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Role of Serum NT-proBNP Levels in Early Prediction of Prognosis in Severe COVID-19 Pneumonia

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ABSTRACT

Introduction: Coronavirus disease-2019 (COVID-19) infection is a viral disease characterized by fast transmission and heterogeneous clinical manifestations in people. Cardiac complications with different clinical presentations are observed during the disease course. In this study, we aimed to determine the importance of the N-terminal of the prohormone brain natriuretic peptide (NT-proBNP) level to predict the prognosis in severe COVID-19 pneumonia and its optimal cut-off value.

Methods: A total of 131 patients who were admitted to a hospital with severe COVID-19 pneumonia and who did not have a history of heart failure, chronic obstructive pulmonary disease, or chronic renal disease were included in the study. Diabetes mellitus and hypertension rates were recorded. Inflammatory markers (ferritin, C-reactive protein, procalcitonin, interleukin-6) and proBNP levels were measured. In-hospital mortality and recovery rates were recorded. The relationship between proBNP levels and chronic disease existence, inflammatory markers, and in-hospital mortality was evaluated using SPSS.

Results: ProBNP levels were significantly higher in the non-survivor group than in the survivor group. The cut-off value of proBNP to predict in-hospital mortality was 650 pg/mL with 87% sensitivity and 62% specificity. The ProBNP >650 pg/mL group had higher hypertension rates, procalcitonin levels, intensive care unit admittance rates, and in-hospital mortality than ProBNP ≤650 pg/mL group ($p<0.05$).

Conclusion: This study showed that NT-proBNP levels can be used to predict prognosis in severe COVID-19 pneumonia and that it is an independent risk factor for in-hospital mortality.

Keywords: COVID-19 pneumonia, NT-proBNP, prognosis

Introduction

The coronavirus disease-2019 (COVID-19) severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) created an unpredictable health catastrophy causing a pandemic. This virus is characterized by quick transmission and affects several organ systems, especially the respiratory system. The clinical spectrum ranges from asymptomatic carriage of infection to critical diseases with multi-organ failure and ARDS resulting in mortality. Although it has been 3 years since the first case was diagnosed in Wuhan, the pandemic continues and mortal cases occur.

Respiratory diseases, particularly pneumonia, are the most common and mortal clinical presentation, but cardiac complications are also common and are related to poor prognosis (1). Cardiac complications can include acute cardiac injury or worsening of a prior cardiac condition. The cardiac injury rate was found to be 19.7% (1) and 27.8% (2) in different studies. The pathogenesis consists of the direct cytopathic effect of virus on cardiomyocytes, systemic inflammation causing oxygen deprivation, thromboinflammation, and endotel dysfunction, and microvascular dysfunction caused by high angiotensin-converting enzyme 2 expression in cardiac capillary pericytes (3-5). Clinical findings include heart failure (HF), abnormal electrocardiography changes, and acute ischemic injury (6).

Although vaccine and medical treatment studies are available, clinical biomarkers are needed to predict prognosis and mortality. Cardiac injury markers are still arguable to predict the amount of cardiac injury (7).

In this study, we aimed to search N-terminal of the prohormone brain natriuretic peptide (NT-proBNP) as a prognostic factor in severe COVID-19 pneumonia, determine its optimal cut-off value for mortality prediction, and evaluate its relationship with common inflammatory markers.

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Methods

Study Design and Participants

This study was designed as a single center, prospective, cross-sectional study. One hundred thirty one patients who had clinical, radiological, and laboratory criteria for severe COVID-19 pneumonia according to the living guidance for clinical management of COVID-19 (3-7) and were admitted to hospital for treatment were included in the study. The protocol for this study was approved by the Ethics Committee of University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 99, date: 11.03.2022). Written informed consent was obtained from the participants. The study complies with relevant ethical regulations and is performed under the Declaration of Helsinki ethical principles for medical research involving human subjects.

All patients' SARS-CoV-2 infection diagnoses were confirmed by oropharyngeal and nasal swap analysis using polymerase chain reaction method. Patients with prior HF, chronic obstructive pulmonary disease, or chronic renal disease were excluded. Diabetes mellitus and hypertension (as most common accompanying diseases of COVID-19 infection) rates and general features were recorded, and inflammatory markers [ferritin, C-reactive protein (CRP), procalcitonin, interleukin-6] and NT-proBNP levels were measured (Table 1).

Primary end points (recovery, in-hospital mortality) were followed and recorded. The relationship between NT-proBNP levels and chronic disease existance, inflammatory markers, in-hospital mortality, and the optimal cut-off value of proBNP were evaluated.

Statistical Analysis

Statistical analysis was performed using SPSS 28.0 for Windows program. Descriptive statistics are reported as mean, standard deviation, median, minimum, maximum, frequency, and percentage values. The distribution of variables was tested with the Kolmogorov-Smirnov test. Quantitative independent data analysis was performed using Independent sample t-test and Mann-Whitney U test. Qualitative independent data analysis was performed using the chi-square test and Fisher's test when the criteria were not met by the chi-square test. The effect size and cut-off point are searched with the ROC curve.

Results

One hundred thirty one patients (mean age: 62.7 years; 47% women) were included in the study. The in-hospital mortality rate among patients was 26% (34 patients). The mean age of the non-survivor group was higher than that of the survivor group. ProBNP and procalcitonin levels were significantly higher in the non-survivor group than in the survivor group. There was no significant difference in gender distribution, HT presence or hemoglobin A1C (HbA1C), ferritin, and CRP levels between the survivor and non-survivor groups. The length of hospital stay showed no difference between the survivor and non-survivor groups. Thirty four patients (11.1% of survivor group and 95.7% of non-survivor group) were referred to the intensive care unit (ICU). ICU referral was significantly higher in the non-survivor group than in the survivor group (Table 2).

NT-ProBNP level was significant in determining the survivor and non-survivor patients [area under the curve: 0.781 (0.691-0.870)]. The cut-off value of NT-proBNP to predict in-hospital mortality was 650 pg/mL [area under the curve 0.745 (0.644-0.846)] with 87% sensitivity,

Table 1. General features and laboratory values of the patients

		Minimum-maximum	Median	Mean ± SD/(n, %)
Age (years)		18.0-96.0	64.0	62.7±17.8
Sex	Female			62 (47.3%)
	Male			69 (52.7%)
Diabetes mellitus	(+)			37 (28.2%)
	(-)			94 (71.8%)
Hypertension	(+)			67 (51.1%)
	(-)			63 (48.1%)
NT-proBNP pg/mL		10.0-12860.0	600.0	1311.7±1967.3
NT-proBNP pg/mL	<650			70 (53.4%)
	>650			61 (46.6%)
HbA1C		5.4-12.1	6.3	6.8±1.4
Ferritin pg/mL		12.0-2000.0	416.0	651.4±562.2
CRP mg/L		0.0-313.0	65.0	81.4±68.0
Prokalcitonin pg/mL		0.02-24.20	0.10	0.53±2.53
IL-6		2.0-376.0	16.0	38.8±62.7
Duration of hospitalization day		1.0-27.0	6.0	6.8±4.0
ICU	(+)			34 (26.0%)
	(-)			97 (74.0%)

SD: Standard deviation, NT-proBNP: N-terminal of the prohormone brain natriuretic peptide, CRP: C-reactive protein, HbA1C: Hemoglobin A1C, IL-6: Interleukin-6, ICU: Intensive care unit

positive prediction 32.8%, 62% specivity, and negative prediction 95.7% (Table 3, Figure 1-3).

The NT-ProBNP >650 pg/mL group had higher hypertension rates, procalcitonin levels, ICU admittance rates, and in-hospital mortality than the NT-ProBNP ≤650 pg/mL group ($p<0.05$). There was no significant difference for gender distribution, diabetes rates, HbA1C, ferritin, and CRP levels between the NT-ProBNP ≤650 pg/mL and NT-ProBNP >650 pg/mL groups (Table 4, Figure 4).

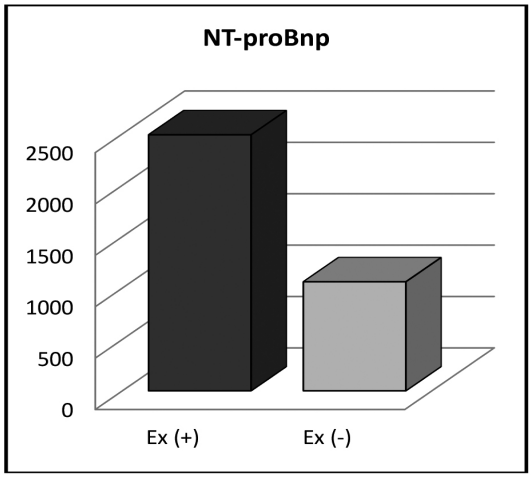

Figure 1. ProBNP cut-off value and mortality

NT-proBNP: N-terminal of the prohormone brain natriuretic peptide, proBNP: Prohormone brain natriuretic peptide

Discussion

This single-center, cross-sectional study showed that high proBNP levels are associated with poor prognosis in patients with severe COVID-19 infection. In addition, in-hospital mortality and ICU referral rates were higher in patients with high proBNP levels. The mortality rate was as high as 26%, and there was also a relationship between age, hypertension, mortality. The hypertension rate was high among patients

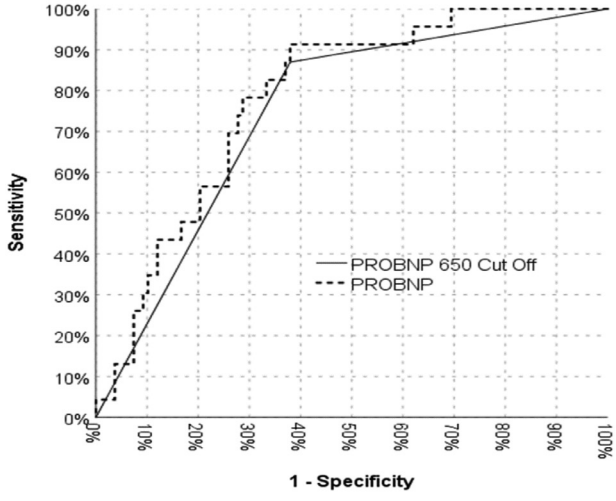

Figure 2. Ideal value of NT-proBNP in predicting in-hospital mortality in COVID-19 cases without HF

NT-proBNP: N-terminal of the prohormone brain natriuretic peptide, proBNP: Prohormone brain natriuretic peptide, COVID-19: Coronavirus disease-2019, HF: Heart failure

Table 2. General features and laboratory values of the survivors and non-survivor groups

		Ex (+)		Ex (-)		p	
		Mean ± SD/(n, %)	Median	Mean ± SD/(n, %)	Median		
Age (years)		72.1±18.3	77.0	60.7±17.1	62.0	0.005	t
Sex	Female	10 (43.5%)		52 (48.1%)		0.684	X^2
	Male	13 (56.5%)		56 (51.9%)			
Diabetes mellitus	(+)	6 (26.1%)		31 (28.7%)		0.800	X^2
	(-)	17 (73.9%)		77 (71.3%)			
Hypertension	(+)	16 (69.6%)		51 (47.2%)		0.052	X^2
	(-)	7 (30.4%)		57 (52.8%)			
NT-proBNP pg/mL		2491.0±2760.1	1471.0	1060.5±1665.3	455.0	0.001	m
HbA1C		6.8±1.1	6.3	6.8±1.5	6.3	0.656	m
Ferritin pg/dL		819.6±613.9	673.0	615.6±547.0	380.5	0.106	m
CRP mg/dL		96.4±58.6	89.0	78.2±69.6	56.0	0.071	m
Prokalsitonin pg/mL		2.1±5.8	0.2	0.2±0.4	0.1	0.001	m
IL-6		82.0±91.6	29.0	29.9±51.1	14.0	0.001	m
Duration of hospitalization day		6.7±3.5	7.0	6.9±4.1	6.0	0.864	m
ICU	(+)	22 (95.7%)		12 (11.1%)		0.001	X^2
	(-)	1 (4.3%)		96 (88.9%)			

[t]Independent sample t-test/[m]Mann-Whitney U test/[X²]chi-square test, SD: Standard deviation, NT-proBNP: N-terminal of the prohormone brain natriuretic peptide, HbA1C: Hemoglobin A1C, CRP: C-reactive protein, IL-6: Interleukin-6, ICU: Intensive care unit

Table 3. ROC analysis of ProBNP

		Area under the curve		95% CI	p
NT-proBNP		0.781		0.691-0.870	**0.001**
NT-proBNP 650 cut-off		0.745		0.644-0.846	**0.001**
		Ex (-)	**Ex (+)**		**(%)**
NT-proBNP pg/mL	<650	67	3	Sensivity	87.0%
	>650	41	20	Pozitive prediction	32.8%
				Specivity	62.0%
				Negative prediction	95.7%

ROC: Receiver operating characteristic, proBNP: Prohormone brain natriuretic peptide, NT-proBNP: N-terminal of the prohormone brain natriuretic peptide, CI: Confidence interval

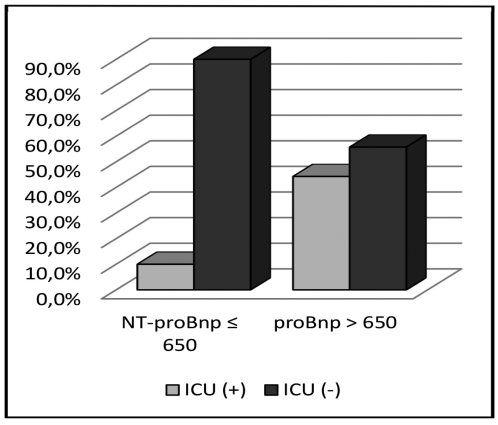

Figure 3. ICU admittance according to the ProBNP cut-off value

ICU: Intensive care unit, NT-proBNP: N-terminal of the prohormone brain natriuretic peptide, proBNP: Prohormone brain natriuretic peptide

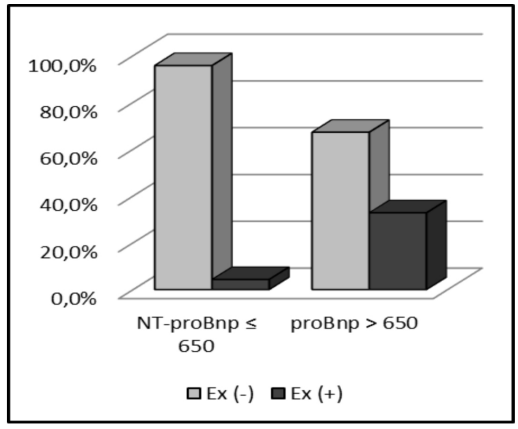

Figure 4. Mortality rates according to the proBNP cut-off value

NT-proBNP: N-terminal of the prohormone brain natriuretic peptide, proBNP: Prohormone brain natriuretic peptide

Table 4. General features and laboratory values of proBNP ≤650 and proBNP >650 groups

		NT-proBNP ≤650		NT-proBnp >650		p	
		Mean ± SD/(n, %)	**Median**	**Mean ± SD/(n, %)**	**Median**		
Age (years)		54.3±15.5	52.5	72.4±15.1	76.0	***0.001***	t
Sex	Female	29 (41.4%)		33 (54.1%)		0.147	x^2
	Male	41 (58.6%)		28 (45.9%)			
Diabetes mellitus	(+)	17 (24.3%)		20 (32.8%)		0.281	x^2
	(-)	53 (75.7%)		41 (67.2%)			
Hypertension	(+)	30 (42.9%)		37 (60.7%)		***0.042***	x^2
	(-)	40 (57.1%)		24 (39.3%)			
HbA1C		6.8±1.5	6.2	6.8±1.3	6.3	0.687	m
Ferritin pg/mL		632.0±549.8	386.0	673.6±579.9	521.0	0.755	m
CRP mg/L		72.4±64.2	51.0	91.6±71.1	69.6	0.081	m
Prokalsitonin pg/mL		0.4±1.9	0.1	0.7±3.1	0.1	***0.001***	m
IL-6		31.0±63.4	11.5	47.3±61.3	19.0	***0.005***	m
Duration of the haspitalization day		6.4±3.6	6.0	7.4±4.5	7.0	0.211	m
ICU	(+)	7 (10.0%)		27 (44.3%)		***0.001***	x^2
	(-)	63 (90.0%)		34 (55.7%)			
Exitus	(-)	67 (95.7%)		41 (67.2%)		***0.001***	x^2
	(+)	3 (4.3%)		20 (32.8%)			

[t]Independent sample t-test/[m]Mann-Whitney U test/[x²]chi-square test, NT-proBNP: N-terminal of the prohormone brain natriuretic peptide, proBNP: Prohormone brain natriuretic peptide SD: Standard deviation, HbA1C: Hemoglobin A1C, CRP: C-reactive protein, IL-6: Interleukin-6, ICU: Intensive care unit

with high NT-proBNP levels. HT and preserved left ventricular systolic function, plasma NT-proBNP is an important cardiovascular risk marker, regardless of traditional risk factors and prevalent cardiovascular disease (8). Mortality was higher in the advanced age group with the presence of high proBNP, showing that cardiac complication rates increased in this group, especially with the presence of HT.

Abnormal NT-proBNP levels show cardiac injury and cardiac dysfunction in the COVID-19 infection course and have prognostic value (7). Early studies where clinical features of patients were declared showed that an increase in cardiac biomarkers, including troponin and NT-proBNP, predicted poor outcomes in COVID-19 patients (9,10). Following meta-analyses showed that high proBNP levels were related to disease severity, mechanical ventilation, and in-hospital mortality, and evaluating NT-proBNP levels could discriminate COVID-19 patients under high risk (11,12).

Cardiac biomarkers predict worsening prognosis and in-hospital mortality risk in COVID-19 patients with and without myocardial injury (13).

Our study showed a significant relationship between mortality and NT-proBNP levels above 650 pg/mL. NT-ProBNP cut-off levels ≥650 pg/mL were found to be significant in predicting the survival of survivor and non-survivor patients.

In a study where bottom and top cut-off points were determined for proBNP, proBNP levels <331 pg/mL and >11,126 pg/mL were found to be related to the longest and shortest durations in order, starting from admittance to hospital to mortality period (14). ProBNP cut-off level to predict in-hospital mortality in the presence of cardiac disease was found to be 1022.50 pg/mL [sensitivity 87.5%, specificity (87.1%)] (15). This level is significantly higher than our finding, but it should be noted that our study excluded patients with existing HF.

Our study showed that mortality increased with advanced age and that HT was more common in patients with NT-proBNP >650 pg/mL. Similarly, COVID-19 infection is associated with advanced age, inflammatory response, underlying cardiovascular co-morbiditesand myocardial injury (16).

Multiple pathophysiological pathways are responsible for proBNP increase. Several cytokines are shown in COVID-19 patients' serum samples (17). Inflammation is the main reason for the increase (12) but also presence of pulmonary emboli, ARDS, and sepsis, which accompanies pneumonia, can also cause the increase (18,19).

In our study, procalcitonin levels but not CRP levels were found to be high in the increased proBNP level group. Caro-Codón et al. (9) CRP levels were not significantly high in the early phases of the disease but developed a correlation during proBNP pick measurement. CRP picks at 12-24 hours and lasts up to 3-7 days, but procalcitonin increases earlier than CRP and decreases to normal levels faster (20). In our study, proBNP levels did not show any correlation with CRP levels, but a strong correlation was found with procalcitonin. Because the laboratory values at admittance were evaluated in our study, procalcitonin levels should be the test of choice for early disease evaluation.

Extensive alveolar microthrombosis found postmortem in COVID-19 is one of the important reasons of mortality of the disease (9). Pro BNP is increased in pneumonia and pulmonary emboli because of cardiac shear stress but should also be accepted as an inflammation indicator because of its parallelity with inflammatory markers. Its role in direct cardiac injury, of course, requires more research.

Study Limitations

The small number of patients in our study is a limitation of the study.

Conclusion

Although vaccine and medical treatment studies are available, clinical biomarkers are needed to predict prognosis and mortality. Cardiac injury markers are still arguable to predict the amount of cardiac injury. This study showed that NT-proBNP levels can be used to predict prognosis in severe COVID-19 pneumonia and that it is an independent risk factor for in-hospital mortality.

Ethics Committee Approval: The protocol for this study was approved by the Ethics Committee of University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 99, date: 11.03.2022).

Informed Consent: Written informed consent was obtained from the participants.

Peer-review: Internally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - H.U.A., N.E.Ç.; Concept - H.U.A.; Design - H.U.A., N.E.Ç.; Data Collection or Processing - H.U.A., N.E.Ç.; Analysis or Interpretation - H.U.A., M.E.P.; Literature Search - H.U.A., M.E.P.; Writing - H.U.A.

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References

1. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, et al. Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. JAMA Cardiol 2020; 5: 802-10.
2. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, et al. Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19). JAMA Cardiol 2020; 5: 811-8.
3. Chen L, Li X, Chen M, Feng Y, Xiong C. The ACE2 expression in human heart indicates new potential mechanism of heart injury among patients infected with SARS-CoV-2. Cardiovasc Res 2020; 116: 1097-100.
4. Wynants L, Van Calster B, Collins GS, Riley RD, Heinze G, Schuit E, et al. Prediction models for diagnosis and prognosis of covid-19: systematic review and critical appraisal. BMJ 2020; 369: 1328.
5. Zakeri A, Jadhav AP, Sullenger BA, Nimjee SM. Ischemic stroke in COVID-19-positive patients: an overview of SARS-CoV-2 and thrombotic mechanisms for the neurointerventionalist. J Neurointerv Surg 2021; 13: 202-6.
6. Mohamed Abdel Shafi A, Hewage S, Harky A. The impact of COVID-19 on the provision of cardiac surgical services. J Card Surg 2020; 35: 1295-7.
7. World Health Organization. COVID-19 clinical management: living guidance https://apps.who.int/gb/COVID-19/pdf_files/2021/17_06/Item1.pdf

8. Pedersen F, Raymond I, Kistorp C, Sandgaard N, Jacobsen P, Hildebrandt P. N-terminal pro-brain natriuretic peptide in arterial hypertension: a valuable prognostic marker of cardiovascular events. J Card Fail 2005; 11(5 Suppl): S70-5.

9. Caro-Codón J, Rey JR, Buño A, Iniesta AM, Rosillo SO, Castrejon-Castrejon S, et al. Characterization of NT-proBNP in a large cohort of COVID-19 patients. Eur J Heart Fail 2021; 23: 456-64.

10. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395: 497-506.

11. Bansal A, Kumar A, Patel D, Puri R, Kalra A, Kapadia SR, et al. Meta-analysis Comparing Outcomes in Patients With and Without Cardiac Injury and Coronavirus Disease 2019 (COVID 19). Am J Cardiol 2021; 141: 140-6.

12. Sorrentino S, Cacia M, Leo I, Polimeni A, Sabatino J, Spaccarotella CAM, et al. B-Type Natriuretic Peptide as Biomarker of COVID-19 Disease Severity-A Meta-Analysis. J Clin Med 2020; 9: 2957.

13. Calvo-Fernández A, Izquierdo A, Subirana I, Farré N, Vila J, Durán X, et al. Markers of myocardial injury in the prediction of short-term COVID-19 prognosis. Rev Esp Cardiol (Engl Ed) 2021; 74: 576-83.

14. Chehrazi M, Yavarpour H, Jalali F, Saravi M, Jafaripour I, Hedayati MT, et al. Optimal cut points of N-terminal of the prohormone brain natriuretic peptide (NT-proBNP) in patients with COVID-19. Egypt Heart J 2022; 74: 16.

15. Sabanoglu C, Inanc IH, Polat E, Peker SA. Long-term predictive value of cardiac biomarkers in patients with COVID-19 infection. Eur Rev Med Pharmacol Sci 2022; 26: 6396-403.

16. Shi S, Qin M, Cai Y, Liu T, Shen B, Yang F, et al. Characteristics and clinical significance of myocardial injury in patients with severe coronavirus disease 2019. Eur Heart J 2020; 41: 2070-9.

17. Roshanravan N, Seif F, Ostadrahimi A, Pouraghaei M, Ghaffari S. Targeting Cytokine Storm to Manage Patients with COVID-19: A Mini-Review. Arch Med Res 2020; 51: 608-12.

18. Wang F, Wu Y, Tang L, Zhu W, Chen F, Xu T, et al. Brain natriuretic peptide for prediction of mortality in patients with sepsis: a systematic review and meta-analysis. Crit Care 2012; 16: 74.

19. Pasha SM, Klok FA, van der Bijl N, de Roos A, Kroft LJ, Huisman MV. NT-pro-BNP levels in patients with acute pulmonary embolism are correlated to right but not left ventricular volume and function. Thromb Haemost 2012; 108: 367-72.

20. Ruzgar O, Bilge AK, Bugra Z, Umman S, Yilmaz E, Ozben B, et al. The use of human heart-type fatty acid-binding protein as an early diagnostic biochemical marker of myocardial necrosis in patients with acute coronary syndrome, and its comparison with troponin-T and creatine kinase-myocardial band. Heart Vessels 2006; 21: 309-14.