

SARS-CoV-2 and finding of vein thrombosis: can IMPROVE and IMPROVEDD scores predict COVID-19 outcomes?

S. GRECO¹, G. ZENUNAJ², B. BONSI¹, A. BELLA¹, M. LOPREIATO¹, F. LUCIANI¹, D. PEDRINI¹, G. VESTITA¹, E. DALLA NORA³, A. PASSARO^{1,3}

¹Department of Translational Medicine, University of Ferrara, Ferrara, Italy

²Vascular Surgery Unit, Surgery Department, University Hospital of Ferrara Arcispedale Sant'Anna, Ferrara, Italy

³Medical Department, University Hospital of Ferrara Arcispedale Sant'Anna, Ferrara, Italy

S. Greco and G. Zenunaj equally contributed to the development of this article

Abstract. – OBJECTIVE: Diffuse thrombosis represents one of the most predominant causes of death by COVID-19 and SARS-CoV-2 infection seems to increase the risk of developing venous thromboembolic diseases (VTE). Aim of this study is to analyze the relationship between validated predictive scores for VTE such as IMPROVE and IMPROVEDD and: (1) Intensification of Care (IoC, admission to Pulmonology Department or Intensive Care Unit) (2) in-hospital mortality rate (3) 30-days mortality rate.

PATIENTS AND METHODS: We retrospectively evaluated 51 adult patients with laboratory diagnosis of SARS-CoV-2 infection and calculated IMPROVE and IMPROVEDD scores. All patients underwent venous color-Doppler ultrasound of the lower limbs to assess the presence of superficial vein thrombosis (SVT) and/or deep vein thrombosis (DVT). Patients with normal values of D-dimer did not receive heparin therapy (LMWH); patients with ≥ 4 ULN values of D-dimer or with a diagnosis of DVT were treated with therapeutic LMWH dosage, while the remaining patients were treated with prophylactic LMWH dosages.

RESULTS: We found strong relations between IMPROVE score and the need for IoC and with the in-hospital mortality rate and between the IMPROVEDD score and the need for IoC. We defined that an IMPROVE score greater than 4 points was significantly associated to in-hospital mortality rate ($p = 0.05$), while an IMPROVEDD score greater than 3 points was associated with the need for IoC ($p = 0.04$). Multivariate logistic analysis showed how IMPROVE score was significantly associated to in-hospital and 30-days mortality rates.

CONCLUSIONS: IMPROVE score can be considered an independent predictor of in-hospital and 30-days mortality.

Key Words:

Coronavirus infection, SARS-CoV-2, Thromboembolic risk, Deep vein thrombosis, Clinical outcome.

Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by Severe Acute Respiratory Syndrome CoronaVirus 2 (SARS-CoV-2)¹. COVID-19 is the third coronavirus pandemic of the current century, after SARS (Severe acute respiratory syndrome) that developed in 2002 with more than 8000 cases and a global mortality rate of about 10%, and MERS (Middle East respiratory syndrome syndrome), developed in 2012 with more than 800 cases with a global mortality rate of approximately 38%. Both viruses caused an atypical form of pneumonia with a wide range of common symptoms such as fever, cough, muscle pain, lethargy, sore throat, diarrhea and others. Over 22 million cases were registered since COVID-19 burst, as of August 18, with a partial mortality rate of 5%, affecting 213 countries and territories around the world and 2 international conveyances.

The main cause of death seems to be the Acute respiratory distress syndrome (ARDS), an immunologic event following COVID-19, characterized by an uncontrolled systemic inflammatory response with a cytokine storm following release of pro-inflammatory cytokines (interferons, interleukins, tumor necrosis factor- α and chemokines)².

While COVID-19 predominantly disrupts the respiratory system, there is accumulating experience that the disease, particularly in its more severe manifestations, also affects the cardiovascular system³⁻⁵ with predilection for patients with pre-existing comorbidities such as hypertension, diabetes and other cardiovascular diseases⁶.

Among the suspected causes of death, diffuse thrombotic disease represents one of the most predominant concerns: other respiratory viral illnesses were also reported to predispose patients to venous thromboembolism (VTE)⁷. It is therefore plausible that SARS-CoV-2 infection increases the risk of developing VTE. Recently, Wang et al⁸ reported that patients admitted to hospital with COVID-19 had higher clinical risk scores for thromboembolic events.

Changes in coagulation parameters have also been well documented in patients with COVID-19, including elevation in D-dimer^{4,5} and fibrin degradation product levels on admission⁹.

For these reasons, some national and international medical societies recently updated their recommendations on thromboprophylaxis in patients with SARS-CoV-2 infection^{10,11}.

The mechanisms involved in possible thrombotic complications in COVID-19 remain uncertain. The regulation of pro- and anti-thrombotic pathways is particularly complex and related to both host and pathogen-related properties⁷. Activation of host defense systems results in subsequent activation of coagulation and thrombin generation as critical communication components among humoral and cellular amplification pathways, a term called thromboinflammation or immunothrombosis¹²⁻¹⁴.

Specific mechanistic studies with SARS-CoV-2 still lack, but a prior study on SARS-CoV demonstrated that infection of mice increases the proinflammatory status, resulting in increased levels of interleukin-1beta [IL-1beta], tumor necrosis factor alpha [TNF-alfa], interleukin-6 [IL-6], profibrotic transforming growth factor B [TGF-B], connective tissue growth factor [CTGF] and platelet derived growth factor [PDGF]. These cytokines transcript and upregulates genes associated with induction of a procoagulant state and other fibrinolysis pathway components¹⁵.

Anticoagulant strategies should be taken in consideration for all patients with COVID-19 presenting with high levels of D-dimer and with higher clinical risk of developing thromboembolic disease, according to international and national guidelines.

Primary outcome of the study was to analyze the relationship between IMPROVE and IMPROVEDD scores, usually calculated for estimating VTE risk in hospitalized patients, and 1) Intensification of Care (IoC, meant as admission to Pulmonology department or Intensive Care Unit); 2) in-hospital mortality rate; 3) 30-days mortality rate.

Secondary outcome was to check whether these scores can be used as independent predictors of COVID-19 regardless of existing thromboembolic disease.

Patients and Methods

Study Design

In this study, we enrolled 51 adult patients consecutively admitted in April 2020 in our Internal Medicine department of “S. Anna” Hospital, in Ferrara. All patients got a diagnosis of SARS-CoV-2 infection, confirmed with a laboratory viral RNA detection at oro-pharyngeal and naso-pharyngeal swab. We analyzed clinical history and blood chemistry with particular attention to the coagulative asset. All clinical data were taken from information system and medical records. All patients were equally suspected to suffer from vein thrombosis (deep or superficial) due to the pro-inflammatory status caused by SARS-CoV-2 infection and to the hospitalization. We evaluated the comorbidity status by calculating Charlson Comorbidity Index (CCI) which was proven to be an independent predictor of mortality^{16,17}. CCI items are shown in [Supplementary Table I](#).

We calculated risk scores for VTE with IMPROVE score¹⁸ and IMPROVEDD score¹⁹. IMPROVE Predictive Score Inizio modulo

criteria are: Previous VTE, Treated or untreated Malignancy within the previous 6 months, Thrombophilia, Age >60 yrs. Fine modulo

IMPROVEDD Associative Score criteria: Previous VTE, Thrombophilia, Paralysis of the lower extremities during hospitalization, Current Malignancy, Immobilization for at least 7 days, ICU or CCU on admission, Age > 60 yrs. All patients underwent venous color-Doppler ultrasound of the lower limbs in order to assess the presence of SVT and/or DVT.

Patients were treated or not with LMWH according to their D-dimer levels at admission and to their active mobilization: patients with normal levels of D-dimer and active mobiliza-

tion were not treated with LMWH. We chose a prophylactic dosage of LMWH for patients with increased levels of D-dimer but $< 4\text{ULN}$; patients with levels of D-dimer $\geq 4\text{ULN}$ were treated with a therapeutic dosage of LMWH. Heparin dosage was halved in case of mild or moderate renal insufficiency according to the international guidelines. When the diagnosis of DVT was confirmed, we shifted therapy to a therapeutic LMWH dosage. Steroid therapy was performed when necessary.

Primary outcomes of this study were to evaluate the relations between IMPROVE and IMPROVEDD scores and IoC, in-hospital mortality, and 30-days mortality.

Secondary outcome of the study was to understand whether the predictive scores used could be intended as independent predictors of IoC, 30-days mortality and/or in-hospital mortality.

Inflammation was assessed using white blood count (WBC), C-reactive protein (CRP), procalcitonin and ferritin levels, while organ damage using alanine transferase (ALT), isoamylase, creatine phosphokinase (CPK), and troponin I HS (TnI).

Length of Hospitalization was defined as the length of stay in an acute hospital setting. Time for negativity of the SARS-CoV-2 swabs was defined as time until two consecutive negative oro- and naso-pharyngeal swabs since the first positive viral RNA detection as established by WHO.

The need for intensification of care was defined as admission to the Unit of Pulmonology or to the Intensive Care Unit (ICU).

Mortality was evaluated since the first day of hospital admission to the 30th day of hospital stay.

We followed STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for reporting observational studies as for the compilation of this manuscript.

The local Ethics Committee approved the protocol of this study: the protocol code is 712/2020/Oss/AOUFe.

Data Collection

Demographic, anamnestic and clinical data of the patients were entered into an electronic case report form. Diagnoses of patients infected with COVID-19 were confirmed by at least one positive oro- and naso-pharyngeal swab to SARS-CoV-2 RNA detection.

Data included the following: demographic characteristics (age and sex), clinical history,

laboratory data (D-dimer, mg/LFEU; PT, sec; APTT, sec), need for hospital admission and for IoC, mortality at the 30th day since hospital admission, in-hospital mortality.

Statistical Analysis

Data analysis were performed by using SPSS 26.0 (IBM SPSS Statistics, IBM Corporation) software. Normal distribution of the continuous variables was analyzed using Kolmogorov-Smirnov and Shapiro-Wilk tests. Variables not normally distributed were log transformed before entering parametric statistical analysis. Categorical variables were summarized by using frequencies and percentages and continuous data were presented as mean \pm standard deviation (SD). The Mann-Whitney U test was used for continuous variables, and the χ^2 test or the Fisher exact test was used for categorical variables. Variables with a p value < 0.05 in the univariate analysis were entered into multivariate logistic regression analysis. All p values < 0.05 are considered statistically significant.

Results

In April 2020, 51 patients were hospitalized with a laboratory diagnosis of SARS-CoV-2 infection in the Internal Medicine department of “Sant’Anna” Hospital in Ferrara, Italy. All patients underwent venous color-Doppler ultrasound of the lower limbs in order to assess the presence of SVT and/or DVT; 11 patients developed a DVT (21.6%) while no patient developed a SVT. Of these 11 patients, 7 already were having therapeutic LMWH dosages, while 4 patients were shifted from a prophylactic to a therapeutic LMWH dosage.

4 patients underwent an IoC (7.8%), 9 of the 51 patients died after 30 days since hospital admission (17.6%) while 12 died during hospitalization (23.5%).

Table I illustrates the characteristics of the population. We analyzed differences between groups in terms of IoC, 30-days mortality and in-hospital mortality and calculated demographic, laboratory and clinical data for all these patients.

Statistically significant differences were found for some of the evaluated variables. Strong relations were found between the two prediction scores used (IMPROVE and IMPROVEDD) and patients’ need for IoC ($p = 0.005$ for both vari-

Table I. Characteristics of population and relations with the three main outcomes of the study: Intensification of Care (IoC), in-hospital mortality, and 30-days mortality.

| | All (N. 51) Mean ± SD (Min-Max) | IoC (N. 4) | | | In-hospital death (N. 12) | | | 30-days mortality (N. 9) | | |
|--------------------------|---------------------------------------|------------|-----------|----------------|---------------------------|-----------|----------------|--------------------------|-----------|----------------|
| | | Yes | No | <i>p</i> value | Death | Survival | <i>p</i> value | Death | Survival | <i>p</i> value |
| Age (years) | 78 ± 14 (44-99) | 74 ± 8 | 79 ± 15 | 0.17 | 86 ± 6 | 76 ± 16 | 0.31 | 88 ± 7 | 76 ± 15 | 0.74 |
| CCI (points) | 3.0 ± 2.4 (0-9) | 1.5 ± 3.0 | 3.1 ± 2.3 | 0.12 | 3.7 ± 2.3 | 2.8 ± 2.4 | 0.63 | 4.4 ± 2.0 | 2.7 ± 2.4 | 0.45 |
| Length of stay (days) | 20 ± 15 (3-77) | 37 ± 16 | 18 ± 14 | 0.14 | 21 ± 14 | 19 ± 15 | 0.62 | 14 ± 8 | 21 ± 16 | 0.78 |
| D-dimer (mg/LFEU) | 3.0 ± 4.3 (0.3-18.3) | 2.2 ± 1.6 | 3.1 ± 4.5 | 0.64 | 1.7 ± 1.8 | 3.4 ± 4.8 | 0.22 | 2.0 ± 2.0 | 3.2 ± 4.7 | 0.78 |
| PT (sec) | 1.2 ± 0.3 (0.9-2.1) | 1.2 ± 0.3 | 1.2 ± 0.3 | 0.60 | 1.3 ± 0.4 | 1.1 ± 0.2 | 0.12 | 1.4 ± 0.4 | 1.1 ± 0.2 | 0.04 |
| APTT (sec) | 1.2 ± 0.2 (0.7-1.9) | 1.3 ± 0.1 | 1.1 ± 0.2 | 0.76 | 1.2 ± 0.2 | 1.1 ± 0.2 | 0.16 | 1.2 ± 0.2 | 1.1 ± 0.2 | 0.25 |
| IMPROVE score (points) | 6.8 ± 3.6 (1,5-15) | 9.3 ± 4.0 | 6.6 ± 3.5 | 0.005 | 9.3 ± 3.6 | 6.0 ± 3.2 | 0.01 | 9.3 ± 3.6 | 6.2 ± 3.3 | 0.42 |
| IMPROVEDD score (points) | 2.9 ± 1.6 (0-7) | 4.3 ± 2.1 | 2.8 ± 1.6 | 0.005 | 3.2 ± 1.4 | 2.8 ± 1.7 | 0.50 | 3.1 ± 1.5 | 2.8 ± 1.7 | 0.69 |

IoC, Intensification of Care; CCI, Charlson Comorbidity Index; PT, Prothrombin Time; APTT, Activated Partial Thromboplastin Time.

Table II. Characteristics of population with deep vein thrombosis (DVT) and relations with the three main outcomes of the study: Intensification of Care (IoC), in-hospital mortality, and 30-days mortality.

| N = 11 | Min-max | Mean ± SD | <i>p</i> (between groups) | IoC* (<i>p</i> -value) | 30-days mortality (<i>p</i> -value) | In-hospital mortality (<i>p</i> -value) |
|---------------|---------|-----------|---------------------------|-------------------------|--------------------------------------|--|
| Age (years) | 59-94 | 82 ± 11 | 0.42 | 0.17 | 0.74 | 0.31 |
| CCI* (points) | 0-7 | 3.3 ± 2.6 | 0.69 | 0.12 | 0.45 | 0.63 |

*IoC: intensification of care, CCI: Charlson Comorbidity Index.

ables). IMPROVE score had a statistically significant relation with in-hospital mortality as well ($p = 0.01$).

In Table II we marked the characteristics of population with deep vein thrombosis (DVT) in terms of age and Charlson Comorbidity Index (CCI); we compared both variables between groups of patients with and without confirmation of DVT, finding no significant differences.

Table III summarizes relations of the chosen variables with IoC, 30-days mortality and in-hospital mortality. We chose a threshold of 4ULN for D-dimer levels in order to choose a treatment with a prophylactic or with a therapeutic dosage of LMWH, while patients with normal levels of D-Dimer and with active mobilization were not treated with LMWH at all. Similarly, we chose an IMPROVE score ≥ 4 points as indirect sign of high VTE risk²⁰ and a score ≥ 3 points for the IMPROVEDD¹⁹. The only two significant associations were found between an IMPROVE score ≥ 4 points and the in-hospital mortality and between an IMPROVEDD score ≥ 3 points and the need for IoC.

Multivariate logistic regression analysis was also performed to check whether the IMPROVE

and the IMPROVEDD scores can be considered as independent predictors of IoC, 30-days mortality and/or in-hospital mortality regardless the ultrasound findings of thrombosis.

Table IV and V illustrate multivariate analysis' results. The only statistically significant differences regarded the IMPROVE score in relation to 30-days mortality and in-hospital mortality ($p = 0.03$ and 0.008 , respectively). We performed the same analysis including age and gender, without finding any significant difference compared to the analysis reported in Table IV and V ($p < 0.05$ in both analysis, data not shown); IMPROVE score includes both variables for its determination and this is the reason why the first two multivariate analysis did not include age and gender.

There were no significant associations in multivariate analysis between the prediction scores used and IoC, nor any association between IMPROVEDD score and the three variables of analysis.

Moreover, having a DVT was not predictive of a different probability of undergoing an IoC, or of dying during the hospital stay or within 30 days in this cohort of patients (data not shown).

Table III. Relations between variables. With prophylactic LMWH (low molecular weight heparin) it is meant a dosage of 4000 IU or 2000 IU (renal adjusted dosage) sid, while with therapeutic LMWH it is meant a dosage of 100 IU/kg, bid.

| N = 51 | All N. (%) | IoC | | In-hospital mortality | | 30-days mortality | |
|--------------------------|------------|----------|-----------------|-----------------------|-----------------|-------------------|-----------------|
| | | N. (%) | <i>p</i> -value | N. (%) | <i>p</i> -value | N. (%) | <i>p</i> -value |
| D-dimer ≥ 4 ULN | 17 (33.3) | 2 (11.8) | 0.50 | 2 (11.8) | 0.19 | 2 (11.8) | 0.53 |
| Prophylactic LMWH | 29 (56.9) | 1 (3.4) | 0.18 | 8 (27.6) | 0.43 | 6 (20.7) | 0.51 |
| Therapeutic LMWH | 14 (27.5) | 2 (14.3) | 0.29 | 3 (21.4) | 0.83 | 2 (14.3) | 0.70 |
| Steroid therapy | 19 (37.3) | 3 (15.8) | 0.10 | 7 (36.8) | 0.08 | 4 (21.1) | 0.62 |
| DVT | 11 (21.6) | 0 (0) | 0.28 | 4 (36.4) | 0.26 | 3 (27.3) | 0.34 |
| IMPROVE score ≥ 4 | 35 (68.6) | 4 (11.4) | 0.16 | 11 (31.4) | 0.05 | 8 (22.9) | 0.15 |
| IMPROVEDD score ≥ 3 | 34 (66.7) | 3 (8.8) | 0.04 | 9 (26.5) | 0.48 | 7 (20.6) | 0.44 |

IoC: iintensification of care, LMWH: low molecular weight heparin, Prophylactic LMWH: dosage of 4000 IU or 2000 IU (renal adjusted dosage) sid, Therapeutic LMWH: dosage of 100 IU/kg, bid.

Table IV. Logistic analysis results in the population. Variables independently associated with 30-days mortality rate.

| Variable | OR | 95% CI | p-value |
|------------------------|------|------------|-------------|
| D-dimer | 0.87 | 0.63-1.20 | 0.40 |
| Prophylactic LMWH | 0.84 | 0.05-13.13 | 0.90 |
| Therapeutic LMWH | 0.45 | 0.02-10.03 | 0.62 |
| CCI | 1.25 | 0.87-1.80 | 0.23 |
| IMPROVE score ≥ 4 | 1.36 | 1.03-1.79 | 0.03 |

LMWH, low molecular weight heparin; Prophylactic LMWH, LMWH dosage of 4000 IU or 2000 IU (renal adjusted dosage) sid; Therapeutic LMWH, LMWH dosage of 100 IU/kg, bid; CCI, Charlson Comorbidity Index.

Discussion

In this study, we evaluated the prevalence of venous thrombotic events in our population of 51 inpatients; none of them developed a SVT during the stay while 11 upon 51 developed a DVT (21.6%). We also evaluated the relations between the venous thrombotic events and the main disease outcomes: the need for IoC, the 30-days mortality rate and the in-hospital mortality rate.

The current literature gives an increasing evidence of relations between SARS-CoV-2 infection and thrombotic events; therefore, it is interesting to stratify the population depending on their risk of needing an intensification of care or of undergoing a worse short-term prognosis.

We performed venous color-Doppler ultrasound of the lower limbs to all patients, checking whether there was a significant difference in terms of age or CCI between the group with DVT and the group without DVT. No statistically significant differences between groups, nor significant relations with the three variables (need for intensification of care, 30-days mortality, in-hospital mortality) were found, suggesting how the presence of DVT, as for our cohort of patients, did not predict any of the COVID-19 outcomes.

D-Dimer is certainly the most used laboratory index evaluating the risk of thrombotic events.

For this reason, many national and international medical societies have updated their recommendations on thromboprophylaxis in patients with SARS-CoV-2 infection depending on D-Dimer levels, in particular when higher than the reference values (ULN).

Nevertheless, we did not find significant differences in terms of IoC, 30-days and in-hospital mortality, as for specific laboratory (D-Dimer) and therapeutic (steroid, prophylactic or therapeutic LMWH dosage) data. We decided thus to use a multiparametric score to better stratify the thrombotic risk.

Spyropoulos et al²⁰ defined predictive and associative models to acutely identify patients hospitalized in Medicine departments who were at risk for VTE. The IMPROVE score is a validated VTE assessment tool to risk-stratify hospitalized, medically ill patients based on personal and clinical variables. Successively, Gibson et al¹⁹ hypothesized that addition of D-dimer measurements, in order to derive a new IMPROVEDD score, would improve identification of patients at risk for VTE.

Significant differences ($p = 0.005$) were found between IMPROVE and IMPROVEDD scores with patients' need for intensification of care.

We further performed multivariate analysis for the whole group of patients. We tried to understand whether there were confounding factors

Table V. Logistic analysis results in the population. Variables independently associated with in-hospital mortality rate.

| Variable | OR | 95% CI | p-value |
|------------------------|------|-----------|--------------|
| D-dimer | 0.81 | 0.55-1.19 | 0.29 |
| Prophylactic LMWH | 0.51 | 0.03-7.94 | 0.63 |
| Therapeutic LMWH | 0.24 | 0.01-5.18 | 0.36 |
| CCI | 1.06 | 0.75-1.50 | 0.73 |
| IMPROVE score ≥ 4 | 1.47 | 1.10-1.95 | 0.008 |

LMWH, low molecular weight heparin; Prophylactic LMWH, LMWH dosage of 4000 IU or 2000 IU (renal adjusted dosage) sid; Therapeutic LMWH, LMWH dosage of 100 IU/kg, bid; CCI, Charlson Comorbidity Index.

that could make the two scores predictive factors for a worse prognosis in our cohort of patients with SARS-CoV-2 infection.

We chose D-dimer, prophylactic/therapeutic LMWH and IMPROVE score as variables in this kind of analysis. Thus, we performed a multivariate analysis with the three variables to check whether a relation with the risk of undergoing an IoC or mortality (30-days and in-hospital mortality rates) in the patients with SARS-CoV-2 existed. In this case, we found IMPROVE score to be an independent risk factor for 30-days and in-hospital mortality.

In particular, according to the existing literature, we defined a specific reference value for both IMPROVE and IMPROVEDD score. A value of IMPROVE score greater than 4 points seemed to be associated with a higher risk of in-hospital mortality only, while an IMPROVEDD score greater than 3 points might be related with a greater need for intensification of care. Logistic analysis was also performed for this score, but we did not find any significant result that could make IMPROVEDD score an independent predictor for in-hospital or 30-days mortality or for an IoC.

Having DVT was not significantly related to the chosen outcomes.

The limitations of the study are related to its retrospective nature and to the restricted sample size, which could have limited the significance of our findings. It is still necessary to better investigate and deepen the relations between the thrombotic events and viral infections such as SARS-CoV-2 infection.

Conclusions

In consideration of the wide range of manifestations and of the degree of severity associated with the new coronavirus infection, it is particularly important to define a score that allows predicting the risk of short-term mortality and the need for an intensification of cares for any single patient.

In our study, IMPROVE score had a strong relation with in-hospital mortality rate and with the need for IoC. A score greater than 4 points was statistically related to in-hospital mortality too. Moreover, logistic analysis showed how the IMPROVE score seems to be an independent predictor for 30-days and in-hospital mortality in the small cohort of patients enrolled.

IMPROVEDD score was also shown to have a strong relation with the need for IoC and a score

greater than 3 points was statistically related to the need for IoC. However, the logistic analysis did not demonstrate any significant relation that could make this score an independent predictor for the three different outcomes chosen.

The diagnosis of deep vein thrombosis, in this cohort of subjects, was not useful to predict the outcomes of the patients in terms of IoC, 30-days mortality or in-hospital mortality.

Further and targeted studies are necessary to deepen the pro-thrombotic aspects of SARS-CoV-2 infection, while a greater number of enrolled patients could help to understand whether prediction scores like IMPROVE and IMPROVEDD could effectively be used in the clinical practice to stratify the COVID-19 population. It is important to underline that this population is at higher risk of venous thromboembolism compared to the normal hospitalized population with the same age, functional autonomy and pro-thrombotic factors.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Author Statement

Greco Salvatore: acquisition, analysis and interpretation of data; drafting the article. Zanunaj Gladiol: acquisition, analysis and interpretation of data; drafting the article. Bonisi Beatrice: acquisition, analysis and interpretation of data; drafting the article. Bella Alessandro: acquisition, analysis and interpretation of data; drafting the article. Mariarosaria Lopreato: acquisition and analysis of data. Luciani Francesco: acquisition and analysis of data. Pedrini Dario: acquisition and analysis of data. Vestita Grazia: acquisition and analysis of data. Dalla Nora Edoardo: revising the article critically for important intellectual content. Passaro Angelina: the conception and design of the study; drafting the article and revising it critically for important intellectual content, final approval of the version to be submitted.

ORCID

Angelina Passaro; ORCID code: 0000-0001-8462-7000.

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