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High mortality in COVID-19 patients with mild respiratory disease

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Abstract

Introduction: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected 189 000 people in Italy, with more than 25 000 deaths. Several predictive factors of mortality have been identified; however, none has been validated in patients presenting with mild disease.

Methods: Patients with a diagnosis of interstitial pneumonia caused by SARS-CoV-2, presenting with mild symptoms, and requiring hospitalization in a non-intensive care unit with known discharge status were prospectively collected and retrospectively analysed. Demographical, clinical and biochemical parameters were recorded, as need for non-invasive mechanical ventilation and admission in intensive care unit. Univariate and multivariate logistic regression analyses were used to identify independent predictors of death.

Results: Between 28 February and 10 April 2020, 229 consecutive patients were included in the study cohort; the majority were males with a mean age of 60 years. 54% of patients had at least one comorbidity, with hypertension being the most commonly represented, followed by diabetes mellitus. 196 patients were discharged after a mean of 9 days, while 14.4% died during hospitalization because of respiratory failure. Age higher than 75 years, low platelet count ($<150 \times 10^3/mm^3$) and higher ferritin levels (>750 ng/mL) were independent predictors of death. Comorbidities were not independently associated with in-hospital mortality.

Conclusions: In-hospital mortality of patients with COVID-19 presenting with mild symptoms is high and is associated with older age, platelet count and ferritin levels. Identifying early predictors of outcome can be useful in the clinical practice to better stratify and manage patients with COVID-19.

KEYWORDS
COVID-19, pneumonia, predictive factors

Masetti, Generali and Colapietro equally contributed to this work.

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1 | INTRODUCTION

Since December 2019, a novel beta-coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), initially identified in Wuhan (China),[1] has expanded to 185 Countries infecting more than 2.5 million people up to 24 April 2020.[2] Italy has been dramatically exposed to SARS-CoV-2, with 189 000 confirmed cases and more than 25 000 deaths.[2]

SARS-CoV-2 is spread by respiratory droplets and diagnosed by detection of viral genome by real-time reverse transcription-polymerase chain reaction (RT-PCR) testing of a nasopharyngeal swab or other specimen.[3] The clinical manifestations vary widely, ranging from asymptomatic carriers to mild flu-like symptoms including fever, cough, sore throat, malaise and myalgias. Coronavirus disease (COVID-19) refers to interstitial pneumonia associated with SARS-CoV-2 and has been diagnosed in up to 14% of cases.[4] The median incubation time, from exposure to symptom onset, is approximately 4-5 days.[5]

Case series of COVID-19 showed that risk factors for severe illness were represented by male sex, advanced age [6,7] and comorbidities,[8] especially obesity and cardiovascular disease.[9,10] Furthermore, radiology and laboratory markers have also been associated with worse outcomes, in particular elevated inflammatory markers (C-reactive protein—CRP, ferritin), lymphopaenia, D-dimer and signs of organ failure (ie elevated liver enzymes, prothrombin time, troponin, creatine phosphokinase (CPK) and creatinine).[11] However, no biomarker has been demonstrated to have prognostic value, especially in patients with mild clinical symptoms at hospital admission.

Clinical evaluation of COVID-19 patients depends on the severity of the disease, and since no proven therapy has been so far approved, hospitalization is warranted for observation and supportive care.[12,13] In Italy, COVID-19 case fatality rate has been reported to be higher than 7 in hospitalized patients, being much higher than what has been reported in China and South Korea.[14] In this view, the identification of predictive factors for severity and death would allow to stratify patients at higher risk, and thus the need of hospitalization and eventually transfer into intensive care unit (ICU), allowing a better allocation of resources. For this reason, we conducted a retrospective analysis of all consecutive patients admitted to our Hospital with mild-moderate signs and symptoms of COVID-19 with the aim to identify predictive factors of in-hospital mortality.

Highlights

- COVID-19 frequent presents with mild symptoms
- Even COVID-19 patients with mild symptoms at admission deteriorate, with a 14% mortality
- Older age, high serum ferritin levels and low platelet count are predictive factors for death in patients presenting with mild disease

2 | METHODS

This retrospective cohort study included all patients who were consecutively admitted to a single-centre emergency room (ER) in Milan from 28 February to 10 April 2020. Inclusion criteria were as follows: diagnosis of COVID-19 with documented pneumonia requiring hospitalization in a non-intensive care unit because of mild Acute Respiratory Distress Syndrome (ARDS) (the ratio of arterial oxygen partial pressure to fractional inspired oxygen, PaO2/FiO2 > 200),[15] without further signs or symptoms or organ dysfunction. The study received approval by the local Ethics Committee.

For each patient, the following data were collected: age, comorbidities (including arterial hypertension, diabetes mellitus, atrial fibrillation, coronary heart disease, active or previous cancer, chronic pulmonary disease and chronic kidney disease), duration of symptoms before admission to the ER, vital parameters at admission (arterial pressure, heart rate, respiratory rate, temperature). Only patients with a definitive outcome (dismission or death) were included, patients who were still hospitalized were not included. If an arterial blood gas analysis was performed, pO2/FiO2 ratio was calculated and lactate levels were recorded. Laboratory parameters at the time of admission, including complete blood cell count, liver and renal function, coagulation tests and inflammation indexes were collected. Laboratory normal range was used as cut-off: ferritin < 368 ng/mL; CRP < 0.5 mg/dL; lactate dehydrogenase (LDH) <248 IU/L; lymphocytes between 1 and $4 \times 10^3/mm^3$. Eventual need for non-invasive mechanical ventilation or admission to intensive care unit was recorded.

All the included patients had a diagnosis of COVID-19 obtained by viral RNA, detected by either real-time PCR in nasopharyngeal swabs to confirm the diagnosis of viral infection, or in the bronchoalveolar fluid after bronchoalveolar lavage. Chest X-ray and thoracic computed tomography (CT) scan was used to confirm the diagnosis of pneumonia: interstitial pneumonia, bilateral ground-glass area and absence of pleural effusion were considered typical features.

Statistical analysis was performed by NCSS 10 statistical software (East Kaysville, Utah, USA) and STATA 13.1 (Stata Corp, College Station, Texas). Continuous variables were expressed as means ± standard deviation, while categorical variables as absolute numbers and percentages. Univariate analyses were performed using chi-square for categorical variables and Student t test for continuous variables. All

TABLE 1 Demographical, clinical and biochemical characteristics of the study cohort

	Total (n = 229)	Survivors (n = 196)	Non-survivors (n = 33)	*P*-values
Age (y), mean (SD)	60.7 (14.2)	58.3 (13.5)	75.2 (8.3)	**<.001**
Age ≥ 75 y, n (%)	42 (18.3)	22 (11.2)	20 (60.6)	**<.001**
Male, n (%)	148 (64.6)	122 (62.2)	26 (78.8)	.06
BMI (kg/m^2), mean (SD)	26.7 (4.5)	26.7 (4.4)	26.8 (5.5)	.96
Any comorbidity, n (%)	124 (54.1)	94 (47.9)	30 (90.9)	**<.001**
Hypertension, n (%)	87 (38)	63 (32.1)	24 (72.7)	**<.001**
Diabetes, n (%)	43 (18.8)	30 (15.3)	13 (39.4)	**<.001**
CHD, n (%)	21 (9.2)	12 (6.1)	9 (27.3)	**<.001**
Atrial fibrillation, n (%)	19 (8.3)	10 (5.1)	9 (27.3)	**<.001**
Cancer, n (%)	24 (10.5)	16 (8.2)	8 (24.2)	**<.001**
Chronic kidney disease, n (%)	11 (4.8)	5 (2.5)	6 (18.2)	**<.001**
COPD, n (%)	16 (7)	11 (5.6)	5 (15.1)	.05
MAP (mm Hg), mean (SD)	87 (13)	87 (13)	86 (14)	.76
Heart rate (no/min), mean (SD)	86 (15)	85 (15)	87 (15)	.67
Respiratory rate (no/min), mean (SD)	18 (3)	18 (3)	18 (3)	.76
Temperature (°C), mean (SD)	37.3 (1.2)	37.2 (1.3)	37.4 (1.0)	.33
paO2/FiO2, mean (SD)	328 (94)	338 (91)	264 (88)	**<.001**
Lactates (mmol/L), mean (SD)	1.1 (0.8)	1.1 (0.6)	1.4 (1.5)	.07
AST (U/L), mean (SD)	42 (34)	41 (25)	52 (67)	.07
ALT (U/L), mean (SD)	36 (34)	36 (27)	35 (59)	.79
Total bilirubin (mg/dL), mean (SD)	0.7 (1)	0.7 (0.3)	1.1 (2.5)	**.01**
Creatinine (mg/dL), mean (SD)	1.0 (0.9)	0.9 (0.6)	1.6 (1.8)	**<.001**
C-reactive protein (mg/dL), mean (SD)	8.6 (12.7)	8.0 (12.9)	12.3 (10.4)	.07
White blood cell count (10^3/mm^3), mean (SD)	6.8 (4.6)	6.6 (2.8)	7.9 (10.1)	.14
Lymphocyte count (10^3/mm^3), mean (SD)	1.1 (0.9)	1.1 (0.9)	0.8 (0.5)	**.01**
Platelet count (10^3/mm^3), mean (SD)	209 (90)	218 (89)	159 (79)	**<.001**
INR, mean (SD)	1.17 (0.4)	1.14 (0.4)	1.38 (0.66)	**.004**
Fibrinogen (ng/mL), mean (SD)	545 (152)	545 (147)	537 (189)	.81
Ferritin (ng/mL), mean (SD)	657 (777)	577 (545)	1332 (1675)	**<.001**
LDH (IU/L), mean (SD)	316 (142)	303 (113)	395 (246)	**<.001**
D-dimer (ng/mL), mean (SD)	854 (4395)	461 (641)	3943 (12 799)	**<.001**
CPK (U/L), mean (SD)	222 (572)	215 (594)	262 (426)	.66
Admission to ICU, n (%)	6 (2.6)	3 (1.5)	3 (9.1)	**.01**
C-PAP, n (%)	23 (10.1)	12 (6.1)	11 (34.4)	**<.001**
Hospital stay (days), mean (SD)	9.2 (5.0)	9.2 (4.8)	9.1 (6.2)	.96

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; CPK, creatine phosphokinase; ICU, intensive care unit; INR, International Normalized Ratio; LDH, lactate dehydrogenase; MAP, mean arterial pressure.

Significant values are in bold.

variables which were significant at univariate analysis were included in the multivariate analysis that was performed using logistic regression. Continuous variables were switched into categorical ones, using as cut-off the mean value at univariate analysis for death. Finally, the area under the receiver operating characteristic curve (ROC) was calculated. Statistical significance was taken as P-value < 0.05.

3 | RESULTS

Between 28 February and 10 April 2020, 370 patients affected by COVID-19 were admitted to our ER, of which 229 (62%) patients presenting with mild disease were included in the cohort study. Their main characteristics are descripted in Table 1. About two-thirds of patients were males with a

TABLE 2 Independent predictive factors of death

Independent variable	Odds ratio	Lower 95% CI	Upper 95% CI	*P*-value
Age ≥ 75 y	10.63	4.29	26.31	<.01
Platelet count $<150 \times 10^3/mm^3$	3.64	1.47	9.00	<.01
Ferritin >750 ng/mL	3.33	1.29	8.61	.01

Note: Logistic regression analysis of predictors of death in patients with mild COVID-19. Logistic regression was adjusted for: sex, comorbidities, vital parameters and blood tests at admission.

Abbreviations: CI Confidence interval.

mean age of 60.7 ± 14.2 years. 54% of patients had at least one comorbidity, with arterial hypertension being the most commonly represented (38%), followed by diabetes mellitus (18.8%) and history of both previous neoplasia (10.5%) or concomitant neoplasia (13%-5.7%).

Blood analysis at admission showed a marked increase in acute phase protein levels, such as ferritin, C-reactive protein, LDH and D-dimer, while total white cell count and lymphocytes count were within the normal range, as liver and renal function tests. The mean hospitalization length was 9.2 ± 5.1 days; about 10% of patients (23/229) required

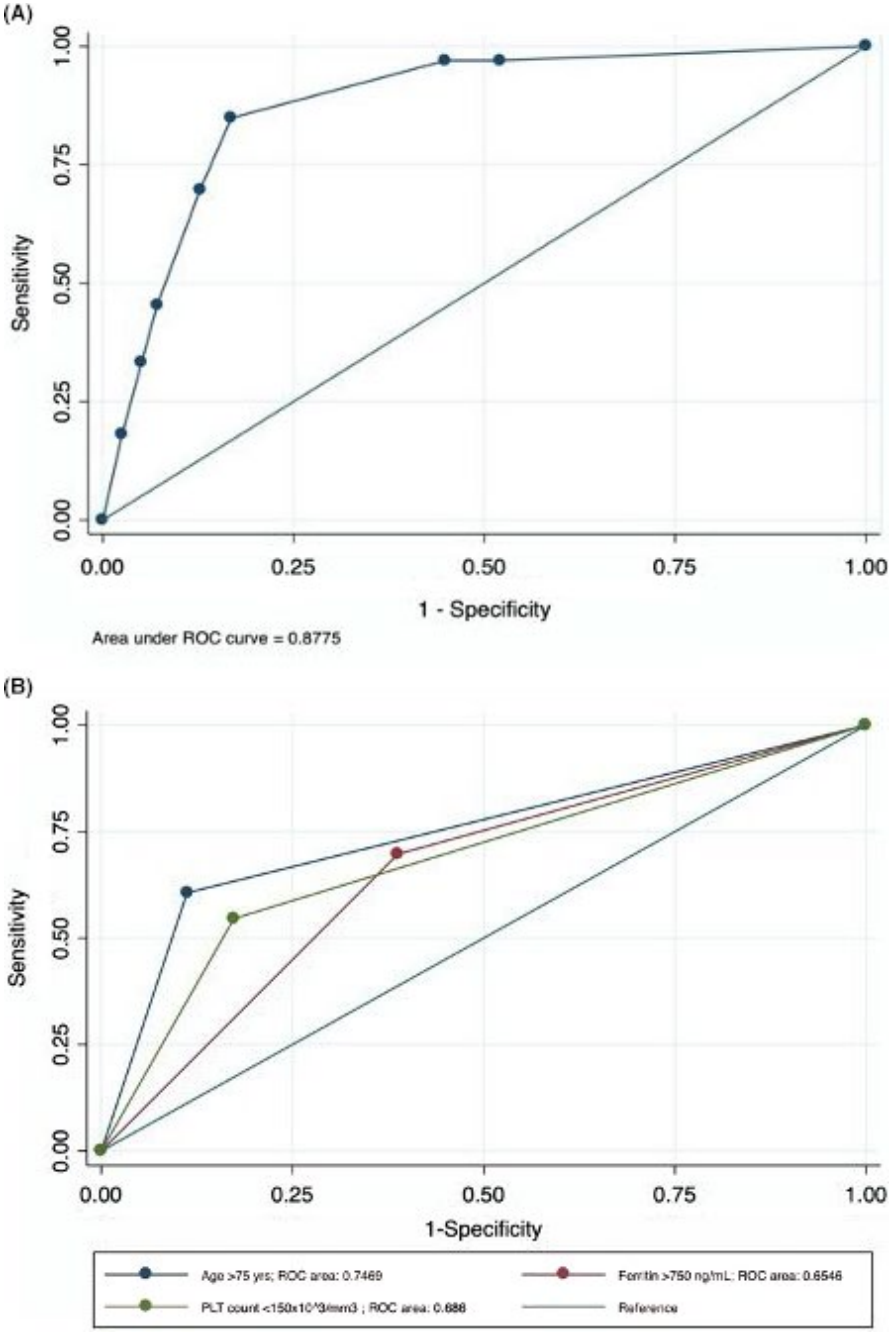

FIGURE 1 ROC curves for multivariate and univariate analyses. A, Receiver operating characteristic (ROC) curve and corresponding area under the curve (AUC) statistics for the risk score of death with age >75 y; platelets $<150 \times 10^3/mm^3$; ferritin >750 ng/mL. N = 229. B, ROC curve and AUC statistics for age >75 y (n = 42); platelets $< 150 \times 10^3/mm^3$ (n = 52); ferritin > 750 ng/mL (n = 99)

non-invasive mechanical ventilation and 2.5% (6/229) of them were subsequently admitted in the intensive care unit for mechanical ventilation.

During the observation period, 196 patients were discharged while 33 patients (14.4%) patients died during hospitalization because of respiratory failure. At univariate analysis, patients who died were significantly older (75.2 ± 8.3 vs 58.3 ± 13.5; $P < .001$) and had at least 1 comorbidity in 90.9% of (30/33) the cases compared with 47.9% (94/196) of patients who survived ($P < .01$). Sex and body mass index (BMI) did not result statistically different between the two groups. There were no significative differences regarding vital parameters at admission, excepting for the PaO2/FiO2 ratio, which was significantly lower in patients that died during the hospitalization period, as compared to survivors (264 ± 88 vs 338 ± 91, respectively; $P < .001$; Table 1). Total bilirubin, creatinine, LDH, ferritin and D-dimer levels were significantly higher while platelet and lymphocyte counts were significantly lower in patients who died during the study (Table 1).

Using logistic regression analysis, age higher than 75 years (n = 42, 18.3%), platelet count lower than $150 \times 10^3/mm^3$ (n = 52, 22.7%) and ferritin levels higher than 750 ng/mL (n = 99, 43.2%) were independent predictors of death, as shown in Table 2, resulting in an area under ROC curve of 0.87 (Figure 1).

4 | DISCUSSION

Rapid spread of SARS-CoV-2 all over the world has raised the need to optimize medical resources in order to minimize the ongoing crisis of Health Care Systems in pandemic areas.

Early identification of patients with worst predictable outcome would help physicians in the clinical management and the creation of protocol of safety.

In our analysis, our aim was to identify risk factors for a predictor model in COVID-19 patients accessing to ER with mild symptoms. Presenting symptoms, comorbidities, vital signs and laboratory findings at admission was collected.

Older age and comorbidities have been associated with increased risk of death in COVID-19 [6-8,11,16,17]; we confirm that age and comorbidities (one among arterial hypertension, diabetes coronary heart disease (CHD), atrial fibrillation, chronic kidney disease and chronic obstructive pulmonary disease (COPD)) have been found to be associated with poor prognosis and increased mortality. In particular, even if in our cohort elderly patients were not highly represented, we observed that age older than 75 years is a strong independent risk factor for death, with almost 50% of mortality in this age subgroup. In line with Chinese cohorts, we reported that ageing is independently associated with worst outcome with an increased 12% risk of death per year.[11] Despite more than 50% of patients in our cohort being affected by at least one comorbidity, comorbidities are not independently associated with mortality at after adjusting for demographic and laboratory findings; suggesting that comorbid conditions do not affect in-hospital mortality.

Laboratory tests in patients with COVID-19 have both diagnostic and prognostic value and also are used for monitoring during hospitalization.[18] Lymphopaenia is common in patients with COVID-19 [7]; however, in our study, it did not reach significance as a prognostic marker. This could be due to both data collection at early one time point and mild-moderate disease. In our cohort, thrombocytopenia at admission was found in almost one-fourth of patients infected by SARS-CoV-2, lower than what previously reported in larger cohorts.[16] This finding could be explained by our study focusing on patients presenting with a mild-moderate form of COVID-19. Indeed, in other studies, platelet count has been validated as a biomarker associated with disease severity and mortality risk in the intensive care unit (ICU).[19-22] In our analysis, thrombocytopenia was an independent risk factor for mortality in COVID-19 despite ICU admission which occurred in only 6 patients out of 229. This was in line with recent studies confirming low platelet count association with increased risk of severe disease, need of mechanical ventilation and mortality in COVID-19.[22] A large analysis of 1476 patients showed the lower the platelet count, the higher the risk.[23] Serum ferritin has been suggested as serological parameter for monitoring prognosis in COVID-19 patients during hospitalization [24]; an increase in its value has been associated with the so called "cytokine storm," anticipating development of ARDS and tissue damage progressing into multiorgan failure (MOF). Wu et al observed that increased serum ferritin was associated with evolution toward ARDS.[25] In our study, we showed for the first-time serum ferritin to be independently associated with increased mortality both at univariate and multivariate analysis.

Our study has several limitations. First, it is a single-centre study conducted on a limited sample of patients that requires external validation. Secondly, given its retrospective design, we could not retrieve a complete clinical and/or serological documentation from all patients. On the other hand, our study benefits from being conducted in an area which has been at the centre of the Italian COVID-19 outbreak. Also, patients were managed by the same team of dedicated physicians who followed codified management protocols granting for homogeneous standard protocol of care and extensive laboratory testing.

5 | CONCLUSIONS

We observed that old age, high ferritin concentration and platelet count are associated with in-hospital mortality of

hospitalized patients with COVID-19 infection and mild ARDS. External validation by larger database is needed.

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CONFLICT OF INTEREST

All the authors have given substantial contribution to the completion of this work and have seen and approved the text in the current version. None reported a conflict of interest with respect to this manuscript.

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REFERENCES

1. Phelan AL, Katz R, Gostin LO. The novel coronavirus originating in Wuhan, China: challenges for global health governance. *JAMA*. 2020;323(8):709.
2. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. *Lancet Infect Dis*. 2020;20(5):533-534.
3. Zhang N, Wang L, Deng X, et al. Recent advances in the detection of respiratory virus infection in humans. *J Med Virol*. 2020;92(4):408-417.
4. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *JAMA*. 2020;323(13):1239.
5. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. *J Autoimmun*. 2020;109:102433.
6. Verity R, Okell LC, Dorigatti I, et al. Estimates of the severity of coronavirus disease 2019: a model-based analysis. *Lancet Infect Dis*. 2020;20(6):669-677.
7. Myers LC, Parodi SM, Escobar GJ, Liu VX. Characteristics of hospitalized adults with COVID-19 in an integrated health care system in California. *JAMA*. 2020;323(21):2195.
8. Xie J, Tong Z, Guan X, Du B, Qiu H. Clinical characteristics of patients who died of coronavirus disease 2019 in China. *JAMA Netw Open*. 2020;3(4):e205619.
9. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med*. 2020;46:846-848.
10. Yang J, Zheng YA, Gou XI, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. *Int J Infect Dis*. 2020;94:91-95.
11. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *The Lancet*. 2020;395(10229):1054-1062.
12. Tu Y-F, Chien C-S, Yarmishyn AA, et al. A review of SARS-CoV-2 and the ongoing clinical trials. *Int J Mol Sci*. 2020;21(7):2657.
13. Grasselli G, Pesenti A, Cecconi M. Critical care utilization for the COVID-19 outbreak in Lombardy, Italy: early experience and forecast during an emergency response. *JAMA*. 2020;323(16):1545.
14. Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. *JAMA*. 2020;323(18):1775-1776. https://doi.org/10.1001/jama.2020.4683
15. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin definition. *JAMA*. 2012;307:2526-2533.
16. Guan W, Ni Z, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382(18):1708-1720.
17. Liu K, Chen Y, Lin R, Han K. Clinical features of COVID-19 in elderly patients: a comparison with young and middle-aged patients. *J Infect*. 2020;80(6):e14-e18.
18. Terpos E, Ntanasis-Stathopoulos I, Elalamy I, et al. Hematological findings and complications of COVID-19. *Am J Hematol*. 2020;95(7):834-847.
19. Mattiuzzi C, Lippi G. Which lessons shall we learn from the 2019 novel coronavirus outbreak? *Ann Transl Med*. 2020;8(3):48.
20. Khurana D, Deoke SA. Thrombocytopenia in critically ill patients: clinical and laboratorial behavior and its correlation with short-term outcome during hospitalization. *Indian J Crit Care Med*. 2017;21(12):861-864.
21. Vanderschueren S, De Weerdt A, Malbrain M, et al. Thrombocytopenia and prognosis in intensive care. *Crit Care Med*. 2000;28(6):1871-1876.
22. Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: a meta-analysis. *Clin Chim Acta*. 2020;506:145-148.
23. Yang X, Yang Q, Wang Y, et al. Thrombocytopenia and its association with mortality in patients with COVID-19. *J Thromb Haemost*. 2020;18(6):1469-1472.
24. Henry BM, de Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. *Clin Chem Lab Med*. 2020;58(7):1021-1028.
25. Wu C, Chen X, Cai Y, et al. Factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med*. 2020; https://doi.org/10.1001/jamainternmed.2020.0994

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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