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Prognostic value of routine blood parameters in intensive care unit COVID-19 patients

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ABSTRACT

Introduction

Laboratory medicine has an important role in the management of COVID-19. The aim of this study was to analyze routinely available blood parameters in intensive care unit COVID-19 patients and to evaluate their prognostic value.

Patients and methods

This is a retrospective, observational, single-center study including consecutive severe COVID-19 patients who were admitted into the intensive care unit of Ben Arous Regional Hospital in Tunisia from 28 September 2020 to 31 May 2021. The end point of the study was either hospital discharge or in-hospital death. We defined two groups based on the outcome: survivors (Group 1) and non-survivors (Group 2). Demographical, clinical, and laboratory data on admission were collected and compared between the two groups. Univariate

and multivariate logistic regression analysis were performed to determine the predictive factors for COVID-19 disease mortality.

Results

A total of 150 patients were enrolled. Eighty patients (53.3%) died and 70 (46.7%) survived during the study period. Based on statistical analysis, median age, Simplified Acute Physiology Score (SAPS II) with the serum levels of urea, creatinine, total lactate dehydrogenase (LDH), creatine kinase, procalcitonin and hs-troponin I were significantly higher in non-survivors compared to survivors. On multivariate analysis, LDH activity ≥ 484 U/L (OR=17.979; 95%CI [1.119-2.040]; p = 0.09) and hs-troponin I ≥ 6.55 ng/L (OR=12.492; 95%CI [1.691- 92.268]; p = 0.013) independently predicted COVID-19 related mortality.

Conclusion

Total LDH and hs-troponin I were independent predictors of death. However, further clinical investigations with even larger number of patients are needed for the evaluation of other laboratory biomarkers which could aid in assessing the prediction of mortality.

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INTRODUCTION

The outbreak of the SARS-CoV-2 infection began in Wuhan, Hubei, China and spread rapidly around the world (1). Since March 2020, Coronavirus Disease 2019 (COVID-19) has been declared as a pandemic (2). The clinical manifestations of COVID-19 vary highly, ranging from asymptomatic or mild infection to severe forms of pneumonia requiring hospitalization at intensive care unit (ICU). In severe forms, respiratory distress syndrome may be often accompanied by life-threatening multi-organ failure (3). Several recent studies have investigated serum biomarkers closely associated with COVID-19 severity (4). However, only a few studies have focused on the prognostic role of laboratory findings in ICU COVID-19 patients.

Therefore, the aim of this study was to analyze routine blood parameters of severe COVID-19 patients and to explore the mortality predicting factors in these ICU patients.

SUBJECTS AND METHODS

Study population

It is a retrospective, observational, single-center study including all patients hospitalized between 28 September 2020 to 31 May 2021 in a Tunisian ICU in Ben Arous Regional Hospital. COVID-19 infection was confirmed by using reverse-transcriptase polymerase-chain reaction (RT-PCR) assay, and/or a rapid antigen test, and/or a chest computed tomography scan (CT), and/or a positive serological test (positive for serum SARS-CoV-2 specific IgM or IgM and IgG antibodies). We excluded those patients who were still under treatment at the time of data collection. Two groups were defined: survivors (Group 1) and non-survivors (Group 2).

Data collection

Demographical, clinical, and laboratory data were collected and statistically analyzed. These data involved age, gender, comorbidities (hypertension, diabetes mellitus, dyslipidemia, coronary heart disease, kidney disease, respiratory disease, thyroid disorders, obesity) and the Simplified Acute Physiology Score (SAPS II) which is a severity clinical score and mortality estimation tool. It was designed to measure the severity of disease for patients admitted to ICU aged 15 years or above. The score is made of 12 physiological variables and 3 disease-related variables. Score point ranges between 0 and 163 and a predicted mortality between 0% and 100% (5).

The measurement of routinely available blood tests was performed on the date of ICU admission in the Central Laboratory of Ben Arous Regional Hospital. The laboratory tests included general parameters, such as C-reactive protein (CRP), procalcitonin (PCT), complete blood count and D-dimer. Hs-troponin I measurement was performed on admission since its prognostic value has been reported in several studies.

Evaluation criteria

Patients were followed up during their hospitalization. Our study's primary endpoint was COVID-19 related mortality. The clinical and laboratory data were compared between the two study groups.

Statistical analysis

Statistical analysis was performed with SPSS version 25.0 software. Continuous variables were presented as median values with interquartile range (IQR) and were compared by the Student's t-test or Mann-Whitney U-test according to the normality of the distribution. Qualitative variables were presented as counts and percentages and were compared by the Pearson χ^2 and Fisher's exact tests. Univariate and multivariate logistic regression analysis was used to determine the predictive factors for COVID-19 disease mortality. A p value < 0.05 was considered to be statistically significant.

RESULTS

Demographical and clinical characteristics of COVID-19 patients

In this study, 150 patients, 88 men and 62 women (gender-ratio M/F=1.41), were enrolled. The median age was 64.5 years. Among study participants, 121 patients (80.66%) had at least one comorbidity, while 47 patients (31.3%) were mechanically ventilated during ICU treatment.

The following medication was administered before ICU admission: antibiotic therapy (n=104, 69.3%), corticosteroid therapy (n=148, 98.6%),

Table 1 Drugs and other ICU treatment administrated in both study groups

	Group 1 (n=70)	Group 2 (n=80)	p value	RR [95% CI]
Prone position	10	59	0.000	2.636 [1.639; 4.240]
Dialysis	3	12	0.017	1.691 [1.214; 2.356]
Antibiotic therapy	48	56	0.193	1.06 [0.731 ; 2.157]
Corticosteroid therapy	73	75	0.515	1.66 [0.932 ; 1.873]
Curative anticoagulation	35	69	0.000	3.898 [2.043; 7.436]
Mechanical ventilation	16	73	0.000	12.713 [4.903; 32.966]
Tracheotomy	5	4	0.149	0.68 [0.521 ; 2.147]

curative anticoagulation (n=104, 69.3%), and mechanical ventilation (n=89, 59.3%) (Table 1).

Eighty patients (53.3%) in Group 2 died of COVID-19 and 70 individuals (46.7%) survived and were discharged from the hospital (Group 1) (Table 2). The median hospitalization duration in ICU was 10 days for non-survivors (IQR [6, 17.5] days). Mortality causes were the following: hypoxemia (n=99, 66%), septic shock (n=32, 21.3%), cardiogenic shock (n=1, 0.7%), and multi-organ failure (n=18, 12%). We noted one case of coronary syndrome in Group 2 during the hospitalization in ICU.

Comparison of clinical characteristics between the two groups is presented in Table 2. The median age and the SAPS II score were significantly

Table 2 Comparison of clinical characteristics between the two patient groups

Characteristics	Total (n=150)	Group 1 (n= 70)	Group 2 (n=80)	p value
Age (years) median (IQR)	64.5 [20-92]	61 [20-92]	65[31-68]	**0.004**
Gender, n (%) Male Female	 88 (58.7%) 62 (41.3%)	 38(54.3%) 32(45.7%)	 50 (62.5%) 30 (37.5%)	0.324
Median SAPS II score	32 [27-38]	29 [24-33]	34 [29-46]	**<0.001**
Comorbidities, n (%)	121 (80.6%)	58 (82.8%)	63 (78.7%)	0.52
Hypertension, n (%)	68 (45.3%)	27 (38.6%)	41 (51.2%)	0.14
Diabetes mellitus, n (%)	61(40.7%)	28 (40%)	41 (51.2%)	0.876
Dyslipidemia, n (%)	19 (12.7%)	9 (12.9%)	10 (12.5%)	0.948
Coronary disease, n (%)	24 (16%)	11 (15.7%)	13 (16.3%)	0.929
Renal disease, n (%)	10 (6.7%)	4 (5.7%)	6 (7.5%)	0.752
Respiratory disease, n (%)	23 (15.3%)	11 (15.7%)	12 (15%)	0.904
Thyroid disorders, n (%)	8 (5.3%)	5 (7.1%)	3 (3.8%)	0.474
Obesity, n (%)	13 (8.7%)	7 (10%)	6 (7.5%)	0.772
Mechanical ventilation, n (%)	97 (64%)	20(28%)	77 (96%)	**<0.001**

*IQR: interquartile range; SAPSII: Simplified Acute Physiology Score. Bold **p values** mean statistically significant difference.*

higher in Group 2 vs Group 1. There was no significant difference in terms of gender and comorbidities (hypertension, diabetes mellitus, dyslipidemia, coronary heart disease, kidney disease, respiratory disease, thyroid diseases and obesity) between the two groups. Mortality ratio was significantly higher in invasive ventilated patients.

Laboratory parameters of COVID-19 survivors and non-survivors

Blood routine parameter results studied on admission are presented and compared between the two groups in Table 3. The levels of blood glucose, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltranspeptidase (GGT), alkaline phosphatases (ALP), total bilirubin, sodium, potassium, chloride, calcium, magnesium, phosphorus, total protein, N-terminal prohormone of brain natriuretic peptide (NT-proBNP), D-dimer, CRP, hemoglobin, white blood cells (WBC), neutrophils, lymphocytes and platelets were not significantly different between the two groups (Table 3). In contrast, blood urea, creatinine, Lactate dehydrogenase (LDH), Creatine kinase (CK), PCT and hs-troponin I levels were significantly higher in Group 2 (non-survivors) than in Group 1 (survivors).

Multivariate analysis

Variables with statistically significant differences between the two groups (median age, SAPS II score, BUN, creatinine, LDH, CK, PCT and hs-troponin I) were included in logistic regression analysis. Accordingly, LDH ≥ 484 U/L (OR=17.979; 95%CI [1.119-2.040]; p = 0.09) and hs-troponin I ≥ 6.55 ng/L (OR=12.492; 95%CI [1.691- 92.268]; p = 0.013) were independent predictors for mortality.

Table 3 Comparison of blood routine parameters between the two groups

Laboratory tests, median (IQR)	Total (n=150)	Group 1 (n=70)	Group 2 (n=80)	p value
Glucose, mmol/L	9.72 (6.64-15.41)	8.87 (6.04-15.64)	10.35 (7.28-15.2)	0.36
ALT, U/L	30 (18.5-44)	33 (20-48.5)	28(18-42)	0.115
AST, U/L	41(27-58)	36 (25-55)	42(28-60)	0.245
GGT, U/L	50.5 (27.7-77.7)	49 (27-78.5)	52(28-80)	0.904
ALP, U/L	65 (52-86.2)	60.5 (49.7-84.2)	69(57-89)	0.055
Total bilirubin, µmol/L	9.05 (6.9-12.7)	8.75 (6.6-12.10)	10 (7.7-13.1)	0.225
Urea, mmol/L	6.85 (5.2-10.95)	5.65(4.45-8.22)	8.85(6.37-13.47)	**<0.01**
Creatinine, µmol/L	71.9 (61.1-104.4)	66.5(55.1-86-1)	77.85(66.5-123.2)	**<0.01**
LDH, U/L	528.5 (411.25-660.75)	480(361-587)	608 (472-740)	**<0.01**

CK, U/L	69.5 (42-209.25)	55.5 (39.2-146.2)	91 (48.5-346.2)	**0.011**
Sodium, mmol/L	137(134-140)	136.5(133-139)	138(136-141)	0.13
Potassium, mmol/L	4.2 (3.9-4.62)	4.15 (3.8-4.6)	4.25 (3.9-4.7)	0.291
Chlorides, mmol/L	102 (99.75-105)	101 (99.75-104)	102 (99.25-105)	0.47
Calcium, mmol/L	2.08 (1.95-2.21)	2.09 (2.00-2.22)	2.04 (1.93-2.2)	0.56
Magnesium, mmol/L	0.9 (0.8-1.0)	0.9 (0.8-1.0)	1.0 (0.9-1.1)	0.50
Phosphorus, mmol/L	0.95 (0.81-1.21)	0.91 (0.79-1.14)	0.96 (0.82-1.28)	0.137
Total protein,g/L	66 (59-70.75)	67 (61-71)	65 (57-70)	0.079
CRP, mg/L	108 (52.8-120)	96(43-112)	118 (68-120)	0.732
hs-Troponin I,ng/L	12.1 (4.6-57.3)	5.5 (3.1-19.4)	21.6 (7.4-125.5)	**<0.001**
NT-proBNP, pg/mL	376 (137-1277)	245 (90.5-738.7)	565 (177-1608)	0.59
PCT, ng/mL	0.22 (0.0057-0.597)	0.1 (0-0.26)	0.32 (0.14-1.35)	**0.002**
D-dimer, ng/mL	1305.47 (738.8-2784.2)	1305 (730-2225)	1371 (732-4142)	0.527
Hemoglobin, g/dL	12.2 (10.87-13.4)	12.2 (10.8-13.4)	12.15 (10.9-13.6)	0.792
WBC, *10^3/µL	10.58 (7.43-13.5)	9.87 (6.77-12.85)	10.89 (8.02-14.5)	0.131
Neutrophils, *10^3/µL	9.41 (6.21-12.04)	8.83 (5.40-11.17)	9.75 (7.30-13.56)	0.076
Lymphocytes, *10^3/µL	0.77 (0.53-1.09)	0.84 (0.60-1.07)	0.69 (0.48-1.13)	0.086
Platelets, *10^3/µL	251 (197-313)	277 (217-327)	232 (184-306)	0.093

ALP: Alkaline phosphatases; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CK: Creatine kinase; CRP: C-reactive Protein; GGT : Gamma-glutamyl-transpeptidase; LDH: Lactate dehydrogenase; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; PCT: Procalcitonin; WBC: White blood cells. Bold p values mean statistically significant difference.

DISCUSSION

COVID-19 is now recognized as a multisystem disease that can cause a complex disorder affecting many organs, which may require ICU hospitalization (6). Our study investigated the demographical profile, pre-existing comorbidities and routine blood parameters of 150 COVID-19 patients hospitalized in ICU comparing survivors and non-survivors. The clinical features in our study were comparable with other studies (7). Mortality reported in the literature ranges from 30 to 80% (8–13). These differences can be explained by the wide variety and population heterogeneity in different clinical studies. Economic and organizational obstacles in some countries may also partly explain the worse outcomes. For instance, the reduced number of ICU beds in developing countries may delay the hospitalization of severe COVID-19 patients in ICU wards.

As in other cohorts, the demographical and clinical risk factors for mortality were the age, SAPS II score and need for mechanical ventilation. Comorbidities did not significantly influence the COVID-19 related mortality in our study. Many authors showed that comorbidities were associated with a higher risk for death in patients with COVID-19. Estenssoro *et al.* identified cardiovascular disease, chronic kidney disease and diabetes as important mortality risk factors in mechanically-ventilated COVID-19 patients (14). The gender role in mortality was observed in different series; male gender was associated with worse outcomes and death (7). In our study, non-survivors were predominantly males (50 vs. 30). These non-significant differences can be explained by the retrospective nature of the study and the relatively low number of recruited patients.

Consistent with previous findings, univariate analysis showed that urea, creatinine, PCT, total LDH, CK and hs-troponin I were significantly different between the two groups. Renal injury was frequently reported in patients with COVID-19, even in those who had no underlying kidney disease (15). The systemic immune response to the SARS-COV-2 leading to so-called a cytokine storm can be an explanation for the high prevalence of kidney injury in patients with COVID-19 (16,17). Therefore, kidneys may be a susceptible target of the SARS-COV-2 infection. Elevated level of urea at admission maybe an indicator for early kidney injury. Consequently, early detection of acute kidney injury may facilitate appropriate treatment, including avoiding nephrotoxic drugs and adequate fluid therapy (2).

We also found that PCT was significantly associated with death without being an independent factor of mortality. Similarly, a study investigating this marker as a COVID-19 mortality predictor, showed an upward trend of acute-phase proteins, including PCT in non-survivors, and a stable or downward trend in survivors (18). PCT levels appeared to be disease-severity-dependent and may be associated with bacterial co-infection (19). In addition, a recent study hypothesized that a progressive increase in PCT levels may predict a worse prognosis (20). Consistently to other studies, CK, a marker of muscle tissue damage, was associated with an increased mortality in patients with COVID-19 (21,22).

It is relatively common that COVID-19 patients have clinical signs of dehydration and hypovolemia. This may contribute to renal impairment and consequently to a mild increase in CK levels. In addition, muscle damage and CK elevation, even without respiratory symptoms, should be considered as a potential COVID-19 manifestation. Consequently, it is important to monitor CK levels in COVID-19 patients, especially when they complain of muscle pain and weakness (23).

We used logistic regression analysis to screen independent significant factors associated with in hospital-mortality in ICU. LDH ≥ 484 U/L (OR=17.979; [95% CI: 1.119-2.04]; p = 0.09) was an independent predictor for mortality. LDH, an ubiquitous enzyme, is well recognized as a prognostic marker related to the severity of several pathologies. LDH elevation in COVID-19 occurs in cell lysis syndrome and may reflect the extent of lung and other tissue damage (24-26). Additionally, LDH levels are elevated in thrombotic microangiopathy, which is associated with renal failure and myocardial injury (25). In the latter, the elevation of LDH can be associated to the elevation of troponin. In our study, hs-troponin I ≥ 6.55 ng/L (OR=12.492; 95% CI [1.691-92.268]; p = 0.013) was an independent predictor of mortality. Interestingly, a meta-analysis concluded that cardiac injury biomarkers mainly increased in COVID-19 non-survivors (26). Data on acute myocardial injury associated with COVID-19 shows a very strong independent association between increased troponin concentrations and disease severity, including mortality. It has been hypothesized that the acute inflammatory response in COVID-19 disease can cause rupture of atherosclerotic plaques leading to ischemia. Inflammation also causes endothelial dysfunction and increases the procoagulant activity of the blood, which can contribute to the formation of an occlusive thrombus over a ruptured coronary plaque (27,28).

In contrast to other studies, we did not find any prognostic value of CRP. However, Zhang et al. did not find any significant difference in CRP levels between survivors and non-survivors on ICU admission. However, at 1-3 days after admission CRP levels were significantly altered between the two groups (29). Interestingly, D-dimer did not differ between our two groups. The same results were reported by a multicentric study including 1260 patients (30). However, this marker has been considered as a prognostic marker in COVID-19 (31). Survival analysis by Zhang *et al*. find an association between 14-day mortality and an increase in D-dimer with no difference in 7-day mortality rate. Monitoring CRP and D-dimer levels during hospitalization would be interesting to evaluate the prognostic role of these markers.

Our study has several limitations. First, this was a retrospective single center investigation with a relatively low number of patients. Therefore, the only evaluated event was mortality. Second, laboratory parameters were analyzed only at admission. The evaluation of the kinetics of some biological markers would be interesting, thus further studies are needed to overcome these limitations.

In conclusion, our study showed that the levels of LDH and troponin on admission, were independent predictors of mortality. This can help clinicians to predict disease prognosis and perform early therapeutic interventions.

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Ethical approval

The study was approved by the Institutional Ethics Committee and was in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

REFERENCES

1. Liu Y, Yang Y, Zhang C, Huang F, Wang F, Yuan J, et al. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. Sci China Life Sci. 2020;63(3):364-74.

2. Ye B, Deng H, Zhao H, Liang J, Ke L, Li W. Association between an increase in blood urea nitrogen at 24 h and worse outcomes in COVID-19 pneumonia. Ren Fail. 2021;43(1): 347-50.

3. Bennouar S, Bachir Cherif A, Kessira A, Hamel H, Boudahdir A, Bouamra A, et al. Usefulness of biological markers in the early prediction of corona virus disease-2019 severity. Scandinavian Journal of Clinical and Laboratory Investigation. 2020;80(8):611-8.

4. Cheng A, Hu L, Wang Y, Huang L, Zhao L, Zhang C, et al. Diagnostic performance of initial blood urea nitrogen combined with D-dimer levels for predicting in-hospital mortality in COVID-19 patients. Int J Antimicrob Agents. 2020; 56(3):106110.

5. Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/ North American multicenter study. JAMA. 1993;270(24): 2957-63.

6. Roberts CM, Levi M, McKee M, Schilling R, Lim WS, Grocott MPW. COVID-19: a complex multisystem disorder. Br J Anaesth. 2020;125(3):238-42.

7. Jin JM, Bai P, He W, Wu F, Liu XF, Han DM, et al. Gender Differences in Patients With COVID-19: Focus on Severity and Mortality. Front Public Health. 2020;8:152.

8. 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):1239-42.

9. Grasselli G, Greco M, Zanella A, Albano G, Antonelli M, Bellani G, et al. Risk Factors Associated With Mortality Among Patients With COVID-19 in Intensive Care Units in Lombardy, Italy. JAMA Intern Med. 2020;180(10):1345-55.

10. Ñamendys-Silva SA, Gutiérrez-Villaseñor A, Romero-González JP. Hospital mortality in mechanically ventilated COVID-19 patients in Mexico. Intensive Care Med. 2020;46(11):2086-8.

11. Ranzani OT, Bastos LSL, Gelli JGM, Marchesi JF, Baião F, Hamacher S, et al. Characterisation of the first 250 000 hospital admissions for COVID-19 in Brazil: a retrospective analysis of nationwide data. The Lancet Respiratory Medicine. 2021;9(4):407-18.

12. COVID-ICU Group on behalf of the REVA Network and the COVID-ICU Investigators. Clinical characteristics and day-90 outcomes of 4244 critically ill adults with COVID-19: a prospective cohort study. Intensive Care Med. 2021;47(1):60-73.

13. Ferrando C, Suarez-Sipmann F, Mellado-Artigas R, Hernández M, Gea A, Arruti E, et al. Clinical features, ventilatory management, and outcome of ARDS caused by COVID-19 are similar to other causes of ARDS. Intensive Care Med. 2020;46(12):2200-11.

14. Estenssoro E, Loudet CI, Ríos FG, Kanoore Edul VS, Plotnikow G, Andrian M, et al. Clinical characteristics and outcomes of invasively ventilated patients with COVID-19 in Argentina (SATICOVID): a prospective, multicentre cohort study. Lancet Respir Med. 2021;9(9):989-98.

15. Meena P, Bhargava V, Rana DS, Bhalla AK, Gupta A. COVID-19 and the kidney: A matter of concern. Curr Med Res Pract. 2020;10(4):165-8.

16. He Q, Mok TN, Yun L, He C, Li J, Pan J. Single-cell RNA sequencing analysis of human kidney reveals the presence of ACE2 receptor: A potential pathway of COVID-19 infection. Mol Genet Genomic Med. 2020;8(10):e1442.

17. Werion A, Belkhir L, Perrot M, Schmit G, Aydin S, Chen Z, et al. SARS-CoV-2 causes a specific dysfunction of the kidney proximal tubule. Kidney International. 2020;98(5): 1296-307.

18. Chen R, Sang L, Jiang M, Yang Z, Jia N, Fu W, et al. Longitudinal hematologic and immunologic variations associated with the progression of COVID-19 patients in China. Journal of Allergy and Clinical Immunology. 2020;146(1): 89-100.

19. Hu R, Han C, Pei S, Yin M, Chen X. Procalcitonin levels in COVID-19 patients. Int J Antimicrob Agents. 2020;56(2): 106051.

20. Lippi G, Plebani M. Laboratory abnormalities in patients with COVID-2019 infection. Clin Chem Lab Med. 2020;58(7):1131-4.

21. Akbar MR, Pranata R, Wibowo A, Lim MA, Sihite TA, Martha JW. The prognostic value of elevated creatine kinase to predict poor outcome in patients with COVID-19 - A systematic review and meta-analysis. Diabetes Metab Syndr. 2021;15(2):529-34.

22. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, Ma K, Xu D, Yu H, Wang H, Wang T, Guo W, Chen J, Ding C, Zhang X, Huang J, Han M, Li S, Luo X, Zhao J, Ning Q. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ. 2020;368:m1091.

23. Rivas-García S, Bernal J, Bachiller-Corral J. Rhabdomyolysis as the main manifestation of coronavirus disease 2019. Rheumatology (Oxford). 2020;59(8):2174-6.

24. Li X, Xu S, Yu M, Wang K, Tao Y, Zhou Y, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol. 2020;146(1):110-8.

25. Zhang J, Wang X, Jia X, Li J, Hu K, Chen G, et al. Risk factors for disease severity, unimprovement, and mortality in COVID-19 patients in Wuhan, China. Clinical Microbiology and Infection. 2020;26(6):767-72.

26. Yuan J, Zou R, Zeng L, Kou S, Lan J, Li X, et al. The correlation between viral clearance and biochemical outcomes of 94 COVID-19 infected discharged patients. Inflamm Res. 2020;69(6):599-606.

27. Patschan D, Witzke O, Dührsen U, Erbel R, Philipp T, Herget-Rosenthal S. Acute myocardial infarction in thrombotic microangiopathies - clinical characteristics, risk factors and outcome. Nephrol Dial Transplant. 2006; 21(6):1549-54.

28. Zhang T, Chen H, Liang S, Chen D, Zheng C, Zeng C, et al. A Non-Invasive Laboratory Panel as a Diagnostic and Prognostic Biomarker for Thrombotic Microangiopathy: Development and Application in a Chinese Cohort Study. PLoS One. 2014;9(11):e111992.

29. Zhang W, Sang L, Shi J, Zhong M, Jiang L, Song B, et al. Association of D-dimer elevation with inflammation and organ dysfunction in ICU patients with COVID-19 in Wuhan, China: a retrospective observational study. Aging (Albany NY). 2021;13(4):4794-810.

30. Zanella A, Florio G, Antonelli M, Bellani G, Berselli A, Bove T, et al. Time course of risk factors associated with mortality of 1260 critically ill patients with COVID-19 admitted to 24 Italian intensive care units. Intensive Care Med. 2021;47(9):995-1008.

31. Short SAP, Gupta S, Brenner SK, Hayek SS, Srivastava A, Shaefi S, et al. D-dimer and Death in Critically Ill Patients With Coronavirus Disease 2019. Crit Care Med. 2021; 49(5):e500-11.