

Sars-CoV-2 Induced Coagulopathy and Prognosis in Hospitalized Patients: A Snapshot from Italy

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After Wuhan, in China, Italy has become the European country with the highest number of cases and deaths by Sars-Cov-2.^{1,2}

It has been reported from China the presence of altered coagulation parameters in a significant proportion of hospitalized patients.^{3–5} In addition, increased D-dimer (DD) levels have gained particular attention as predictors of acute respiratory distress syndrome development, the need of intensive care unit (ICU) admission, or death.^{6,7} It is well known that DD is a highly nonspecific marker which may be only the mirror of the clotting activation following the inflammatory process.^{8,9} Nevertheless, several thrombotic complications have been reported in patients with Covid-19 treated in ICU and the possible treatment with heparin appears to be very attractive.¹⁰

Before this therapeutic application, it is mandatory to verify and report to the scientific community which is the trend of coagulation parameters, so that we can accumulate several observations useful to design ad hoc interventional trials.

In this scenario, we decided to analyze the routine coagulation parameters—prothrombin time (PT), activated partial thromboplastin time (aPTT), DD, and platelet count—of a consecutive series of patients with documented infection by Sars-Cov-2 hospitalized in Careggi Hospital, Florence, Italy.

Methods

Two hundred and nine consecutive patients (133 males/76 females) with confirmed Sars-Cov-2 infection (according to the World Health Organization criteria), admitted to the Careggi Hospital, Florence, from March 2 to April 7, 2020, were enrolled. Exclusion criterion was the direct admission in ICU.

The clinical outcomes were monitored up to April 7, 2020 (median follow-up: 11 days [interquartile range [IQR]: 7–14]).

The results were given as mean ± standard deviation or median (IQR), wherever appropriate. Distributed quantita-

tive variables were compared using the Student's *t*-test and the Mann–Whitney *U* test, as appropriate. A receiver operating characteristic (ROC) curve analysis was used to determine the ability of the analyzed parameters to distinguish between patients with different endpoints: death or hospital discharge. The optimal cut-off point was calculated by determining the level that provided the greatest sum of sensitivity and specificity.

Results

Thirty-one patients died (14.8%) and 117 patients had been discharged (56%). Fifty-one patients (24.4%) have been transferred to an ICU. Eight thrombotic events were documented (3.8%) in symptomatic patients, in the absence of routine compression ultrasound execution.

Laboratory values in the total population are reported in **Table 1**.

We compared coagulation parameters at hospital admission between survivors versus nonsurvivors.

Nonsurvivor patients were older and, at hospital admission, they had significantly higher PT-international normalized ratio (INR), PT seconds, and mean platelet volume (MPV) values with respect to survivors (**Table 1**). No differences were detected in aPTT ratio and platelet count. ROC curves revealed that the cut-offs with the highest sensitivity and specificity for the endpoint “death” were: 1.40 for PT-INR, 1,000 ng/mL for DD, and 11.9 fL for MPV. By defining “Sars-Cov-2 induced coagulopathy” as a combination of the three parameters (i.e., the presence of a value EQUAL or HIGHER than the reported cut-off for more than one parameter), area under the curve (AUC) increased to 0.78 ± 0.06 ($p < 0.05$; **Fig. 1A**). The addition of the so-defined “Sars-Cov-2 induced coagulopathy,” to a model that included age, which is “per se”

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Table 1 Demographic and laboratory parameters of enrolled Sars-Cov-2 patients

Variables	All (n = 209)	Alive (n = 178)	Dead (n = 31)	p-Values	Discharged (n = 117)	Nondischarged (n = 92)	p-Values
Age, mean ± SD	65.9 ± 14.6	63.5 ± 14.0	79.8 ± 9.8	< 0.001	59.9 ± 14.0	73.6 ± 11.6	< 0.001
Sex, M N (%)	133 (63.6)	112 (62.9)	21 (67.7)	0.607	74 (63.2)	59 (64.1)	0.895
PT, s	14.0 ± 2.5	13.8 ± 2.4	15.2 ± 3.1	0.003	13.4 ± 1.1	14.8 ± 3.5	< 0.001
INR	1.23 ± 0.21	1.22 ± 0.21	1.31 ± 0.21	0.002	1.18 ± 0.10	1.30 ± 0.28	< 0.001
aPTT ratio	1.02 ± 0.14	1.02 ± 0.14	1.02 ± 0.15	0.858	1.00 ± 0.09	1.03 ± 0.19	0.786
Platelet count, ×10 ⁹ /L	187 (145–231)	189 (149–233)	174 (111–204)	0.127	191 (156–235)	183 (141–217)	0.088
MPV, fL	10.6 (10.1–11.4)	10.5 (10.0–11.3)	11.4 (10.6–12.4)	< 0.001	10.4 (9.9–11.1)	10.9 (10.5–11.9)	0.001
D-dimer, ng/mL (n = 135)	794 (513–1,247)	739 (498–1,160)	1,149 (757–2,049)	0.002	669 (490–960)	969 (550–1,670)	0.011

Abbreviations: aPTT, activated partial thromboplastin time; M, males; INR, international normalized ratio; MPV, mean platelet volume; PT, prothrombin time; SD, standard deviation.

Note: Statistical significant values ($p < 0.05$) are depicted in bold.

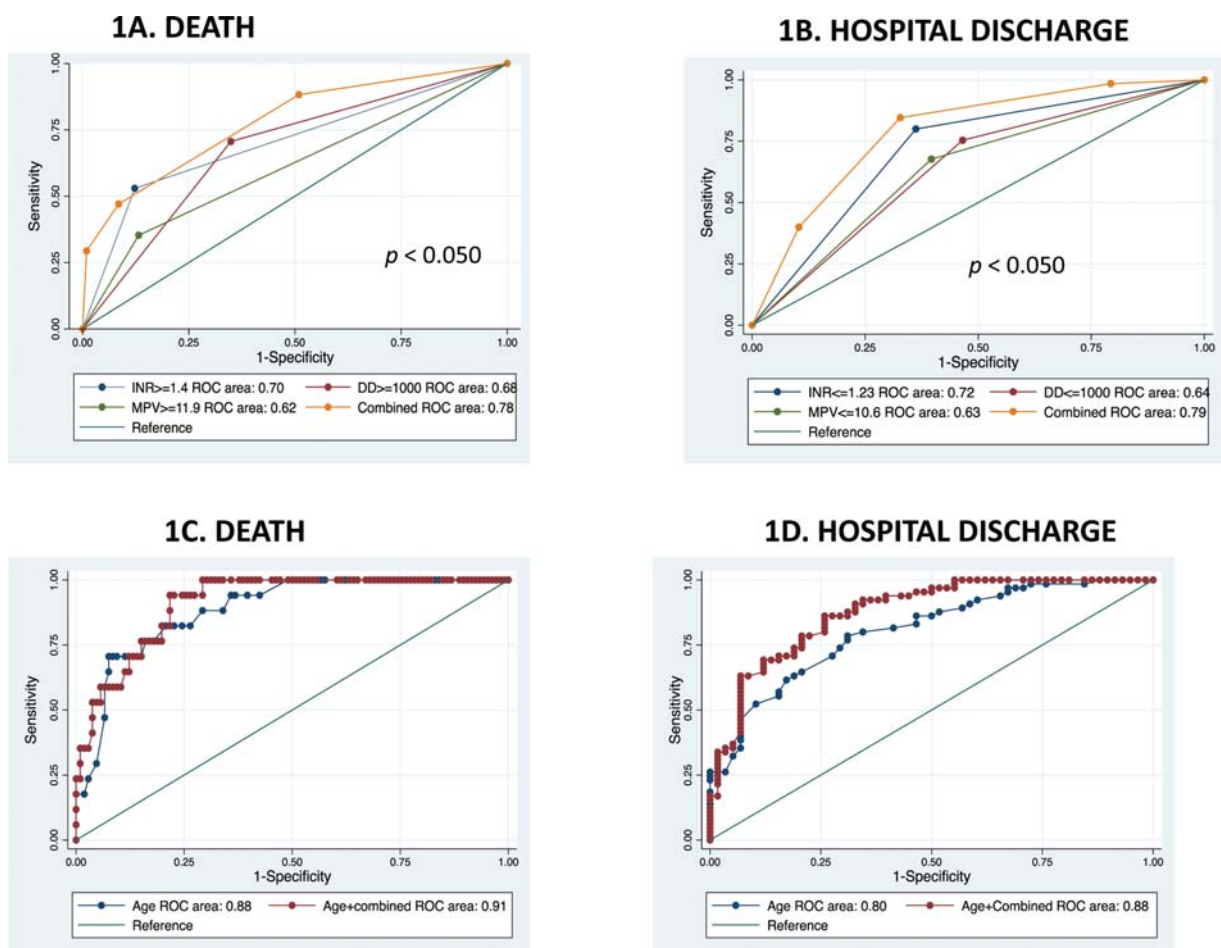


Fig. 1 Receiver operating characteristic (ROC) curves according to death and hospital discharged. ROC curves of PT-International Normalized Ratio (INR), D-dimer (DD) and Mean Platelet volume (MPV) according to death (1-A) and hospital discharge (1-B), when the three parameters were above (1-A) or below (1-B) the cut-off values. ROC curves for death of the two models of logistic regression: model 1 (age) or model 2 (age + combined coagulative parameters*) (1-C). ROC curves for hospital discharge of the two models of logistic regression: model 1 (age) or model 2 (age + combined coagulative parameters*) (1-D).

a strong predictor of death (AUC 0.89 ± 0.04), slightly increased the AUC (0.92 ± 0.03 ; $p = 0.10$) for the detection of death (►Fig. 1C). At multivariate regression analysis, adjusted for age and sex, age and Sars-Cov2-induced coagulopathy were independent predictors of death (age: odds ratio [OR] = 1.17, 95% confidence interval [CI] 1.07–1.27; $p < 0.0001$ /Sars-Cov2-induced coagulopathy: OR = 2.72, 95% CI 1.20–6.17; $p = 0.016$).

In addition, we compared coagulation parameters at hospital admission between discharged versus nondischarged patients. Discharged patients were younger and, at admission, had significantly lower PT-INR, PT seconds, DD, and MPV values with respect to the others (►Table 1). No differences were detected in aPTT ratio and platelet count. ROC curves revealed that the cut-offs with the highest sensitivity and specificity for the endpoint “hospital discharge” were: 1.23 for PT-INR, 1,000 ng/mL for DD, and 10.6 fL for MPV. By defining “NO Sars-Cov-2 induced coagulopathy” as a combination of the three parameters (i.e., the presence of a value LOWER than the reported cut-off for more than one parameter), AUC increased to 0.79 ± 0.04 ($p < 0.05$; ►Fig. 1B). By adding the “NO Sars-Cov-2 induced coagulopathy” to a model that included age, which is “per se” a strong predictor of hospital discharge (AUC 0.80 ± 0.04), significantly increased the AUC (0.88 ± 0.03 ; $p = 0.016$) for the detection of hospital discharge (►Fig. 1D).

Discussion

These results demonstrate that patients at hospital admission for Sars-Cov-2 infection often have an alteration in the routine coagulation parameters. In particular, PT-INR, DD, and MPV are the three parameters which, together with age, resulted to be significantly associated with death and discharge, so allowing us to identify two clusters of inpatients with worse or better prognosis.

In particular, the absence, at hospital admission, of an involvement in clotting and fibrinolytic pathways identifies a group of patients at low risk of complications.

We think that the most relevant result is that this score not only maintains but increases the AUC for death or discharge if associated with age, which is “per se” the strongest clinical predictor of outcome.

It is well known that thrombosis is associated with inflammation and vice versa.^{11,12} In the model of sepsis, it has just been validated as score (SIC – sepsis-induced coagulopathy score) in which PT-INR, fibrinogen, and platelet count are associated with a worse prognosis. In the setting of Sars-Cov-2 infection, it has been demonstrated that both clotting activation and fibrinolysis are crucial.^{13–18} Indeed, our data demonstrate that also DD levels help us to identify patients at higher or lower risk. In addition, in our group, platelet size and not platelet count is significantly associated with clinical outcomes: we know that MPV is a marker of platelet function as it is positively associated with indicators of platelet activity, including aggregation and release of thromboxane A₂, platelet factor 4, and b-thromboglobulin.^{19,20}

A subsequent step might be a clinical trial designed to randomize patients with “Sars-Cov-2 coagulopathy” to an intensive antithrombotic treatment, to verify a possible impact on prognosis. Possible intervention in this area might be heparin treatment at intermediate or therapeutic dosage or other treatment able to interfere with the inflammatory process as suggested by the study of Tang et al.⁶

A limitation of this study is the limited number of patients recruited from a single center; in addition, some patients are still hospitalized at the time of manuscript submission.

Nonetheless, these data suggest a possible clinical utility of a score based on routine coagulation parameters to stratify the prognosis of hospitalized patients with Sars-Cov-2 infection.

Conflict of Interest

None declared.

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