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The effect of diagnostic value of biochemical parameters on mortality in COVID-19 patients

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Abstract

The present study aims to investigate the effect of the predictive value of Neutrophil to Lymphocyte Ratio (NLR) and several routine laboratory tests on mortality in patients with positive Coronavirus disease-2019 (COVID-19) tests who were treated at Istanbul Training and Research Hospital. Routine laboratory data of patients with positive COVID-19 Real Time-Polymerase Chain Reaction (RT-PCR) results were obtained via the hospital information system. The laboratory tests included ferritin, C-reactive protein (CRP), lactate dehydrogenase (LDH), aspartate transaminase, creatinine, urea, D-dimer, neutrophil, and lymphocyte count. The number of patients was 2774 and they were admitted to Istanbul Training and Research Hospital between March 10 and June 10, 2020. The statistical data were obtained using SPSS 17.0 version. The patients were divided into two groups, one for mortality (n= 74 patients) and the other for non-mortality (N=2700 patients). In both mortality and non-mortality groups, the ratio of males was higher than females and the difference was not significant ($p>0.05$). 87.8% of those who lost their lives were treated in the intensive care unit ($p<0.05$). All parameters were statistically significant between mortality and non-mortality groups ($p<0.05$). In patients with mortality, diabetes mellitus, hypertension, chronic obstructive pulmonary disease (COPD), malignity, kidney failure, immunosuppressive treatment, and COVID-19-associated computerized tomography findings were higher ($p<0.05$). By the univariate analysis outcomes, all research parameters were significantly associated with mortality ($p<0.05$). Binary logistic regression analysis demonstrated that NLR, CRP, and LDH had predictive values for mortality in multivariate analysis ($p<0.05$). It is prominent that the NLR, CRP, and LDH were discrete from all other parameters and had a high predictive value among the values at the time of admission to the hospital in the study.

Keywords: COVID-19, biochemical tests, hemogram parameters, immunochemical method, mortality

Introduction

In December 2019, pneumonia cases induced by a new coronavirus called Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) were first seen in the Hubei province of China. The disease caused by SARS-CoV-2 and named Coronavirus disease- 2019 (COVID-19) spread rapidly around the world and the epidemic was proclaimed a pandemic by the World Health Organization (WHO) on March 11, 2020 [1,2].

COVID-19 first presents as an infection of the lower airways spread by air droplets, but then the multisystemic feature of the disease becomes evident. While the lungs are the main target organ, COVID-19 can have severe effects on many other important organs, such as the brain, gastrointestinal tract, kidney, heart, liver, and vascular system [3,4].

COVID-19 cases may include patients with asymptomatic carriers, common symptoms, such as headache, tiredness, dry cough, and fever, as well as patients with severe clinical conditions like heart failure, acute respiratory distress syndrome (ARDS), septic shock, thrombosis, lung tissue damage, and multi-organ insufficiency [5].

Therewithal, biochemical tests have an effective and prominent place in the diagnosis and following of COVID-19 patients, staging the severity of the disease, determining the prognosis, evaluating complications, and responding to treatment. For this purpose, many biochemical tests such as hematological parameters, coagulation parameters, and cardiac, inflammatory, liver, and kidney function tests have been measured [6,7].

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Moreover, algorithms that can be helpful for COVID-19 are created using data such as laboratory test results, and radiological, clinical, and epidemiological information. These can be guiding in early diagnosis, classification, and prognosis [8].

Additionally, the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) shares recommendations and knowledge established on current literature on both information regarding COVID-19 and the intended usage, choice, assessment, and application of laboratory tests [9,10].

In the current study, it was purposed to assess the effect of the predictive value of Neutrophil to Lymphocyte Ratio (NLR), lactate dehydrogenase (LDH), C-reactive protein (CRP), and some other biochemical tests on mortality in COVID-19 Real-Time-Polymerase Chain Reaction (RT-PCR) positive patients who applied to Istanbul Training and Research Hospital where was determined as a pandemic hospital after the first case was officially reported in our country.

Materials and Methods

Study Population

This study analyzed the data collected COVID-19 RT-PCR (+) 2774 patients' laboratory values and clinical features at admission and last at departure were obtained retrospectively between 10 March and 10 June 2020 from the hospital/laboratory information system of Istanbul Training and Research Hospital. Patients under the age of 18, who had missing research parameters for hospital admission were excluded from the study. Laboratory parameters were compared by grouping the patients as mortality (n=74) and non-mortality (n=2700). The Medical Ethics Committee of Istanbul Training and Research Hospital (Decision Date & Number: June 12, 2020/2401) approved this study, which conformed to the Helsinki Declaration.

Laboratory Analysis

COVID-19 was diagnosed only in patients identified as SARS-CoV-2 by RT-PCR in nasopharyngeal and oropharyngeal swabs at our hospital during the research period. Sysmex XN-1000/9000 (Sysmex Corporation, Kobe, Japan) was used for the hemogram. Routine biochemical parameters such as LDH, CRP, aspartate transaminase (AST), creatinine, and urea were measured by AU680/5800 analyzers (Beckman Coulter Inc., Brea, CA, USA) from serum. Ferritin was assessed by an immunoassay of chemiluminescence DxI800/Access 2 Analyzers (Beckman Coulter Inc., Brea, CA, USA). D-dimer was determined with BCS-XP analyzers (Siemens Healthcare GmbH, Erlangen, Germany).

Statistical Analysis

Frequency analysis was used to represent categorical data, whereas mean and standard deviation or median (25th-75th percentile) were used to represent continuous variables. A Chi-square test was performed to compare categorical variables. The Kolmogorov-Smirnov test was employed to check the parameters' normality. The Independent Samples T-test was used for parameters with a normally distributed distribution, whereas the Mann-Whitney U test was employed for parameters with a non-normal distribution. Binary logistic regression analysis was used for multivariate analysis of parameters. For the diagnostic value of laboratory parameters, Receiver Operating Curve (ROC) analysis was used. The Youden index was used to determine the optimal cut-off value. All analysis was performed at SPSS (version 17.0, SPSS Inc, Chicago, United States) for windows at a 95% confidence interval. The p-value was regarded as significant when it was less than 0.05.

Results

2774 RT-PCR (+) patients were divided into two groups mortality (n=74) and non-mortality (n=2700). The mortality group's average age was shown to be significantly higher than the non-mortality group's ($p<0.001$). In both groups, male patients were more frequent with a statistically insignificant difference ($p=0.561$). Of the mortality group, 9.5% were treated in the service, 2.7% in outpatient treatment, and 87.8% in the intensive care unit ($p<0.001$). Diabetes mellitus (DM), hypertension (HT), chronic obstructive pulmonary disease (COPD), malignancy, chronic kidney disease (CKD), immunosuppressive treatment, and COVID-19 compatible computerized tomography (CT) findings were more common in the mortality group ($p<0.05$) (Table 1).

Table 1. Demographic and comorbidity parameters comparisons based on mortality groups

Parameter	Non-mortality (n=2700; 97.3%)	Mortality (n=74; 2.7%)	P
Females, n (%)	1149(42.6)	34(45.9)	0.561[a]
Age, (years)	41(29-53)	70(57-78)	<0.001[b]
Service, n (%)	1386(51.3)	7(9.5)	<0.001[a]
Outpatient, n (%)	1306(48.4)	2(2.7)	
Intensive Care Unit, n (%)	8(0.3)	65(87.8)	
DM, n (%)	84(3.1)	10(13.5)	<0.001[a]
HT, n (%)	112(4.1)	14(18.9)	<0.001[a]
COPD, n (%)	43(1.6)	5(6.8)	0.001[a]
Malignancy, n (%)	22(0.8)	7(9.5)	<0.001[a]
CKD, n (%)	15(0.6)	4(5.4)	<0.001[a]
Immunosuppressive treatment, n (%)	15(0.6)	6(8.1)	<0.001[a]
COVID-19 compatible CT findings, (among patients with CT) n (%)	310(41.7)	8(100.0)	<0.001[a]

[a]: Chi-Square test, [b]: Mann Whitney-U test, SD: standard deviation, DM: diabetes mellitus, HT: hypertension, COPD: chronic obstructive pulmonary disease, CKD: chronic kidney disease, CT: computerized tomography

According to different analysis results, all parameter differences were statistically significant between mortality groups (p<0.05). While lymphocyte levels were statistically significantly lower in the mortality group, other parameters were higher in the mortality group (Table 2).

All research parameters had a significant relationship with mortality (p<0.05) in the univariate regression analysis (Table 3).

NLR, ferritin, CRP, D-dimer, LDH, AST, creatinine, and urea that had a significant relationship according to the results of the univariate regression analysis were included in the multivariate regression (p<0.05). Binary logistic regression analysis (in multivariate analysis) indicated that NLR>4.41, CRP>57.3, LDH>286 would have predictive value for COVID-19-related in-hospital mortality, respectively [odds ratio (95% CI)=5.087 (1.988-133.0), p=0.001, odds ratio (95% CI)=10.15 (2.466-41.78), p=0.001, odds ratio (95% CI)=4.259 (1.457-12.45), p=0.008] (Table 3).

For NLR >4.41 cut-off value, sensitivity was 83.1%, specificity was 85.2% and Area Under Curve (AUC) for ROC analysis was 0.882 (95% CI=0.837-0.926). For CRP >57.3 cut-off value, sensitivity was 90.0%, specificity was 87.6% and AUC for ROC analysis was 0.942 (95% CI=0.931-0.951). For LDH >286 cut-off value, sensitivity was 82.6%, specificity was 76.3% and AUC for ROC analysis was 0.841 (95% CI=0.817-0.862) (Table 4), (Figure 1).

Table 2. Laboratory parameters comparisons based on mortality groups

Parameter	Non-mortality (n=2700; 97.3%)	Mortality (n=74; 2.7%)	P value
Neutrophil (10^9/L)	3.41(2.52-4.59)	6.39(4.17-9.31)	<0.001[a]
Lymphocyte (10^9/L)	1.56(1.14-2.09)	0.85(0.62-1.18)	<0.001[a]
NLR	2.09(1.44-3.35)	6.99(4.87-11.97)	<0.001[a]
Ferritin (µg/L)	78.10(32.80-177.6)	239.2(134.8-672.2)	<0.001[a]
CRP (mg/L)	8.17(3.13-23.72)	132.4(88.3-210.1)	<0.001[a]
D-dimer (µg/mL)	0.49(0.32-0.80)	1.39(0.86-3.52)	<0.001[a]
AST (U/L)	27.00(21.00-37.00)	37.00(26.39-66.00)	<0.001[a]
Creatinine (mg/dL)	0.76(0.63-0.90)	0.93(0.68-1.45)	<0.001[a]
Urea (mg/dL)	27.20(21.40-34.20)	45.00(30.45-66.67)	<0.001[a]
LDH (U/L)	222(181-284)	389(295-553)	<0.001[a]

[a]: Mann Whitney-U test, CRP: C-reactive protein, AST: aspartate transaminase, LDH: lactate dehydrogenase, NLR: neutrophil to lymphocyte ratio

Table 3. Binary Logistic regression analysis results for mortality

Unadjusted Univariate Regression				Adjusted Multivariate Regression			
Parameter	**OR***	**%95 CI**	**P****	**Parameter**	**OR***	**%95 CI**	**P****
NLR (>4.41)	28.2	15.0-53.0	<0.001	NLR (>4.41)	5.09	1.99-13.0	**0.001**
Ferritin (>106.1 µg/L)	10.7	4.15-27.5	<0.001	Ferritin (>106.1 µg/L)	0.42	0.11-1.61	0.206
CRP (>57.3 mg/L)	63.5	28.8-140	<0.001	CRP (>57.3 mg/L)	10.2	2.47-41.8	**0.001**
D-dimer (>0.63 µg/mL)	16.6	7.08-39.1	<0.001	D-dimer (>0.63 µg/mL)	1.78	0.58-5.43	0.313
LDH (>286 U/L)	15.3	8.04-28.9	<0.001	LDH (>286 U/L)	4.26	1.46-12.5	**0.008**
AST (>33.6 U/L)	3.44	2.09-5.68	<0.001	AST (>33.6 U/L)	0.44	0.17-1.12	0.085
Creatinine (>1.06 mg/dL)	7.11	4.29-11.8	<0.001	Creatinine (>1.06 mg/dL)	1.33	0.47-3.79	0.590
Urea (>34.7 mg/dL)	9.11	5.25-15.8	<0.001	Urea (>34.7 mg/dL)	1.41	0.50-3.96	0.515
Age (years)	1.10	1.07-1.11	<0.001	Age (years)	1.03	0.99-1.06	0.091

*: Odds ratio in the binary logistic regression model, **: p significance level was accepted as <0.05. CI: confidence interval, CRP: C-reactive protein, AST: aspartate transaminase, LDH: lactate dehydrogenase, NLR: neutrophil to lymphocyte ratio

Table 4. Receiver Operating Curve (ROC) analysis results for laboratory parameters

Parameter	Cut-off	Sensitivity %	Specificity %	Area Under Curve (95% CI)	P*
NLR	>4.41	83.10	85.20	0.882(0.837-0.926)	<0.001
Ferritin (µg/L)	>106.1	87.18	61.09	0.791(0.767-0.814)	<0.001
CRP (mg/L)	>57.3	90.00	87.62	0.942(0.931-0.951)	<0.001
D-dimer (µg/mL)	>0.63	89.47	66.18	0.846(0.825-0.866)	<0.001
LDH (U/L)	>286	82.61	76.25	0.841(0.817-0.862)	<0.001
AST (U/L)	>33.6	60.29	69.39	0.689(0.663-0.715)	<0.001
Creatinine (mg/dL)	>1.06	45.07	89.65	0.659(0.632-0.685)	<0.001
Urea (mg/dL)	>34.7	74.65	75.56	0.757(0.733-0.781)	<0.001

*: p significance level was accepted as <0.05. CI: confidence interval, CRP: C-reactive protein, AST: aspartate transaminase, LDH: lactate dehydrogenase, NLR: neutrophil to lymphocyte ratio

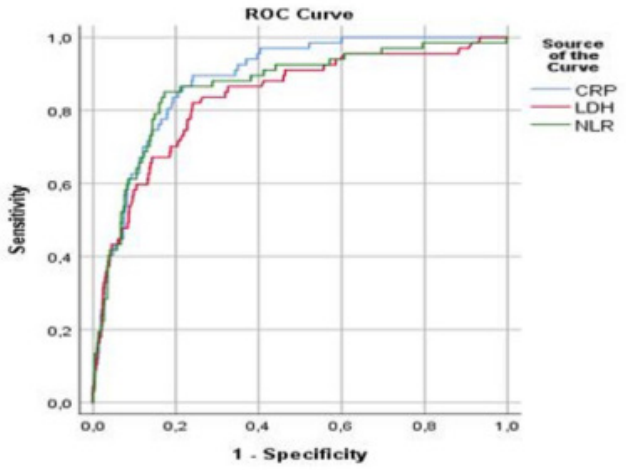

Figure 1. ROC analysis results for the diagnostic value of NLR, CRP, and LDH on COVID-19 mortality

Discussion

In this study, we evaluated the predictive values of some biochemical parameters (neutrophil count, lymphocyte count, NLR, ferritin, CRP, D-dimer, AST, creatinine, urea, LDH) on mortality in COVID-19 RT-PCR positive patients. In all of the analytes we evaluated, parameter differences were statistically significant between non-mortality and mortality groups. Moreover, it was demonstrated that NLR, CRP, and LDH could have predictive value for COVID-19-related in-hospital mortality.

Since it first appeared in December 2019, the COVID-19 outbreak has infected many people globally and some of which have resulted in deaths, according to constantly updated data [11]. In addition, those who have had the disease may develop complications in the future. This pandemic remains a mystery and has no clear diagnosis and treatment. Additionally, the studies reported that, as expected, comorbidities such as DM, HT, COPD, malignancy, CKD, and immunosuppressive therapy were more common in the COVID-19 death group. These comorbidities, which are involved in the pathophysiology of COVID-19 and affect the expression of ACE-2 receptors, which the virus uses to penetrate the host cell, cause the disease to be more severe and even result in death. Age >55 years, several pre-existing diseases, specialized CT images indicating diffuse lung infiltration, various laboratory test abnormalities, and indicators of end-organ failure have been emphasized as findings linked to higher disease severity or death [12,13]. Similar to these findings, our study revealed that the mortality group had more advanced age, COVID-19 - compatible CT findings, and more comorbidity than non-mortality.

In the literature, lymphopenia and neutrophilia were reported to be common hematological disorders in COVID-19 patients, and they were suggested as useful predictors of disease severity and poor prognosis. It was stated that the NLR index was closely associated with the severity of COVID-19 [14-17].

NLR remains an easy-to-use, affordable, near real-time, accessible indicator, particularly for medical institutions with limited healthcare resources, because of its low cost and lack of the requirement for sophisticated assay equipment [18].

The well-known systemic inflammatory marker NLR is frequently used to predict mortality in patients with sepsis and the prognosis of cardiovascular illness. Higher NLR levels at admission were linked with increased risk of severity and mortality in COVID-19, according to a meta-analysis. This finding raises the possibility that this easily accessible indicator might be utilized to predict the prognosis of COVID-19 patients. Various cut-off values were also indicated for NLR, which could be used as a prognostic factor to predict severity and mortality NLR was reported to be an independent predictor for mortality for COVID-19, especially among males [14,19].

In our study, it was demonstrated that a higher NLR value had a significant predictive value for COVID-19-related mortality (Table 3). This finding confirms previous findings in the literature. As a consequence, evaluating NLR might help determine COVID-19 high-risk patients. For COVID-19 patients, clinicians can identify high-risk patients at an early stage and develop treatment algorithms for this, as NLR can be calculated quickly and easily through laboratory information systems based on routine hemograms at hospital admission.

Moreover, the studies reported that significantly elevated CRP level was associated with severe disease status and mortality [20,21,22]. In concordance with previous studies, in our study, the CRP level was significantly elevated in the mortality group. According to its statistical analysis, CRP could have predictive value for COVID-19-related in-hospital mortality (Table 3).

In the literature, elevated LDH was reported as one of the common laboratory abnormalities in COVID-19 patients, and statistically significant high LDH was noted in severe disease and mortality associated with COVID-19 [20,23,24]. Similarly, in the present study, the LDH level was statistically significantly higher in the mortality group. In addition, our study revealed that LDH also could have predictive value for mortality (Table 3).

Furthermore, high serum ferritin level was stated as a poor prognostic factor in COVID-19 patients. The ferritin increase was also reported to be associated with mortality and severe disease in COVID-19 patients [23, 25]. Consistent with the literature, we determined the ferritin level was statistically significantly higher in the mortality group.

In the literature, increased D-dimer was associated with severe disease, poor prognosis, and high mortality in patients with COVID-19. It was stated that the increase in D-dimer was associated with systemic hypercoagulability and frequent venous thromboembolic events [26-29]. Consistent with these findings, in our study, the D-dimer level was found statistically significantly higher in the mortality group.

Additionally, in previous studies, it was reported that increased levels of AST, creatinine, and urea were associated with severe disease and mortality in COVID-19 patients [23,30-32]. Similarly, in our study, ALT, creatinine, and urea levels were statistically significantly higher in the mortality group.

However, in our study, although many other parameters were high in the mortality group, NLR, CRP, and LDH were found to be

independent risk factors among them.

The limitations of this study were the being single-center and retrospective and inaccessibility to all data in the hospital records. Therefore, multicenter, prospective studies are recommended.

Conclusion

Although it is expected that most of the routine biochemical parameters will be high as a result of end-organ damage, vascular damage, and tissue destruction in the mortality group, it is crucial that the NLR, CRP, and LDH differ from all other variables and has a substantial predictive value within the parameters at the hospitalization time. Furthermore, it demonstrates that NLR, CRP, and LDH can effectively minimize the risk of mortality in COVID-19 cases. As a result of our findings, we recommend that NLR, CRP, and LDH parameters can be followed closely in hospitalized patients with a diagnosis of COVID-19.

Conflict of interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical approval
Ethics Committee of Istanbul Training and Research Hospital (Decision Date & Number: June 12, 2020/2401).

References

1. Hang H, Rao Z. Structural biology of SARS-CoV-2 and implications for therapeutic development. Nat Rev Microbiol. 2021;19:685–700.
2. World Health Organisation, WHO. Virtual Press Conference on COVID-19 (2020). https://www.who.int/docs/default-source/coronaviruse/transcripts/who-audio-emergencies-coronavirus-press-conference-full-and-final-11mar2020.pdf?sfvrsn=cb432bb3_2 access date 08.2022
3. Wadman M, Couzin-Frankel J, Kaiser J, Matacic C. A rampage through the body. Science. 2020;368:356-60.
4. Robba C, Battaglini D, Pelosi P, Rocco PRM. Multiple organ dysfunction in SARS-CoV-2: MODS-CoV-2. Expert Rev Respir Med. 2020;14:865-68.
5. Wiersinga WJ, Rhodes A, Cheng AC, et al. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. JAMA. 2020;324:782-93.
6. Tomo S, Karli S, Dharmalingam K, et al. The clinical laboratory: a key player in diagnosis and management of COVID- 19. eJIFCC. 2020;31:326-46.
7. Lippi G, Plebani M. The critical role of laboratory medicine during coronavirus disease 2019 (COVID-19) and other viral outbreaks. Clin Chem Lab Med. 2020;58:1063–9.
8. Alamin AA, Yahia AIO. Hematological Parameters Predict Disease Severity and Progression in Patients with COVID-19: a Review Article. Clin Lab. 2021;67.
9. Lippi G, Horvath AR, Adeli K. Editorial and executive summary: IFCC interim guidelines on clinical laboratory testing during the COVID-19 pandemic. Clin Chem Lab Med. 2020;58:1965–9.
10. International Federation of Clinical Chemistry and Laboratory Medicine. https://www.ifcc.org/resources-downloads/ifcc-information-guide-on-covid-19-introduction/ access date 08.2022
11. World Health Organization, Coronavirus disease 2019 (COVID-19) Situation Report. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports access date 08.2022
12. Ejaz H, Alsrhani A, Zafar A, et al. COVID-19 and comorbidities: Deleterious impact on infected patients. J Infect Public Health. 2020;13:1833–9.
13. Gallo Marin B, Aghagoli G, Lavine K, et al. Predictors of COVID-19 severity: a literature review. Rev Med Virol. 2021;31:1-10.
14. Liu Y, Du X, Chen J, et al. Neutrophil-to-lymphocyte ratio as an independent risk factor for mortality in hospitalized patients with COVID-19. J Infect. 2020;81:e6-12.
15. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-ınfected pneumonia in Wuhan, China. JAMA. 2020;323:1061-9.
16. Liu X, Zhang R, He G. Hematological findings in coronavirus disease 2019: indications of progression of disease. Ann Hematol. 2020;99:1421-8.
17. Khartabil TA, Russcher H, van der Ven A, de Rijke YB. A summary of the diagnostic and prognostic value of hemocytometry markers in COVID-19 patients. Crit Rev Clin Lab Sci. 2020;57:416-31.
18. Guo J, Fang J, Huang X, et al. Prognostic role of neutrophil to lymphocyte ratio and platelet to lymphocyte ratio in prostate cancer: a metaanalysis of results from multivariate analysis. Int J Surg. 2018;60:216–23.
19. Simadibrata DM, Calvin J, Wijaya AD, Ibrahim NAA. Neutrophil-to-lymphocyte ratio on admission to predict the severity and mortality of COVID-19 patients: A meta-analysis. Am J Emerg Med. 2021;42:60-9.
20. Liu Y, Yang Y, Zhang C, et al. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. Sci China Life Sci. 2020;63:364–74.
21. Ruan Q, Yang K, Wang W, et al. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med. 2020;46:846-8.
22. Liu W, Tao Z-W, Lei W, et al. Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease. Chin Med J. 2020;133:1032-8.
23. Henry BM, de Oliveira MHS, Benoit S, et al. 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;58:1021-8.
24. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, et al. Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. Travel Med Infect Dis. 2020;34:101623.
25. Terpos E, Ntanasis-Stathopoulos I, Elalamy I, et al. Hematological findings and complications of COVID-19. Am J Hematol 2020;95:834-47.
26. Cummings MJ, Baldwin MR, Abrams D, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. Lancet. 2020;395:1763–70.
27. Liao D, Zhou F, Luo L, et al. Haematological characteristics and risk factors in the classification and prognosis evaluation of COVID-19: a retrospective cohort study. Lancet Haematol 2020;7:e671–e678.
28. 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. Lancet. 2020;395:1054–62.
29. Wool GD, Miller JL. The Impact of COVID-19 Disease on Platelets and Coagulation. Pathobiology. 2020;13:1–13.
30. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020;8:475-81.
31. Ponti G, Maccaferri M, Ruini C, et al. Biomarkers associated with COVID-19 disease progression. Crit Rev Clin Lab Sci. 2020;57:389-99.
32. Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ. 2020;368:m1091.