DOI: 10.4149/BLL_2022_062

Bratisl Med J 2022; 123 (6)
395 – 400

CLINICAL STUDY

Can ferritin/lymphocyte percentage ratio, a new indicator, predict the clinical course of COVID-19 cases?

AYGUN Huseyin, ERAYBAR Suna

University of Health Sciences Turkey, Bursa Yuksek Ihtisas Training and Research Hospital, Emergency Department, Bursa Turkey. **drhaygun@gmail.com**

ABSTRACT
OBJECTIVES: COVID-19 maintains its seriousness as a global emergency with its rapid distribution worldwide. Ferritin / lymphocyte percentage ratio (FLPR) may appear as a prognostic value at the initial evaluation stage and thus can be used as a simple, effective, and reliable parameter in critical patient identification with COVID-19.
METHODS: In this retrospective cohort study, we evaluated patients over 18 years old, who were hospitalized after being evaluated as COVID-19 and whose PCR results were positive. We calculated FLPRs from complete blood counts taken during emergency department admissions and classified disease severity due to emergency initial evaluation. The relationship between the severity of the thoracic tomography findings, hospitalization, and intensive care needs, and 28-day mortality with the FLPR were evaluated.
RESULTS: The difference between the groups classified according to COVID-19 severity and the FLPR means was statistically significant (x^2=148.284; SD=3; p=0.000). FLPR levels were found to be high in critical and serious groups. In the ROC analysis for the FLPR level, the area under the curve (AUC) value was found to be 0.909 (95% CI 0.857–0.961). When the cut off value of FLPR was 9.80, the sensitivity was found to be 97.6 %, and the specificity was 65.2 %, whereas, when the cut off value for FLPR was found to be 21.11, the sensitivity was 82.9 % and the specificity was 82.8 %.
CONCLUSION: The FLPR, a new parameter, can be used as a significant marker to predict the 28-day mortality in patients *(Tab. 5, Fig. 1, Ref. 25)*. Text in PDF *www.elis.sk*
KEY WORDS: COVID-19, percentage of lymphocytes, ferritin, FLPR, disease severity, emergency department.

Introduction

In December 2019, an acute respiratory disease, now known as the new coronavirus, emerged in Wuhan, Hubei district, China. The disease quickly spread around Wuhan (1, 2). On January 30, 2020, the World Health Organization recognized this rapidly spreading infectious disease as an international public health emergency, currently known as coronavirus disease 2019 (COVID-19), and then defined it as a pandemic on March 11, 2020 (3).

COVID-19 disease, a systemic infection with a significant effect on the hematopoietic system, is characterized by nonspecific symptoms during the incubation period (approximately 1–14 days), and peripheral leukocyte and lymphocyte levels are normal or slightly decreased during this period. With the viremia developing in the following 7–14 days, SARS Cov-2 causes an increase in Angiotensin Converting Enzyme-2 (ACE-2) levels especially in the lungs, heart and gastrointestinal system and causes a systemic inflammatory response defined as 'cytokine storm' (4). Lymphocytes having ACE receptors on their surfaces are directly lysed by this effect or interleukins and tumor necrosis factor alpha, released in cytokine storm, trigger lymphocyte apoptosis and simultaneously impair lymphocyte turnover by affecting lymphoid organs (5, 6). Although, its mechanism is not clearly defined, lymphopenia appears as a cardinal finding at this stage.

Biomarkers, such as a measurement of inflammatory response, have been frequently evaluated in the follow-up of this inflammatory response and in predicting mortality. Although there is a significant correlation between the percentage of neutrophils and neutrophil count, neutrophil count percentage (NCP) is often used in analytical control of infections. In cases such as community-acquired pneumonia, where lymphocyte response is observed in the foreground, studies have shown that the percentage of lymphocytes is an important marker in predicting the mortality (7). In the presence of high white blood cell, low lymphocyte percentage has been found to be significantly correlated in terms of hospitalization and mortality. Therefore, lymphocyte percentage is associated with poor results (8, 9).

One of the poor prognostic markers in COVID-19 patients is ferritin level. Ferritin H-chain inactivates the secretion of inflammatory cytokines by activating macrophages. It is the pathogenesis of hyperferritinemic syndrome that can be explained in COVID

University of Health Sciences Turkey, Bursa Yuksek Ihtisas Training and Research Hospital, Emergency Department, Bursa, Turkey

Address for correspondence: Suna ERAYBAR, MD, Yuksek Ihtisas Education and Research Hospital, Emergency Department, Mimar Sinan Mah. Emniyet Cad. Polis Okulu Karşısı Yildirim / Bursa, Turkey.
Phone: +905325782903

infection (10). Wu et al. showed the relationship between high serum ferritin levels and development of Acute Respiratory Distress Syndrome (ARDS). In addition, there exist some studies associated with the mortality rates and ferritin levels (11, 12). As the result of this significant change in lymphocyte number and percentage and ferritin level, the use of these values together in COVID-19 cases may present an opportunity to develop a different approach.

In emergency services, where COVID-19 patients are primarily evaluated, it is important to identify the critical patients, especially at the first stage, and to implement appropriate and rapid diagnosis and treatment procedures for survival. Additionally, it is important to use first-line examinations such as hemogram and biochemistry tests and to predict the critical patient at this stage in terms of providing effective treatment. The proportional interpretation of ferritin and lymphocyte percentage values, which are included in routine examinations, these may appear as a prognostic value at the initial evaluation stage and thus can be used as a simple, effective and reliable parameter in critical patient identification.

This study aims to evaluate the relationship between ferritin / lymphocyte percentage ratio (FLPR) calculated in patients with COVID-19 disease with the severity classification of the disease and to determine its prognostic significance in terms of mortality in the course of the disease.

Materials and methods

All the patients over the age of 18, who were hospitalized for COVID-19 disease between 1–30 April 2020 admitted to our emergency department and whose COVID polymerase chain reaction (PCR) test results were positive were retrospectively evaluated.

In addition to the demographic findings such as: age and gender, vital signs at the time of admission, oxygen or advanced airway support applications in the emergency room, laboratory tests results and CT findings and 28-day living status were recorded using patient files on the hospital automation system. Patients' CT results were classified as typical (peripheral, bilateral ground glass opacity (GGO) with or without consolidation or visible intralobular lines, multifocal GGO of rounded morphology or visible intralobular lines, reverse halo sign or other findings of organizing pneumonia), intermediate, atypical and negative according to the Radiological Society of North America Expert Consensus Statement on Reporting Chest CT Findings (13).

According to the clinical severity classification of COVID-19, due to initial evaluation with the vital signs and test results, patients were grouped as mild (presence of mild symptoms and normal or non-pneumonia suggestive radiological findings), moderate (respiratory complaints and fever, presence of pneumonia in radiological examination), severe (dyspnea, respiratory rate 30/min, blood oxygen saturation ≤ 93 %, $paO_2/FiO_2 < 300$ and/or > 50 % of lung area of infiltrates within 24–48 hours) and critical (respiratory failure and need for mechanical ventilation, septic shock and / or multiple organ failure and need for intensive care follow-up and treatment) (14).

The FLPR was calculated by recording the lymphocyte percentage values and ferritin level obtained with hemogram taken in the emergency room at the time of first admission. The relationship between the FLPR with the severity of the patients and 28-day mortality was evaluated.

Statistical analysis

The data of the study were analyzed using the SPSS 22.0 for Windows (SPSS Inc., Chicago, IL, USA) computer program. Descriptive statistics were expressed as the mean ± Standard deviation or median values and an inter quartile range (IQR) of 25–75 %, while categorical variables were expressed as numbers and percentage (%). Kolmogorov-Smirnov test was used for the normality distribution of the data. While the significance of the difference between the groups in terms of continuous numerical variables in which parametric test statistics assumptions were provided was examined with Student's t test, the significance of the difference in terms of continuous numerical variables where parametric test statistics assumptions were not met was evaluated with the Mann Whitney U and Kruskal-Wallis tests. Chi-square and Fisher's exact test were used to analyze whether there was a relationship between categorical variables. Variables that may be effective for mortality were evaluated using the "enter" method in logistic regression analysis. The ROC curve was drawn to investigate the diagnostic value of the Ferritin / lymphocyte percentage ratio. $p < 0.05$ was considered statistically significant. Results were given at 95% confidence interval.

Ethics statement

Ethical approval and the necessary permissions were obtained from the ethics committee of our hospital (2011-Kaek-25 2020 /

Tab. 1. Demographic characteristics of the patients.

		Frequency	%
Gender	Female	174	52.6
	Male	157	47.4
Comorbidities	Yes	176	53.2
	No	155	46.8
Severity	Critical	42	12.7
	Serious	49	14.8
	Moderate	131	39.6
	Mild	109	32.9
Thorax CT	Typical	111	33.5
	İntermediate	120	36.3
	Atypical	43	13
	Negative	57	17.2
Symptom	No	12	3.6
	Fever	35	10.6
	Diarrhea	41	12.4
	Cough	69	20.8
	Dyspnoe	48	14.5
	Weakness-Myalgia	41	12.4
	Fever+Cough	50	15.1
	Fever+Dyspnoe	13	3.9
	Fever+ Cough+Dyspnoe	19	5.7
	Loss of consciousness	3	0.9
28-day mortality	Yes	41	12.4
	No	290	87.6
Total		331	100.0

Tab. 2. Comparison of patients clinical and demographic characteristics with severity classification.

			Severity				Total	
			Critical	Severe	Moderate	Mild		
Gender	Femae	Count	18	14	77	65	174	X^2=17.11.p<0.05
		% within gender	10.3%	8.0%	44.3%	37.4%	100.0%	
	Male	Count	24	35	54	44	157	
		% within gender	15.3%	22.3%	34.4%	28.0%	100.0%	
Comorbidities	Yes	Count	32	34	67	43	176	X^2=22.57.p<0.001
		% within Comorbidities	18.2%	19.3%	38.1%	24.4%	100.0%	
	No	Count	10	15	64	66	155	
		% within Comorbidities	6.5%	9.7%	41.3%	42.6%	100.0%	
Thorax CT	Typical	Count	18	31	47	15	111	X^2=116.73.p<0.001
		% within Thorax CT	16.2%	27.9%	42.3%	13.5%	100.0%	
	İntermediate	Count	19	16	63	22	120	
		% within Thorax CT	15.8%	13.3%	52.5%	18.3%	100.0%	
	Atypical	Count	4	1	12	26	43	
		% within Thorax CT	9.3%	2.3%	27.9%	60.5%	100.0%	
	Negative	Count	1	1	9	46	57	
		% within Thorax CT	1.8%	1.8%	15.8%	80.7%	100.0%	
Total		Count	42	49	131	109	331	
		% within Thorax CT	12.7%	14.8%	39.6%	32.9%	100.0%	

05-14), Ministry of Health, Directorate General of Health Services, and Directorate General of Public Health of Turkey. PCR test results of the patients were recorded over the Republic of Turkey, Ministry of Health, Public Health Management System, and Case Tracking Module.

Results

A total of 5530 patient files were scanned retrospectively. 732 patients hospitalized for probable COVID-19, PCR test results of 357 were found to be positive. 26 patients were excluded from the study due to various reasons. A total of 331 patients were included in the study.

The median age in the study population was 56 (IQR: 25th–75th percentiles 46–66); in critical group the median age was 72.5 (IQR: 25th–75th percentiles 64.75–79.25) and 52 years ((IQR: 25th–75th percentiles 41–62) in mild severity group, respectively. 52.6 % of the patients (n=174) were female and 53.2 % (n=176) had comorbidities. In 20,2 % (n: 67) hypertension, 5,4 % (n: 18) diabetes mellitus and 2,1 % (n: 7) chronic obstructive pulmonary disease (COPD) were determined and 19 % (n: 66) patient have multiple comorbidities. While 12.7 % (n=42) of the patients were clinically serious, 33.5 % (n=111) had a typical CT finding according to the Radiological Society of North America Expert Consensus Statement on Reporting Chest CT Findings Related to COVID-19 classification. The most common symptom in the patients was cough with 20.8 % (n=69). Mortality developed in 12.4 % (n=41) of the patients in the first 28 days (Tab. 1).

The characteristics considering disease severity, demographic and clinical findings are listed in Table 2.

The median fever level of the patients was 37.0 °C (Min: 35.0 – Max: 39.0), median saturation level was 97 (Min: 60 – Max: 99), median pulse rate per minute was 100 (Min: 56 – Max: 148), and median systolic blood pressure value was 110 mmHg (Min: 70 – Max: 180).

The measured mean lymphocyte percentage of the patients was 24.86 ± 11.76, and the mean ferritin level was 346.39 ± 443.88 ng / mL. The mean FLPR was 31.91 ± 85.10.

In the Chi-square test performed to analyze whether there was a relationship between CT findings and 28-day mortality, a sta-

Tab. 3. Presence of the comorbidities and the 28-day mortality

			28-day mortality		Chi-Square analysis
			Yes	No	
Thorax CT	Typical	n	23	88	χ^2=13.685.p<0.05
		%	56.10%	30.30%	
	Intermediate	n	13	107	
		%	31.70%	36.90%	
	Atypical	n	4	39	
		%	9.80%	13.40%	
	Negative	n	1	56	
		%	2.40%	19.30%	
Severity	Critical	n	30	12	χ^2=160.49p=0.000
		%	73.20%	4.10%	
	Serious	n	7	42	
		%	17.10%	14.50%	
	Moderate	n	2	129	
		%	4.90%	44.50%	
	Mild	n	2	107	
		%	4.90%	36.90%	
Comorbidities	Yes	n	32	144	χ^2=11.631.p<0.05
		%	78.00%	49.70%	
	No	n	9	146	
		%	22.00%	50.30%	
Total		n	41	290	
		%	100.00%	100.00%	

Tab. 4. Analysis of Variables with the Mann-Whitney U Test.

	Mortality in 28 days	n	median (IQR: 25th–75th percentiles)	p
Lymphocyte	Survival	290	25.70 (18.85–34.82)	
	Mortality	41	10.10 (6.65–16.40)	<0.001
	Total	331	24.60 (14.00–33.60)	
Ferritin	Survival	290	167.15 (68.72–308.37)	
	Mortality	41	794.00 (566.80–1264.00)	<0.001
	Total	331	188.00 (79.06–416.10)	
FLPR	Survival	290	6.55 (2.47–13.07	
	Mortality	41	83.15 (31.67–184.08)	<0.001
	Total	331	7.64 (2.71–22.33)	

FLPR – Ferritin/ lymphocyte percentage ratio

Tab. 5. Kruskal-Wallis-H test for FLRP and disease severity.

	Severity	n	median (IQR: 25th–75th percentiles)	p
FLPR	Critical	42	84.62 (39.76–148.60)	<0.05
	Serious	49	27.32 (14.18–59.03)	
	Moderate	131	6.24 (2.42–10.35)	
	Mild	109	3.11 (1.91–8.08)	
	Total	331	7.64 (2.71–22.33)	

FLPR – ferritin / lymphocyte percentage ratio

tistically significant relationship was found ($p<0.005$). Additionally, a statistically significant relationship was found between the clinical classification and 28-day mortality in the Chi-square test performed to analyze whether there was a relationship between the clinical classification of the patients and the 28-day mortality ($p=0.000$). Furthermore, there was a statistically significant relationship between the presence of comorbidities and the 28-day mortality in the Chi-square test performed to analyze whether there was a relationship between the presence of comorbidities and the 28-day mortality ($p<0.005$) (Tab. 3).

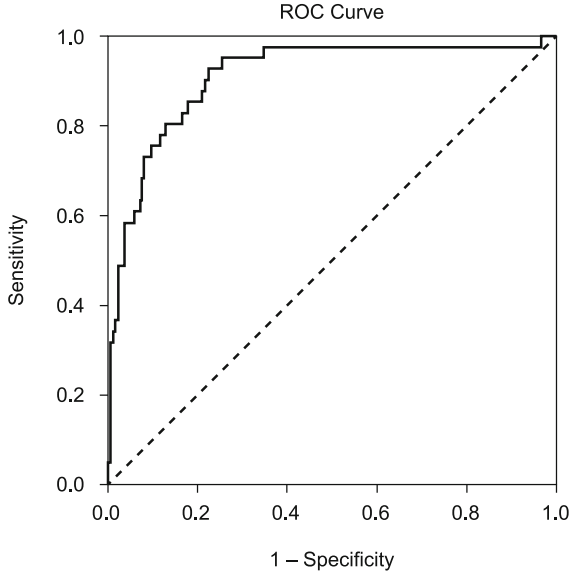

Fig. 1. ROC analysis for the ferritin/lymphocyte percentage ratio.

Tab. 6. Investigation of the usefulness of the FLPR in the prediction of mortality.

AUC (95% CI)	p	Risk Fact	cut-off	sensitivity %	specificity %
0.909 (0.857–0.961)	0	FLPR	9.8	97.6	65.2
			12.69	95.1	74.5
			15.59	90.2	78.3
			21.11	82.9	82.8

AUC – Area Under Curve, FLPR – ferritin / lymphocyte percentage ratio

In the Kolmogorov–Smirnov test conducted to analyze the normality distribution, it was observed that the data were not normally distributed. Therefore, Mann-Whitney U test was performed to investigate whether there was a difference between the mean FLPR levels, ferritin levels and lymphocyte percentage alone and 28-day mortality. As the result of this test, it was seen that FLPR levels were significantly higher in patients with mortality in 28 days ($p<0.01$). When evaluated alone, ferritin levels were high and lymphocyte percentage were low in the mortality group $p<0.001$) (Tab. 4).

In the Kruskal-Wallis-H test performed to determine whether the mean FLPR levels of the patients differ significantly according to the severity classification variable, the difference between the severity classification groups and the mean FLPR was found to be statistically significant ($\chi^2=148.284$; SD=3; $p=0.000$). It was observed that FLPR levels were high in critical and serious groups (Tab. 5).

In the logistic regression analysis performed to investigate whether the gender and comorbidities had an effect on 28-day mortality, it was seen that comorbidities were an independent risk factor.

The ROC curve presented in Figure 1 and the analyses presented in Table 6 were conducted to investigate the usefulness of the FLPR in the prediction of mortality. In the ROC analysis for the FLPR level, the area under the curve (AUC) value was found to be 0.909 (95% CI 0.857–0.961) (Fig. 1). When the cut off value of FLPR was 9.80, the sensitivity was found to be 97.6 % and specificity was 65.2 %. When the cut off value of FLPR was 21.11, the sensitivity was found to be 82.9 % and specificity was 82.8 % (Tab. 6).

Discussion

COVID-19 disease is a systemic infection commonly seen in males and individuals with comorbidities. Although its pathophysiology has not been fully elucidated, it shows itself with hematological findings and increased levels of proinflammatory cytokines associated with pulmonary infection and severe lung damage (3, 15, 16). In our study, the presence of chronic disease was found to be an independent risk factor for 28-day mortality, which is consistent with the literature.

Critical/severe patient group in COVID-19 disease has poor prognosis and high mortality rates. In studies, the rate of critical / serious patients ranges between 18.9 % and 63.3 % (16–18). In our study, this rate was 27.5 %. The number of patients receiv-

ing intensive care and mechanical ventilation support is similar to literature.

The mortality rate varies between 5 % and 7.2 % in various studies and this rate is correlated with age (19, 20). In our study, the patients were evaluated for 28-day mortality and the rate was found to be 12.4 %. According to the clinical classification, mortality is relatively high in the critical and serious groups, and the coexistence of typical CT findings in this group is remarkable.

COVID-19 is a systemic infection affecting the hematological system. Lymphopenia is used especially as a prognostic cardinal finding. In the study conducted by Guan et al. with 1099 COVID-19 patients, the rate of lymphopenia was found to be 83.2 %, while this rate increased to 96.1 %, especially in the critically ill patients (21). In addition to the use of lymphopenia as a poor prognosis marker, there are also studies showing that low lymphocyte values are associated with the development of ARDS (12).

Neutrophil lymphocyte ratio (NLR) and lymphocyte percentage were frequently evaluated after determining the prognostic significance of lymphopenia. As the NLR increased, the percentage of lymphocytes was found to be significantly lower in COVID-19 patients compared to the healthy volunteers, and this decrease was more obvious in the severe and critically ill patients. (7, 22, 23) It was observed that the percentage of lymphocytes tends to decrease even if the lymphocyte count is within the normal range. The decrease in lymphocyte percentage is thought to develop due to the destruction of erythrocytes infected with secondary hemophagocytic lymphohistiocytosis, and thus ferritin level simultaneously increases after destruction (5, 18).

Lymphopenia and ferritin are used as prognostic separately, but the decrease in lymphocyte percentage and increase in ferritin level appear to be related to the mutual destruction of hematological cells caused by the SARS-COV2 virus. Complications that develop with cytokine storm result in multiple organ failure and death (6). The FLPR may be the starting point of an aggressive immune response in the patient and may be prognostically significant.

The relationship of biochemical markers with prognosis in COVID-19 disease was evaluated and increased serum ferritin level was associated with mortality and development of ARDS (12, 24). The mean ferritin level was 346.39 ± 443.88 ng/mL and high in severe / critically ill patients.

The combined use of hematological and biochemical parameters evaluated among poor prognostic markers might provide strong clues about prognosis, as in the example of a decrease in lymphocyte / c reactive protein ratio (22, 25). The FLPR evaluated for this purpose was found to be particularly high in the serious and critically ill patient group. Calculation of FLPR, especially in the first evaluation of the patients in the emergency department, may be a guide in predicting the severity of the disease. Additionally, it can be used effectively when determining the need for clinical or intensive care hospitalization. Even if the clinical condition is good or stable, a high FLPR may give a clue about the prognosis of the disease. Critical patients can be identified on time, and early initiation of necessary treatment and interventions can be life-saving.

Conclusion

In COVID-19 patients, it is important to use FLPR concurrently with patient clinical evaluations. When the cut off value of FLPR is 9.80, sensitivity is 97.6 % and specificity is 65.2 %. When the cut off value of FLPR is 21.11, sensitivity is 82.9 % and specificity is 82.8 %, which is effective in predicting mortality. Our study is the first study in literature to use the FLPR. In this respect, it may contribute as an important mortality marker. We think that our study may form the basis for large-scale and comprehensive research.

Limitations

The most important limitation of our study is its retrospective character. Therefore, there was a loss during the collection of patient information and data.

The FLPR was calculated by recording the lymphocyte percentage values and ferritin level obtained with hemogram taken in the emergency room at the time of first admission. As we made the initial diagnosis and treatment in emergency department we collected PCR tests and gave first line treatment so the admission day is the first day of diagnosis but we did not categorize the patients according to their symptomatic phase and the day of the symptoms.

References

1. Lu H, Stratton CV, Tang YW. Outbreak of pneumonia of unknown etiology in Wuhan, China: The mystery and the miracle. J Med Virol 2020; 92 (4): 401–402.

2. Hui DS, Azhar EI, Madani TA et al. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global Whealth – The latest 2019 novel coronavirus outbreak in Wuhan, China. Int J Infect Dis 2020; 91: 264–266.

3. WHO. Coronavirus disease 2019 Situation Report 51 [Internet] 2020 Mar 11. Available from: https://www.who.int/docs/defaultsource/coronaviruse/situation-reports/20200311-sitrep-51-covid-19.pdf.

4. Xu H, Zhong L, Peng J et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int J Oral Sci 2020; 12 (1): 8.

5. Liao YC, Liang WG, Chen FW et al. IL-19 induces production of IL-6 and TNF-alpha and results in cell apoptosis through TNF-alpha. J Immunol 2002; 169 (8): 4288–4297.

6. Aggarwal S, Gollapudi S, Gupta S. Increased TNF-alpha-induced apoptosis in lymphocytes from aged humans: changes in TNF-alpha receptor expression and activation of caspases. J Immunol 1999; 162 (4): 2154–2161.

7. Curbelo J, Bueno SL, Galvan-Roman JM et al. Inflammation biomarkers in blood as mortality predictors in community-acquired pneumonia admitted patients: Importance of comparison with neutrophil count percentage or neutrophil-lymphocyte ratio. PLoS One 2017; 12 (3): e0173947.

8. Reddan DN, Klassen PS, Szczech LA et al. White blood cells as a novel mortality predictor in haemodialysis patients. Nephrol Dial Transplant 2003; 18 (6): 1167–1173.

9. Kuwae N, Kopple JD, Kalantar-Zadeh K et al. A low lymphocyte percentage is a predictor of mortality and hospitalization in hemodialysis patients. Clin Nephrol 2005; 63 (1): 22–34.

10. Shoenfeld Y. Corona (COVID-19) time musings: Our involvement in COVID-19 pathogenesis, diagnosis, treatment and vaccine planning. Autoimmun Rev 2020; 19 (6): 102538.

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. Lancet 2020; 395 (10229): 1054–1062.

12. Wu C, Chen X, Cai Y et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med 2020 180 (7): 934–943.

13. Simpson S, Kay FU, Abbara S et al. Radiological Society of North America Expert Consensus Statement on Reporting Chest CT Findings Related to COVID-19. Endorsed by the Society of Thoracic Radiology, the American College of Radiology, and RSNA – Secondary Publication. J Thorac Imaging 2020; 35 (4): 219–227.

14. 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.

15. Huang C, Wang Y, Li X et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395 (10223): 497–506.

16. WHO. Report of the WHO-China joint mission on coronavirus disease 2019 (COVID-19) 2020, Geneva.

17. Li K, Wu J, Wu F et al. The Clinical and Chest CT Features Associated With Severe and Critical COVID-19 Pneumonia. Invest Radiol 2020; 55 (6): 327–331.

18. Qin C, Zhou L, Hu Z et al. Dysregulation of Immune Response in Patients With Coronavirus 2019 (COVID-19) in Wuhan, China. Clin Infect Dis 2020; 71 (15): 762–768.

19. Li LQ, Huang T, Wang YQ et al. COVID-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. J Med Virol 2020; 92 (6): 577–583.

20. Onder G, Rezza G, S, Brusaferro S. Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy. Jama 2020; 323 (18): 1775–1776.

21. Guan WJ, Ni Z, Hu Y et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020; 382 (18): 1708–1720.

22. Lagunas-Rangel FA. Neutrophil-to-lymphocyte ratio and lymphocyte-to-C-reactive protein ratio in patients with severe coronavirus disease 2019 (COVID-19): A meta-analysis. J Med Virol 2020; 92 (10): 1733–1734.

23. Yufei Y, Mingli L, Xuejao Li et al. Utility of the neutrophil-to-lymphocyte ratio and C-reactive protein level for coronavirus disease 2019 (COVID-19). Scand J Clin Lab Invest 2020: 1–5.

24. Terpos E, Stathopulos IN, Elalamy I et al. Hematological findings and complications of COVID-19. Am J Hematol 2020; 95 (7): 834–847.

25. Okugawa Y, Toiyama Y, Yamamoto A et al. Lymphocyte-C-reactive Protein Ratio as Promising New Marker for Predicting Surgical and Oncological Outcomes in Colorectal Cancer. Ann Surg 2020; 272 (2): 342–351.

Received April 13, 2021.
Accepted January 18, 2022.