respiratory infection, plus one of respiratory rates >30 breaths/min, severe respiratory distress, or $\text{SpO}_2 < 90\%$ on room air); or acute respiratory distress syndrome.²⁴ Specifically, we obtained the following information for each patient: hospital; date of admission and date of discharge or death; age; sex; the first recorded in-patient laboratory tests at admission (creatinine, C-reactive protein, D-dimer); past and current diagnoses (myocardial infarction, heart failure, diabetes, hypertension, respiratory disease, and cancer), and current drug therapies for COVID-19 (heparin, hydroxychloroquine [HCQ], lopinavir/ritonavir or darunavir/cobicistat, remdesivir, tocilizumab or sarilumab, and corticosteroids). A diagnosis of pre-existing cardiovascular disease was based on a history of myocardial infarction or heart failure. Diagnosis of chronic kidney disease was based on creatinine values at entry and classified as: stage 1: kidney damage with normal or increased glomerular filtration rate (GFR; >90 mL/min/1.73 m²); stage 2: mild reduction in GFR (60–89 mL/min/1.73 m²); stage 3a: moderate reduction in GFR (45–59 mL/min/1.73 m²); stage 3b: moderate reduction in GFR (30–44 mL/min/1.73 m²); stage 4: severe reduction in GFR (15–29 mL/min/1.73 m²); stage 5: kidney failure (GFR <15 mL/min/1.73 m² or dialysis). For statistical analysis, stages 3a and 3b and stages 4 and 5 were combined. GFR was calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

Patients were defined as receiving heparin if they were receiving it at hospital admission or during the follow-up period. Every physician in each hospital decided for himself or herself if and how to treat their patient, including allocation to prophylaxis or therapeutic regimen. This last decision was based on existing Italian guidelines for deep venous thrombosis and pulmonary embolism prevention and therapy, schematized in **►Supplementary Table S1** (available in the online version). Briefly, these guidelines suggest to allocate each patient, for whom heparin treatment was decided, to a prophylactic or therapeutic regimen based on body weight and GFR. We requested to each center the following information: (1) use of heparin during hospitalization (yes/no); (2) type (LMWH, UFH, etc.) and dosage or

regimen (prophylactic or therapeutic). Information on type of heparin used and dosage or regimen was missing for $n = 403$ patients; as a consequence, it was not possible to classify these patients as at prophylactic or therapeutic regimen. They were included in the main analyses but excluded from those by regimen. Additionally, we found $n = 39$ patients treated with LMWH at the dose of 6,000 IU/day and missing data on body weight and regimen. These individuals were considered as at therapeutic regimen; however, such individuals if having body weight >100 kg and $\text{GFR} \geq 30$ mL/min would have been considered as at prophylactic instead of therapeutic regimen. So, we conducted a sensitivity analysis shifting these individuals in the prophylactic group or excluding them from analyses by regimen. Heparin was used in the early phase after hospitalization, with or without previous laboratory evidence of coagulation activation at entry. Precise data at individual level concerning when heparin treatment was started and how long heparin was given for each patient were not available.

Statistical Analysis

The study index date was defined as the date of hospital admission. Index dates ranged from February 19, 2020 to June 5, 2020. The study endpoint was the time from study index date to death. The number of patients who either died, had been discharged alive, or were still hospitalized as of June 30, 2020 were recorded, and hospital duration of stay was determined. Patients alive had their data censored on the date of discharge or as the date of the respective clinical data collection. Data were censored at 35 days of follow-up in $n = 430$ (10.0%) patients with a follow-up longer than 35 days.

Since gathering of information on heparin use started almost 1 month after the CORIST project opening, data on in-hospital heparin use, as anti-COVID-19 treatment, were available for 2,723 patients only. Of them, 149 patients died or were discharged within 24 hours after admission to the hospital, and were thus excluded from the analysis. **►Supplementary Table S2** (available in the online version) shows the comparisons between the entire cohort (with or without information on heparin use) and the final sample used for the present analysis. No difference was found for the prevalence of age, gender, chronic degenerative diseases, and mortality rate.

Among 2,574 COVID-19 patients, 245 (9.5%) had at least one missing value for covariates. Distribution of missing values was as follows: $n = 137$ for C-reactive protein; $n = 64$ for GFR; $n = 74$ for history of ischemic disease; $n = 62$ for history of chronic pulmonary disease; $n = 49$ for diabetes; $n = 49$ for hypertension; and $n = 53$ for cancer. We used multiple imputation techniques (SAS PROC MI, $n = 10$ imputed datasets; and PROC MIANALYZE) to maximize data availability. As sensitivity analysis, we also conducted a case-complete analysis on 2,329 patients.

We used Cox proportional-hazards regression models to estimate the association between heparin use and death. Since we applied multiple imputation, we obtained the final standard error using the Rubin's rule based on the robust variance estimator in Cox regression.²⁵ We assessed the

proportional hazards assumption using weighted Schoenfeld residuals, and identified no violations. To account for the nonrandomized heparin administration and to reduce the effects of confounding, we used the propensity score method. We assessed the individual propensities for receiving heparin treatment with the use of a multivariable logistic-regression model that included age, sex, diabetes, hypertension, history of ischemic heart disease, chronic pulmonary disease, GFR, C-reactive protein, hospital clustering, and use of other drug therapies for COVID-19 (HCQ, lopinavir/ritonavir or darunavir/cobicistat, remdesivir, corticosteroids, tocilizumab, or sarilumab). We then appraised associations between heparin treatment and death by multivariable Cox regression models with the use of propensity score, and further controlling for hospital clustering as a random effect (frailty model). We chose the use of a frailty model as suggested by Glidden and Vittinghoff.²⁶ The primary analysis used inverse probability by treatment weighting; we used the predicted probabilities from the propensity-score model to calculate the stabilized inverse-probability-weighting weight.²⁷ Stabilized weights were normalized so that they added up the actual sample size. Secondary analyses used propensity-score stratification ($n = 5$ strata) or multivariable Cox regression analysis or multivariable logistic regression analyses comparing dead patients versus alive patients, or accounted for hospital clustering via stratification or by a robust sandwich estimator. We conducted pre-established subgroup analyses according to age and sex of patients, degree of COVID-19 severity experienced during the hospital stay, C-reactive protein at baseline, CKD stage, stay in intensive care unit (ICU), and other drug therapies for COVID-19. Additionally, we investigated the association of different regimens (prophylactic or therapeutic doses) with the risk of in-hospital mortality. We performed a further sensitivity analysis according to quartiles of D-dimer in a subsample of 1,792 COVID-19 patients with nonmissing data on D-dimer.

We clustered hospitals according to their geographical distribution: hospitals from northern regions of Italy, Milan excluded ($n = 793$), Milan ($n = 189$); hospitals from central regions of Italy, Rome excluded ($n = 1,003$), Rome ($n = 254$); hospitals from southern regions of Italy ($n = 335$); see the list of centers in the Supplementary Material (available in the online version). To quantify the potential for an unmeasured confounder to render apparent statistically significant hazard ratios (HRs) nonsignificant, we calculated the E-value.²⁸ We performed all analyses with the aid of the SAS version 9.4 statistical software for Windows.

Results

In the final current analyses, we included 2,574 patients who were hospitalized with confirmed SARS-CoV-2 infection at 30 clinical centers across Italy who either died or had been discharged or were still in hospital as of June 30, 2020. Of these patients, 1,804 (70.1%) received heparin during hospitalization. The information on type of heparin used was missing for $n = 403$ out of 1,804. In the others, LMWH and UFH were the types used in 99.5 and 0.5%, respectively.

Baseline characteristics according to heparin use are shown in ►Table 1. Patients receiving heparin were more likely older, had higher levels of C-reactive protein at entry, and showed higher prevalence of diabetes, hypertension, chronic pulmonary disease and cancer, but a lower prevalence of ischemic heart disease (►Table 1). Patients in the heparin group had a higher degree of COVID-19 severity and were more likely to receive another drug for COVID-19 treatment (75.5%; lopinavir/ritonavir or darunavir/cobicistat, remdesivir, tocilizumab or sarilumab, corticosteroids, or 83.7% HCQ), in comparison with non-heparin-receiving patients ($p < 0.0001$; ►Table 1). D-dimer levels were not associated with heparin therapy.

The unadjusted differences and differences adjusted by propensity scores between heparin-treated and nonheparin-treated patients for each variable included in the propensity score are shown in ►Supplementary Fig. S1 (available in the online version). All pretreatment differences disappeared after adjustment by propensity score weighting. The C-statistic of the propensity-score model was 0.78.

Primary Outcome

Out of 2,574 patients, 398 died (15.5%), 1,687 were discharged alive (65.5%), and 489 (19.0%) were still at the hospital. The median follow-up was 15 days (interquartile range: 9–25; range: 2–35; 43,773 person-days). The death rate (per 1,000 person-days) was 7.4 in heparin- and 14.0 in nonheparin-treated patients (►Table 2). At univariable analysis, HR for mortality was 0.54 (95% confidence interval [CI]: 0.44–0.67). In the primary multivariable analysis with inverse probability weighting according to the propensity score, heparin use was associated with a 40% (95% CI: 26–51%) lower risk of death (►Fig. 1 and ►Table 2; E-value = 2.04).

Secondary multivariable analyses, as well as case-complete analyses restricted to 2,329 patients without missing data, yielded very similar results (►Table 2). Considering secondary multivariable analyses overall, HR for mortality associated with heparin ranged between 0.53 and 0.62 according to the type of analysis. Control of hospital clustering with different approaches also yielded similar results for the primary analysis (►Supplementary Table S3 [available in the online version]). As an additional sensitivity analysis, we present in ►Supplementary Table S4 (available in the online version) the main findings after exclusion of $n = 403$ patients for whom the type of heparin used was missing. Heparin used remains clearly associated with a lower mortality (HR = 0.52; 95% CI: 0.41–0.65).

We present subgroup analyses in ►Table 3. Heparin use remained consistently associated with a lower mortality in almost all subgroups. The inverse association of heparin use with in-hospital mortality was more evident in patients who experienced a higher degree of COVID-19 severity or were staying in the ICU.

Stratification of patients by the number of in-hospital anti-COVID-19 treatments showed that heparin was more effective when other drugs were also used (►Table 3).

Among patients treated with heparin, 54.5% were at prophylactic and 23.2% at the therapeutic regimen, while

Table 1 General characteristics of COVID-19 patients at baseline, according to heparin use

Characteristic	Heparin		p-Value unadjusted
	No (N = 770)	Yes (N = 1,804)	
Age (y), median (IQR)	65 (53–77)	68 (57–79)	<0.0001
Gender, no. (%)			0.064
Women	275 (35.7)	714 (39.6)	
Men	495 (64.3)	1,090 (60.4)	
Diabetes, no. (%)			<0.0001
No	623 (80.9)	1,394 (77.3)	
Yes	121 (15.7)	387 (21.4)	
Missing data	26 (3.4)	23 (1.3)	
Hypertension, no. (%)			<0.0001
No	390 (50.7)	841 (46.6)	
Yes	351 (45.6)	943 (52.3)	
Missing data	29 (3.8)	20 (1.1)	
Ischemic heart disease, no. (%)			0.0074
No	587 (76.2)	1,465 (81.2)	
Yes	152 (19.8)	296 (16.4)	
Missing data	31 (4.0)	43 (2.4)	
Chronic pulmonary disease, no. (%)			<0.0001
No	656 (85.2)	1,480 (82.0)	
Yes	82 (10.6)	294 (16.3)	
Missing data	32 (4.2)	30 (1.7)	
Cancer, no. (%)			<0.0001
No	678 (88.1)	1,563 (86.6)	
Yes	63 (8.2)	217 (12.0)	
Missing data	29 (3.8)	24 (1.3)	
Highest degree of COVID-19 severity experienced at hospital, no. (%)			<0.0001
Mild pneumonia	431 (56.0)	790 (43.8)	
Severe pneumonia	227 (29.5)	509 (28.2)	
Acute respiratory distress syndrome	112 (14.5)	505 (28.0)	
ICU, no. (%)			<0.0001
No	663 (86.1)	1,517 (84.1)	
Yes	65 (8.4)	262 (14.5)	
Missing data	42 (5.5)	25 (1.4)	
CKD stage ^a , no. (%)			<0.0001
Stage 1	286 (37.2)	592 (32.8)	
Stage 2	278 (36.1)	693 (38.4)	
Stage 3a or stage 3b	135 (17.5)	355 (19.7)	
Stage 4 or stage 5	37 (4.8)	134 (7.4)	
Missing data	34 (4.4)	30 (1.7)	
C-reactive protein, no. (%)			<0.0001
< 1 mg/L	90 (11.7)	155 (8.6)	
1–3 mg/L	108 (14.3)	142 (7.9)	
> 3 mg/L	524 (68.1)	1,418 (78.6)	

(Continued)

Table 1 (Continued)

Characteristic	Heparin		p-Value unadjusted
	No (N = 770)	Yes (N = 1,804)	
Missing data	48 (6.2)	89 (4.9)	
In-hospital therapies for COVID-19, no. (%)			<0.0001
No	269 (34.9)	441 (24.5)	
Yes	501 (65.1)	1,363 (75.5)	
Hydroxychloroquine, no. (%)			<0.0001
No	336 (43.6)	295 (16.4)	
Yes	434 (56.4)	1,509 (83.7)	
Subsample, N = 1,792	No (N = 369)	Yes (N = 1,423)	
D-dimer, quartiles, no. (%)			0.13
IQ: ≤470 ng/mL	104 (28.2)	346 (24.3)	
IIQ: 471–899 ng/mL	76 (20.6)	361 (25.4)	
IIIQ: 900–2,020 ng/mL	102 (27.6)	355 (25.0)	
IVQ: >2,020 ng/mL	87 (23.6)	361 (25.4)	

Abbreviations: CKD, chronic kidney disease; ICU, intensive care unit.

^aStage 1: kidney damage with normal or increased glomerular filtration rate (GFR) (>90 mL/min/1.73 m²); stage 2: mild reduction in GFR (60–89 mL/min/1.73 m²); stage 3a: moderate reduction in GFR (45–59 mL/min/1.73 m²); stage 3b: moderate reduction in GFR (30–44 mL/min/1.73 m²); stage 4: severe reduction in GFR (15–29 mL/min/1.73 m²); stage 5: kidney failure (GFR < 15 mL/min/1.73 m² or dialysis).

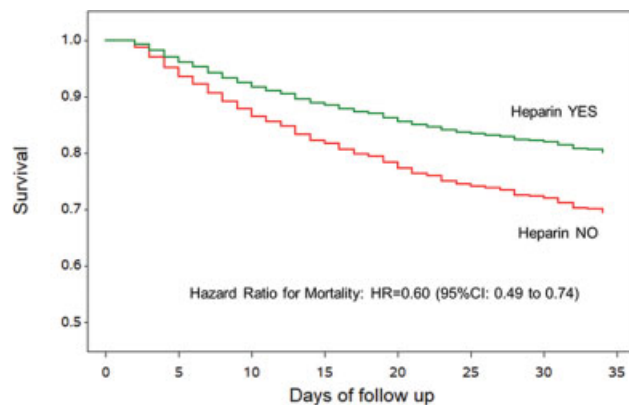


Fig. 1 Survival curves according to heparin use. The curves are adjusted by propensity score analysis (inverse probability weighting) and age and sex as fixed effects and hospital index as random effect, and are generated using the first imputed dataset. The other imputed datasets are similar and thus omitted.

for the remaining 22.3% it was not possible to proceed with this classification because of missing data. In comparison with no heparin use, treatment at prophylactic and therapeutic doses was associated with a 60 and 35% lower relative risk of mortality, respectively (►Table 4). Thirty-nine patients were treated with LMWH at the dose of 6,000 IU/day and they have been considered in the previous analysis as at the therapeutic regimen (see the Methods section for clarification). At sensitivity analysis, we shifted these patients to the prophylactic regimen or excluded them from the analysis, and the findings in ►Table 4 were very similar (*data not shown*).

At the end, in the analysis restricted to 1,792 COVID-19 patients without missing data on D-dimer levels, heparin use

was associated with a lower in-hospital mortality in patients in the highest quartiles (with D-dimer >2,020.00 ng/mL; HR = 0.63, 95% CI: 0.41–0.97) (►Fig. 2).

Discussion

It is not yet clear if heparin use is an effective intervention in all hospitalized COVID-19 patients or should be limited to specific conditions or categories of patients and which doses should be used.^{17,18,20,29} We here show, in a large cohort of unselected COVID-19 patients hospitalized throughout Italy, that treatment with heparin (mainly LMWH) is associated with a lower risk of in-hospital mortality, independently from several possible confounders and taking into account possible differences across centers by either adjustment or stratification. To further minimize the possible bias due to the observational design, we used different analytical approaches aiming at creating an overall balance between comparison groups. Finally, we tried to limit the bias due to missing data by using a multiple imputation approach, but in no case, results were changed.

COVID-19 infection has been clinically divided into three phases: a first phase with unspecific symptoms; followed by a second phase with pulmonary impairment and inflammation activation; and a third phase, affecting only a limited number of patients, characterized by a worsening of clinical symptoms and a widespread inflammatory state. The last has been related to a process of “hypercoagulation” that could be potentially controlled by AC therapy. Therefore, heparin might be useful both in the initial phase as prophylactic treatment in patients with pneumonia and in advanced stages to contain the thrombotic phenomena that originate

Table 2 Incidence rates and hazard ratios for death in COVID-19 patients according to heparin use

Multiple imputation analysis (N = 2,574)				
	Death (N = 398)	Patients at risk (N = 2,574)	Person-days	Death rate (x1,000 person-days)
Heparin				
No, no. (%)	145 (18.8%)	770 (100%)	10,362	14.0
Yes, no. (%)	253 (14.0%)	1,804 (100%)	34,301	7.4
Hazard ratio for mortality (heparin vs. nonheparin)				HR (95% CI)
Crude analysis				0.54 (0.44–0.67)
Multivariable analysis ^a				0.55 (0.43–0.69)
Propensity score analysis, inverse probability weighting ^b (main result)				<u>0.60 (0.49–0.74)</u>
Propensity score analysis, stratification (n = 5 strata) ^b				0.53 (0.42–0.66)
Odds ratio for mortality (heparin vs. no heparin)				OR (95% CI)
Multivariable analysis				0.53 (0.40–0.71)
Case complete analysis (N = 2,329)				
	Death (N = 342)	Patients at risk (N = 2,329)	Person-days	Death rate (x1,000 person-days)
Heparin				
No, no. (%)	126 (18.5%)	682 (100%)	9,287	13.6
Yes, no. (%)	216 (13.1%)	1,647 (100%)	30,832	7.0
Hazard ratio for mortality (heparin vs. nonheparin)				HR (95% CI)
Crude analysis				0.53 (0.42–0.66)
Multivariable analysis ^a				0.58 (0.45–0.74)
Propensity score analysis, inverse probability weighting ^b				0.62 (0.49–0.77)
Propensity score analysis, stratification (n = 5 strata) ^b				0.54 (0.42–0.69)
Odds ratio for mortality (heparin vs. no heparin)				OR (95% CI)
Multivariable analysis ^a				0.55 (0.40–0.76)

Abbreviations: CI, confidence intervals; HR, hazard ratios; OR, odds ratio.

^aControlling for age, sex, diabetes, hypertension, ischemic heart disease, chronic pulmonary disease, chronic kidney disease, C-reactive protein, HCQ, and other in-hospital therapies for COVID-19 as fixed effects and hospital index as a random effect.

^bIncluding hospital index as a random effect covariate.

in the pulmonary circulation as a result of the worsening inflammatory state. Moreover, heparin, and in particular LMWH, may also exert a direct anti-inflammatory effect by inhibiting blood cell functions, such as platelet-leukocyte interactions and the exposure of cellular adhesion molecules, events recognized to play a crucial role in inflammatory responses.^{30,31} We broadly confirm these hypotheses in our cohort of COVID-19-hospitalized patients.

Subgroup analyses in our study showed that heparin treatment was more effective in specific severe situations, such as in patients with a higher disease severity, requiring ICU admission, or with a strong coagulation activation as reported by D-dimer levels. The results of our study are in line with a retrospective analysis of 449 cases of severe COVID-19 pneumonia in China, which suggested first that use of LMWH for at least 7 days could lead to a survival advantage only in patients with higher levels of D-dimers or with a high composite score including laboratory and clinical parameters.⁶ Recently, Billett et al reported that at higher levels of D-dimer (>10 µg/mL), enoxaparin prophylaxis was associated with decreased mortality (odds ratio: 0.13, 95% CI: 0.034–0.49), while UFH and enoxaparin therapies were

not.³² Similarly, in 786 patients (28%) receiving systemic anticoagulation (including intravenous or subcutaneous UFH, LMWH, non-vitamin K antagonist oral ACs or, in few ICU cases, tissue plasminogen activator) during their hospital stay, a lower mortality was evident particularly in patients requiring mechanical ventilation.³³

In late March 2020, the International Society on Thrombosis and Haemostasis recommended that all hospitalized COVID-19 patients, even those not in the ICU, should receive prophylactic doses of LMWH, unless with contraindications.¹⁸ After the publication of the first studies between the end of April and the beginning of May, the use of LMWH at prophylactic doses steeply increased.^{6,33}

In our hospitals, heparin was used in over 70% of cases (very largely as LMWH), in more than half of the cases at prophylactic doses. Heparin was used in the early phase after hospitalization, with or without previous laboratory evidence of coagulation activation at entry, thus supporting its use as a preventive therapy to potentially limit coagulation activation in subsequent phases. However, its efficacy appeared to be potentiated in subjects with evidence of hypercoagulation or with a more severe disease evolution,

Table 3 Hazard ratios for mortality according to heparin use in different subgroups

	Heparin NO (N = 770)	Heparin YES (N = 1,804)	
Subgroups	No. death/patient at risk	No. death/patient at risk	HR (95% CI) ^a
Age			
< 70 y	30/460	51/942	0.53 (0.32–0.88)
≥ 70 y	115/310	202/862	0.67 (0.53–0.84)
Gender			
Women	49/275	95/714	0.74 (0.51–1.07)
Men	96/495	158/1,090	0.51 (0.40–0.66)
Highest degree of COVID-19 severity experienced at hospital			
Mild pneumonia	25/431	33/790	0.62 (0.36–1.08)
Severe pneumonia	57/227	72/509	0.56 (0.38–0.81)
ARDS	63/112	148/505	0.40 (0.30–0.53)
ICU			
No	118/663	197/1,517	0.63 (0.50–0.80)
Yes	27/65	53/262	0.29 (0.17–0.49)
C-reactive protein at baseline ^b			
< 10 mg/L	54/390	60/597	0.44 (0.30–0.65)
≥ 10 mg/L	86/332	174/1,118	0.68 (0.53–0.88)
CKD stage at baseline ^c			
Stage 1	21/286	21/592	0.26 (0.14–0.49)
Stage 2	47/278	76/693	0.61 (0.42–0.89)
Stage 3a or stage 3b	51/135	89/355	0.81 (0.56–1.16)
Stage 4 or stage 5	20/37	59/134	0.66 (0.42–1.05)
Number of in-hospital therapies for COVID-19, including HCQ			
0	25/158	36/131	1.17 (0.64–2.14)
1	48/236	52/429	0.58 (0.39–0.87)
2	49/284	95/709	0.67 (0.47–0.95)
3–5	23/92	70/535	0.30 (0.19–0.46)

Abbreviations: ARDS, acute respiratory distress syndrome; CI, confidence intervals; CKD, chronic kidney disease; ICU, intensive care unit; HCQ, hydroxychloroquine; HR, hazard ratios.

^aPropensity score analysis, inverse probability weighting, including hospital index as a random effect covariate; multiple imputed analysis.

^bMissing data for $N = 137$. Data reported are based on a case complete analysis ($N = 2,437$) without missing for C-reactive protein. Multiple imputed analysis yielded very similar results.

^cMissing data for $N = 64$. Data reported are based on a case complete analysis ($N = 2,510$) without missing for eGFR. Multiple imputed analysis yielded very similar results.

confirming the importance of coagulation activation in the natural history of COVID-19.

A still open question on the use of anticoagulation in COVID-19 patients is if therapeutic doses of heparin are more effective than the low doses used in prophylaxis. In our study, both regimens were effective in reducing mortality, but the prophylactic doses at a higher extent (60 vs. 35%). Probably the hemorrhagic potential of high doses of heparin, increased by the interaction with other drugs and comorbidities present in patients hospitalized with COVID-19, may partly overcome the potential benefit of full anticoagulation in these patients. On the other hand, we cannot exclude that the apparent benefit of prophylactic over therapeutic heparin could be that patients may have started on prophylaxis before they got a diagnosis of VTE qualifying them for therapeutic anticoagulation, hence the final contribution of

therapy may have been diluted by prior prophylactic treatment. Also, indication bias is a potential reason why high-dose heparin was associated with mortality at a lower extent in comparison with a prophylactic dose.

The major and well-known complications of heparin are bleeding and heparin-induced thrombocytopenia (HIT). Unluckily, we could not record information on adverse events. However, Pesavento et al³⁴ showed in a smaller cohort of Italian patients that the rate of relevant bleeding was higher in patients treated with (sub)therapeutic doses of ACs, while overall mortality tended to be higher as compared with patients treated with standard prophylactic doses. Other observational studies reported that treatment with a therapeutic/higher dosage of AC drugs was associated with a higher incidence of bleeding, despite a decrease of in-hospital mortality.^{7,35} HIT is a severe immune-mediated

Table 4 Hazard ratios for mortality according to dosage of heparin

Multiple imputation analysis (N = 2,574)				
	Death (N = 398)	Patients at risk (N = 2,574)	Person-days	Death rate (x1,000 person-days)
Heparin				
No, no. (%)	145 (18.8%)	770 (100%)	10,362	14.0
Yes, no. (%)	253 (14.0%)	1,804 (100%)	34,301	7.4
Prophylactic regimen	114 (11.6%)	983 (100%)	18,857	6.1
Therapeutic regimen	62 (14.8%)	418 (100%)	8,583	7.2
Unknown (<i>missing data</i>)	77 (19.1%)	403 (100%)	6,861	11.2
Hazard ratio for mortality (multivariable analysis ^a)				HR (95% CI)
Prophylactic doses vs. no heparin				0.40 (0.30–0.52)
Therapeutic doses vs. no heparin				0.65 (0.46–0.93)
Therapeutic vs. prophylactic regimen				1.54 (1.06–2.25)

Abbreviations: CI, confidence interval; HR, hazard ratio.

^aControlling for age, sex, diabetes, hypertension, ischemic heart disease, chronic pulmonary disease, chronic kidney disease, C-reactive protein, HCQ, and other in-hospital therapies for COVID-19 as fixed effects and hospital index as a random effect.

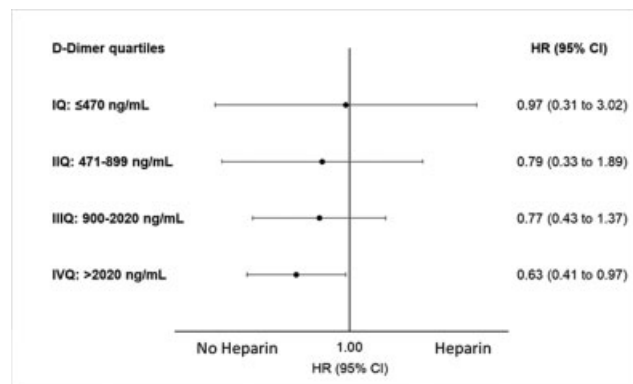


Fig. 2 Hazard ratios for mortality according to heparin use in D-dimer quartiles.

complication of heparin therapy, leading to platelet activation, platelet consumption, and thrombin generation. Paradoxically, HIT is characterized by both thrombocytopenia and a prothrombotic state. Recently, some reports presented the occurrence of HIT in COVID-19 patients.^{36,37} However, larger investigations are warranted to confirm this increased incidence of HIT and to understand its pathophysiology.³⁶

Our findings are similar to those of Ayerbe et al, showing that heparin treatment was associated with reduced mortality in 2,075 unselected patients with COVID-19 admitted to 17 hospitals in Spain.³⁸ Additionally, focusing on LMWH therapy, recently Billett et al³² and Albani et al³⁹ reported 51 and 50%, respectively, lower risk of death in patients receiving prophylactic doses. In line with our findings, Albani et al found an in-hospital mortality reduction of 46% at therapeutic regimen.³⁹

Strengths and limitations

A major strength of this study is the large, unselected patient sample from 30 hospitals, covering the entire Italian territory.

Patient sampling covered all the overt epidemic period in Italy. Several statistical approaches were used to overcome biases due to the observational nature of the investigation.

This study has, however, several recognized limitations. First of all, we are well aware of the limits of a retrospective observational study. However, the CORIST Collaboration was launched at the very beginning of the pandemic, when the general situation in Italy was dramatic and the organization of a randomized controlled clinical trial was considered to be quite difficult. In the absence of any solid data, a prompt, real-life observational study appeared to be the best option at that moment. We took several precautions to account for the non-randomized heparin administration procedure and to reduce the effects of confounders by using a propensity-score method.

Another limitation is that the study population is confined to Italy, and results obtained might not be applicable to other populations with possibly different geographical, racial and socio-economic conditions, and with possibly different natural history of COVID-19. Moreover, several parameters were not collected in all or some patients, and not all in-hospital medications might have been fully recorded. This is mainly due to our decision to interfere in a quite soft way with the dramatic clinical situation present in the majority of participating hospitals by proposing a relatively simple protocol, asking to report an essential dataset rather than a detailed, complete set of information; the latter could have distracted doctors from their therapeutic efforts and would have discouraged the participation of many colleagues. Information about regimen (prophylactic or therapeutic) was missing for 15.7% of the whole cohort. However, after the exclusion of patients for whom the type of heparin used was missing data, the association of heparin use with lower mortality was unchanged. A switch between regimens potentially occurred during hospitalization in some patients, but unfortunately this is missing information. For differing reasons, timing of the first dose of heparin after presentation to the hospital and duration of treatment could not be provided by some

clinical centers. Time of heparin administration was not detailed; thus it was not possible to consider in Cox regression heparin as a time-dependent predictor. Additionally, specific reasons why patients were treated or not with heparin could not be collected; patients might have had contraindications or were considered to be inappropriate by physician's discretion. Adverse events possibly related to drug therapy also could not be documented.

Moreover, information about medication on admission was not collected and the chance that chronic therapy with ACs or platelet inhibitors before admission may be overrepresented in those COVID-19 patients who did not get (additional) prophylaxis should be considered.

Finally, the possibility of unmeasured residual confounders cannot be ruled out. However, the E-value for the lower boundary of the confidence interval for the protective association of heparin from death has the large value of 2.04, indicating that the confidence interval could be moved to include the null only by a strong unmeasured confounder or combination of confounders associated with both heparin treatment and death, with a risk ratio of 2.04-fold, above and beyond all measured confounders. Weaker confounders could not do so.

Conclusion

Our study, including a large real-life sample of patients with COVID-19 hospitalized throughout Italy, shows that heparin use was associated with a 40% lower overall in-hospital mortality. In the absence of clear-cut results from randomized controlled trials, our data support the use of heparin in inpatients with COVID-19, particularly in severely ill patients.

Given the observational design of our study, however, these results should still be treated cautiously.

What is known about this topic?

- A hypercoagulable condition, associated with the presence of microvascular thrombosis, has been described in patients with COVID-19 and proposed as a possible pathogenic mechanism contributing to disease progression and lethality.
- Major guidelines supported the potentially beneficial effect of anticoagulation therapy, mainly low-molecular-weight heparin, in reducing mortality in COVID-19 patients. However, at present, evidence is insufficient.

What does this paper add?

- In a large real-life sample of patients with COVID-19 hospitalized throughout Italy, heparin use, mainly low-molecular-weight heparin, was associated with a 40% lower overall in-hospital mortality.
- In the absence of clear-cut results from controlled randomized trials, these findings support the use of heparin in patients with COVID-19, particularly in severely ill patients or in those with strong coagulation activation.

Author Contributions

Prof. Iacoviello and Di Castelnuovo had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Concept and design:* Di Castelnuovo, Costanzo, Iacoviello, and De Caterina. *Acquisition, analysis, or interpretation of data:* all authors. *Drafting of the manuscript:* Iacoviello, Di Castelnuovo and Costanzo. *Critical revision of the manuscript for important intellectual content:* Iacoviello, Di Castelnuovo, De Caterina, and de Gaetano Donati. *Statistical analysis:* Costanzo, Di Castelnuovo, and Arboretti. *Administrative, technical, or material support:* all authors. *Supervision:* Iacoviello and Di Castelnuovo.

Funding

None.

Conflict of Interest

None declared.

Acknowledgments

We thank the 30 participating clinical centers included in this cohort.

This article is dedicated to all patients who suffered or died, often in solitude, due to COVID-19; their tragic fate gave us moral strength to initiate and complete this research.

The authors alone are responsible for the views expressed in this article. They do not necessarily represent the views, decisions, or policies of the institutions with which they are affiliated.

References

- 1 Lippi G, Favaloro EJ. D-Dimer is associated with severity of coronavirus disease 2019: a pooled analysis. *Thromb Haemost* 2020;120(05):876–878
- 2 Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost* 2020;18(04):844–847
- 3 Llitjos JF, Leclerc M, Chochois C, et al. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. *J Thromb Haemost* 2020;18(07):1743–1746
- 4 Gazzaruso C, Paolozzi E, Valenti C, et al. Association between antithrombin and mortality in patients with COVID-19. A possible link with obesity. *Nutr Metab Cardiovasc Dis* 2020;30(11):1914–1919
- 5 Marongiu F, Grandone E, Barcellona D. Pulmonary thrombosis in 2019-nCoV pneumonia? *J Thromb Haemost* 2020;18(06):1511–1513
- 6 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(05):1094–1099
- 7 Nadkarni GN, Lala A, Bagiella E, et al. Anticoagulation, bleeding, mortality, and pathology in hospitalized patients with COVID-19. *J Am Coll Cardiol* 2020;76(16):1815–1826
- 8 Tremblay D, van Gerwen M, Alsen M, et al. Impact of anticoagulation prior to COVID-19 infection: a propensity score-matched cohort study. *Blood* 2020;136(01):144–147
- 9 Wang T, Chen R, Liu C, et al. Attention should be paid to venous thromboembolism prophylaxis in the management of COVID-19. *Lancet Haematol* 2020;7(05):e362–e363

- 10 Danzi GB, Loffi M, Galeazzi G, Gherbesi E. Acute pulmonary embolism and COVID-19 pneumonia: a random association? *Eur Heart J* 2020;41(19):1858
- 11 Rotzinger DC, Beigelman-Aubry C, von Garnier C, Qanadli SD. Pulmonary embolism in patients with COVID-19: time to change the paradigm of computed tomography. *Thromb Res* 2020; 190:58–59
- 12 Cattaneo M, Morici N. Is thromboprophylaxis with high-dose enoxaparin really necessary for COVID-19 patients? A new “prudent” randomised clinical trial. *Blood Transfus* 2020;18(03): 237–238
- 13 Cattaneo M, Bertinato EM, Birocchi S, et al. Pulmonary embolism or pulmonary thrombosis in COVID-19? Is the recommendation to use high-dose heparin for thromboprophylaxis justified?. *Thromb Haemost* 2020;120(08):1230–1232
- 14 World Health Organization. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected. WHO/2019-nCoV/clinical/2020.4 2020. Accessed February 1, 2021 at: <https://www.who.int/docs/default-source/coronaviruse/clinical-management-of-novel-cov.pdf>
- 15 CDC. Interim clinical guidance for management of patients with confirmed coronavirus disease (COVID-19). Published 2020. Updated April 13, 2020. Accessed September 10, 2020 at: <https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html>
- 16 Matos R, Chung K. DoD COVID-19 practice management guide: clinical management of COVID-19. DoD. Published 2020. Updated March 23, 2020. Accessed September 10, 2020 at: <https://asprtracie.hhs.gov/technical-resources/resource/7899/dod-covid-19-practice-management-guide-clinical-management-of-covid-19>
- 17 Marietta M, Ageno W, Artoni A, et al. COVID-19 and haemostasis: a position paper from Italian Society on Thrombosis and Haemostasis (SISST). *Blood Transfus* 2020;18(03):167–169
- 18 Bikkeli B, Madhavan MV, Jimenez D, et al; Global COVID-19 Thrombosis Collaborative Group, Endorsed by the ISTH, NATF, ESVM, and the IUA, Supported by the ESC Working Group on Pulmonary Circulation and Right Ventricular Function. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC State-of-the-Art Review. *J Am Coll Cardiol* 2020;75(23):2950–2973
- 19 Thachil J, Tang N, Gando S, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. *J Thromb Haemost* 2020;18(05):1023–1026
- 20 Gerotziafas GT, Catalano M, Colgan MP, et al; Scientific Reviewer Committee. Guidance for the management of patients with vascular disease or cardiovascular risk factors and COVID-19: position paper from VAS-European Independent Foundation in Angiology/Vascular Medicine. *Thromb Haemost* 2020;120(12): 1597–1628
- 21 Di Castelnuovo A, De Caterina R, de Gaetano G, Iacoviello L. Controversial relationship between renin-angiotensin system inhibitors and severity of COVID-19: announcing a large multicentre case-control study in Italy. *Hypertension* 2020;76(02): 312–313
- 22 Di Castelnuovo A, Bonaccio M, Costanzo S, et al. Common cardiovascular risk factors and in-hospital mortality in 3,894 patients with COVID-19: survival analysis and machine learning-based findings from the multicentre Italian CORIST Study. *Nutr Metab Cardiovasc Dis* 2020;30(11):1899–1913
- 23 Di Castelnuovo A, Costanzo S, Antinori A, et al. Use of hydroxychloroquine in hospitalised COVID-19 patients is associated with reduced mortality: Findings from the observational multicentre Italian CORIST study. *Eur J Intern Med* 2020;82:38–47
- 24 WHO. Clinical management of severe acute respiratory infection when novel coronavirus (2019-nCoV) infection is suspected: interim guidance, 28 January 2020. Accessed September 10, 2020 at: <https://apps.who.int/iris/bitstream/handle/10665/330893/WHO-nCoV-Clinical-2020.3-eng.pdf?sequence=1&isAllowed=y>
- 25 Rubin DB. Multiple Imputation for Nonresponse in Surveys. New York, NY: John Wiley; 1987
- 26 Glidden DV, Vittinghoff E. Modelling clustered survival data from multicentre clinical trials. *Stat Med* 2004;23(03):369–388
- 27 Garrido MM, Kelley AS, Paris J, et al. Methods for constructing and assessing propensity scores. *Health Serv Res* 2014;49(05):1701–1720
- 28 VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. *Ann Intern Med* 2017;167(04):268–274
- 29 Di Gennaro F, Marotta C, Storto M, et al. SARS-CoV-2 transmission and outcome in neuro-rehabilitation patients hospitalized at neuroscience hospital in Italy. *Mediterr J Hematol Infect Dis* 2020;12(01):e2020063
- 30 Maugeri N, de Gaetano G, Barbanti M, Donati MB, Cerletti C. Prevention of platelet-polymorphonuclear leukocyte interactions: new clues to the antithrombotic properties of parnaparin, a low molecular weight heparin. *Haematologica* 2005;90(06):833–839
- 31 Maugeri N, Di Fabio G, Barbanti M, de Gaetano G, Donati MB, Cerletti C. Parnaparin, a low-molecular-weight heparin, prevents P-selectin-dependent formation of platelet-leukocyte aggregates in human whole blood. *Thromb Haemost* 2007;97(06):965–973
- 32 Billett HH, Reyes-Gil M, Szymanski J, et al. Anticoagulation in COVID-19: effect of enoxaparin, heparin, and apixaban on mortality. *Thromb Haemost* 2020;120(12):1691–1699
- 33 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(01):122–124
- 34 Pesavento R, Ceccato D, Pasquetto G, et al. The hazard of (sub) therapeutic doses of anticoagulants in non-critically ill patients with Covid-19: The Padua province experience. *J Thromb Haemost* 2020;18(10):2629–2635
- 35 Ionescu F, Jaiyesimi I, Petrescu I, et al. Association of anticoagulation dose and survival in hospitalized COVID-19 patients: a retrospective propensity score-weighted analysis. *Eur J Haematol* 2020;106(02):165–174
- 36 Bidar F, Hékimian G, Martin-Toutain I, Lebreton G, Combes A, Frère C. Heparin-induced thrombocytopenia in COVID-19 patients with severe acute respiratory distress syndrome requiring extracorporeal membrane oxygenation: two case reports. *J Artif Organs* 2021;24(2):277–281
- 37 Lingamaneni P, Gonakoti S, Moturi K, Vohra I, Zia M. Heparin-induced thrombocytopenia in COVID-19. *J Investig Med High Impact Case Rep* 2021;13(1):8857
- 38 Ayerbe L, Risco C, Ayis S. The association between treatment with heparin and survival in patients with Covid-19. *J Thromb Thrombolysis* 2020;50(02):298–301
- 39 Albani F, Sepe L, Fusina F, et al. Thromboprophylaxis with enoxaparin is associated with a lower death rate in patients hospitalized with SARS-CoV-2 infection. A cohort study. *EClinicalMedicine* 2020;27:100562