ORIGINAL RESEARCH

Neutrophil–Lymphocyte Ratio in Patients with COVID-19 as a Simple Tool to Predict Requirement of Admission to a Critical Care Unit

Sagar S Maddani[1], Nitin Gupta[2], Shashikiran Umakanth[3], Sowmya Joylin[4], Kavitha Saravu[5]

Abstract

Introduction: Coronavirus disease-2019 (COVID-19) pandemic has overloaded the healthcare system beyond its functional capacity. Late referral to higher levels of care may be one of the factors associated with higher mortality. Therefore, we aimed to find simple demographic and laboratory parameters which predict the requirement of admission to a critical care unit.

Materials and methods: A case–control study was undertaken in adult age population >18 years, admitted in a dedicated COVID hospital in South India. A total of 50 patients with severe disease (cases) were compared with 143 mild or asymptomatic cases (controls). Those demographic and laboratory parameters that were found to be significant on univariate analysis were used for multiple logistic regression analysis.

Results: Univariate analysis of demographic and laboratory data showed higher age, male sex, presence of diabetes mellitus, higher values of C-reactive protein, ferritin, D-dimer, neutrophil–lymphocyte ratio (NLR), and lactate dehydrogenase to be significantly associated with cases. Multivariate logistic regression analysis of these significant variables showed NLR and ferritin to be the independent predictors of the requirement of admission to a critical care unit. The receiver-operating characteristic curve showed an NLR value of 5.2 and a ferritin value of 462 μg/L that were able to predict the requirement of admission in critical care units.

Conclusion: High ferritin and NLR were independent predictors of the requirement of admission in critical care units. NLR is a simple tool that can be used in resource-limited settings for triage and early referral to higher levels of care.

Keywords: Coronavirus disease-2019, C-reactive protein, Ferritin, Neutrophil–lymphocyte ratio.

Indian Journal of Critical Care Medicine (2021): 10.5005/jp-journals-10071-23801

Introduction

Coronavirus disease-2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] Majority of the patients with COVID-19 have a mild or asymptomatic presentation. These patients mainly require strict isolation to prevent transmission of the disease in the community. Around 5–15% of COVID-19 patients may present with or progress to moderate to severe symptoms requiring higher levels of care.[2–4] In a report of 44,500 patients from China, the mortality rate was found to be 2.3%.[5] Early anticipation of the progression of the disease and prompt referral to higher centers for initiation of treatment in moderate to severe cases will prevent mortality. Due to the heavy burden of COVID-19 on the Indian healthcare system, many patients with COVID-19 are being managed in small healthcare centers without an adequate facility for providing intensive care. Late referral to higher levels of care may be one of the factors associated with mortality. Therefore, the study aimed to find simple demographic and laboratory parameters that predict the requirement of admission to a critical care unit.

[1]Department of Critical Care Medicine, Kasturba Medical College, Manipal Academy of Higher Education, Manipal, Karnataka, India

[2,4,5]Department of Infectious Diseases, Kasturba Medical College, Manipal Academy of Higher Education, Manipal, Karnataka, India

[3]Department of Medicine, Melaka Manipal Medical College, Dr TMA Pai Hospital, Manipal Academy of Higher Education, Udupi, Karnataka, India

Corresponding Author: Kavitha Saravu, Department of Infectious Diseases, Kasturba Medical College, Manipal Academy of Higher Education, Manipal, Karnataka, India, Phone: +91 9448107636, e-mail: kavithasaravu@gmail.com

How to cite this article: Maddani SS, Gupta N, Umakanth S, Joylin S, Saravu K. Neutrophil–Lymphocyte Ratio in Patients with COVID-19 as a Simple Tool to Predict Requirement of Admission to a Critical Care Unit. Indian J Crit Care Med 2021;25(5):535–539.

Source of support: Nil

Conflict of interest: None

Materials and Methods

A case–control study was conducted in adult age-group population >18 years, at Dr TMA Pai Hospital, Udupi, Karnataka, between March and August 2020 after taking permission from the Institutional Ethics Committee. Those patients requiring admission in the critical care unit and clinically categorized as severe (pneumonia, with respiratory rate >30/minute or SpO_2 <90% on room air) according to the definition given by World Health Organisation were grouped as "cases."[6] The hospital numbers of all the patients admitted in hospital wards with asymptomatic or mild disease (no clinical signs of pneumonia and no hypoxia) were compiled. Random sampling was done using the random number table to select three times the number of cases. These were designated as "controls."[6] The demographic, clinical parameters, laboratory parameters, and treatment and outcome of both cases and controls were recorded for each of the enrolled patients in a separate predefined case-record form.

Statistical Analysis

A univariate analysis was done to find demographic and laboratory parameters that were significantly associated with the requirement of admission to a critical care unit. For categorical variables, a chi-square test was used. For continuous variables, independent *t*-test and Mann–Whitney *U* test were done. Those with a *p*-value of <0.05 were included in the multivariable logistic regression analysis to find the independent predictors of critical care unit admission. A receiver operating characteristic (ROC) curve was generated for quantitative predictors that were significant on multivariable analysis to determine their optimal cutoffs that can help in predicting individuals requiring critical care admission.

Results

A total of 53 patients were categorized as severe and required admission in the critical care unit. Of these, three patients were excluded because of lack of sufficient data. For these 50 cases, 150 control patients were selected from the asymptomatic or mild category; eight patients were excluded because of lack of sufficient data. A total of 142 patients were taken as controls in the final analysis. A total of 35 patients had a history of travel, while 75 patients had a history of contact with a positive patient. A total of 19 patients were pregnant among the included patients. The details of stay, examination findings, and treatment of patients in the severe and mild categories have been summarized in Table 1. Following complications were noted in patients admitted in critical care unit: acute kidney injury ($n = 13$), the requirement of dialysis ($n = 3$), hepatitis ($n = 9$), myocarditis ($n = 2$), stroke (1), myocardial infarction (1), and shock (3). In patients admitted in the critical care unit, noninvasive ventilation was given to 20 patients, while five patients required oxygen through a high-frequency nasal cannula. Of these patients, 10 patients required invasive mechanical ventilation. There was only one mortality in this group. Five cases were transferred to another center.

The demographic and laboratory parameters of cases and controls are described in Table 2. The result of a univariate analysis comparing cases and controls is also described in Table 2. The presence of diabetes mellitus (DM) and higher duration of illness at presentation were significantly associated with admission to a critical care unit (Table 2). The mean age of cases was significantly higher when compared to controls (Table 2). The incidence of severe disease was higher in males (Table 2). The mean total leucocyte and neutrophil–lymphocyte ratio (NLR) was higher in cases when compared to controls. Similarly, D-dimer, ferritin, C-reactive

Table 1: Details of stay, examination, and treatment of COVID-19 patients requiring critical care admission (cases) as compared to those who did not (controls)

	Cases (n = 50)	*Controls (n = 142)*	*p value*
Days of stay	19.8 (8.4)	8.29 (3.67)	<0.001
Systolic blood pressure	128.8 (18.6)	124.7 (17)	0.006
Diastolic blood pressure	77.2 (11.6)	79.8 (11.7)	0.001
Respiratory rate	24.9 (3.4)	18.23 (2.7)	0.003
SpO_2	90.5 (4.6)	97.7 (1.18)	<0.001
Hospital-acquired infection	4	1	0.005
Antibiotics	31	5	<0.001
Hydroxychloroquine	27	5	<0.001
Steroids	47	13	<0.001
Remdesivir	17	1	<0.001
Death	1	0	<0.001

Table 2: Univariate analysis of demographic and laboratory parameters that can predict the requirement of admission to a critical care unit

	Cases (n = 50)	*Controls (n = 142)*	*p value*
Age	55.22 (13.75)	44.22 (17.42)	0.023
Female sex	14 (28%)	67 (47.2%)	0.018
Duration of illness*	4.50 [3.00, 5.00]	2.00 [1.00, 4.00]	<0.001
DM	33 (66%)	35 (24.6%)	<0.001
CKD	3	2	0.08
HIV	1	0	0.09
Malignancy	2	2	0.270
Asthma/COPD	2	10	0.445
TLC (/μL)	9762.00 (4582.84)	6784.51 (2218.95)	<0.001
NLR*	8.45 [5.40, 13.88]	2.32 [1.50, 3.48]	<0.001
Platelet count (thousand/μL)	298 (133.8)	283.2 (93.9)	0.394
D-dimer* (μg/mL)	0.90 [0.32, 1.80]	0.30 [0.20, 0.50]	<0.001
Ferritin* (μg/L)	761.50 [465.75, 1119.00]	137.50 [76.00, 257.85]	<0.001
CRP*(mg/L)	81.50 [43.00, 123.75]	3.00 [1.00, 13.25]	<0.001
LDH* (U/L)	411.00 [348.00, 652.00]	262.00 [220.75, 309.00]	<0.001

Qualitative variables—percentages in the bracket; quantitative variables—mean (standard deviation); quantitative variables*—median (interquartile range)

DM, diabetes mellitus; CKD, chronic kidney disease; HIV, human immunodeficiency virus infection; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; TLC, total leucocyte count; NLR, neutrophil–lymphocyte ratio; LDH, lactate dehydrogenase

Table 3: Multivariable logistic regression of demographic and laboratory parameters that can predict the requirement of admission to a critical care unit

	Cases (n = 50)	*Controls (n = 142)*	*Unadjusted OR (95% confidence interval)*	*Adjusted OR (95% confidence interval)*	*p value*
Age	55.22 (13.75)	44.22 (17.42)	1.04 (1.02–1.06)	1.05 (0.98–1.13)	0.16
Female sex	14 (28%)	67 (47.2%)	0.435 (0.216–0.876)	0.21 (0.03–1.66)	0.14
Duration of illness*	4.50 [3.00, 5.00]	2.00 [1.00, 4.00]	1.47 (1.26–1.71)	0.95 (0.62–1.45)	0.81
DM	33 (66%)	35 (24.6%)	5.93 (2.95–11.9)	0.12 (0.01–1.14)	0.065
TLC (/μL)	9762.00 (4582.84)	6784.51 (2218.95)	1 (1–1)	1.00 (1.00–1.00)	0.66
NLR*	8.45 [5.40, 13.88]	2.32 [1.50, 3.48]	1.78 (1.48–2.13)	0.67 (0.46–0.97)	0.036
CRP* (mg/L)	81.50 [43.00, 123.75]	3.00 [1.00, 13.25]	1.03 (1.02–1.03)	1.01 (0.99–1.02)	0.29
D-dimer* (μg/mL)	0.90 [0.32, 1.80]	0.30 [0.20, 0.50]	3.51 (1.56–7.93)	0.97 (0.45–2.08)	0.93
Ferritin* (μg/L)	761.50 [465.75, 1119.00]	137.50 [76.00, 257.85]	1 (1–1)	1.00 (0.99–1.00)	0.02
LDH* (U/L)	411.00 [348.00, 652.00]	262.00 [220.75, 309.00]	1.01 (1.01–1.02)	1.00 (0.99–1.00)	0.16

Qualitative variables—percentages in the bracket; quantitative variables—mean (standard deviation); quantitative variables*—median (interquartile range)
DM, diabetes mellitus; CRP, C-reactive protein; TLC, total leucocyte count; NLR, neutrophil–lymphocyte ratio; LDH, lactate dehydrogenase

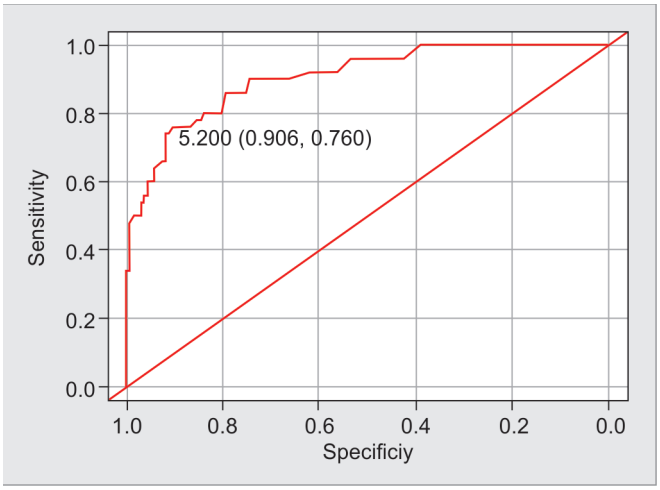

Fig. 1: ROC curve for NLR and determination of cutoff to distinguish patients who require critical care admission from those who do not

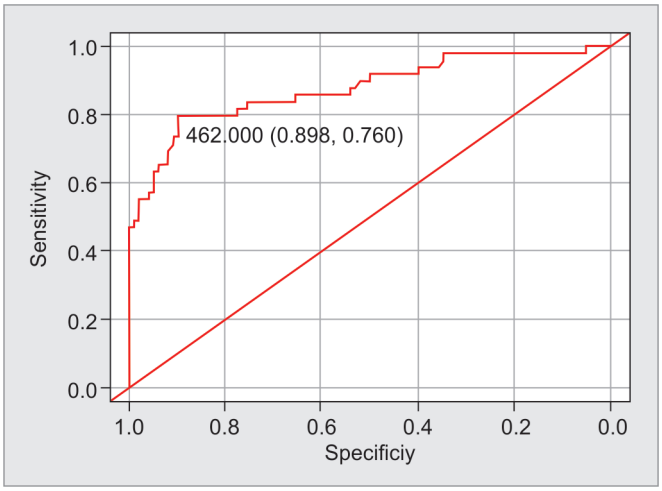

Fig. 2: ROC curve for ferritin and determination of cutoff to distinguish patients who require critical care admission from those who do not

protein (CRP), and lactate dehydrogenase (LDH) were higher in cases compared to controls. On multivariable analysis, ferritin and NLR were found to be significant predictors of the requirement of admission to a critical care unit (Table 3).

An ROC curve was generated for both NLR and ferritin. The optimal cutoff for NLR was found to be 5.2 which gave a sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of 76% [95% confidence interval (CI), 62–87%], 90.6% (95% CI, 84–95%), 74.5% (95% CI, 60–86%), and 91.2% (95% CI, 85–95%), respectively (Fig. 1). The area under the curve (AUC) for NLR was 0.91 (95% CI, 0.86–0.95). The optimal cutoff for ferritin was found to be 462 μg/L which gave a sensitivity, specificity, PPV, and NPV of 79.6% (95% CI, 66–90%), 89.8% (95% CI, 82–95%), 79.6% (95% CI, 66–90%), and 89.8% (95% CI, 82–95%), respectively (Fig. 2). The AUC for ferritin was 0.88 (95% CI, 0.81–0.94).

Discussion

Our case–control study demonstrates the difference in demographic and laboratory parameters between patients requiring critical care admission and those who did not. Although several international studies have been published on this subject, it is important to study these parameters in Indian subjects as studies have shown a disparity in outcomes among various races/ethnicities.[7] Various Indian studies related to COVID-19 have been published, but very few of these studies have systematically studied the risk factors for severity.[4,8–11] Also, none of these studies are from the southern states of India. Those studies where risk factors for severity or mortality were analyzed have been summarized in Table 4. Similar to other published studies, age and male gender were associated with a higher incidence of severe disease in our study.[4,10] In a study from China, the rate of hospitalization varied between the different age-groups as follows: 1% (20–29 years), 4% (50–59 years), and 18% (>80 years).[12] In another study, the risk of death was 20 times higher in those above 80 years of age compared to those between 50 and 59 years of age.[13] Several studies have shown that the male gender has suffered worse outcomes comparatively.[3,4] The presence of comorbidities like DM affects the disease severity as well as mortality. In a study from Italy, among the people who died, most patients had one or more comorbidities. The mean number

Table 4: Comparing various studies related to COVID-19 patients in India

Sl. No.	*Author*	*Study design*	*Study population*	*Sample size*	*Predictors of severity/mortality*	*Mortality(%)*
1	Soni et al. Chandigarh[4]	Prospective, observational study	All severity (severe-18 patients)	114	High inflammatory parameters, NLR ratio of ≥3.5, hypalbuminemia, and deranged creatinine	2.6
2	Mahale et al., Pune[8]	Retrospective study	Patients requiring oxygen and on immunomodulators	134	SpO_2, PaO_2/FiO_2 ratio, leukocytosis, lymphopenia, and creatinine	26.9
3	Bhadade et al., Mumbai[9]	Prospective observational study	Critically ill COVID-19 patients	373	Comorbidities, hypertension, low SpO_2, low P/F ratio, high levels of blood sugar, LDH, ferritin, D-dimer, IL-6	18.5
4	Sharma et al., Jaipur[10]	Prospective observational study	All severity	70	Lymphopenia and higher age	32.8
5	Dosi et al., Indore[11]	Retrospective study	All severity (oxygen requirement-53)	365	Comorbidities, lymphopenia	8.4

of comorbidities in that study was 2.7.[14] Similar to other published studies, DM was found to be associated with severe disease in this study (Table 4).

Similarly, laboratory parameters like increased CRP, D-dimer, ferritin, NLR, and LDH were associated with a higher incidence of severe disease. Higher the degree of the inflammatory state, higher will be the levels of inflammatory markers, and consequently, these markers may help in predicting severity and prognosis. Inflammatory markers like CRP, ferritin, and interleukin-6 were associated with a higher incidence of severe disease in several studies.[15] The SARS-CoV-2 also affects the coagulation pathway and liver result in a prothrombotic state. This results in increased morbidity and mortality. As a consequence, raised D-dimer levels have been used as a predictor for severity/mortality.[15] Similar findings were seen in other Indian studies as well (Table 4).

To negate the effect of covariates, we did a multivariable logistic regression analysis that showed that NLR and ferritin are independent predictors of disease severity. Lymphopenia has been commonly described in patients with COVID-19.[2] This might have been because of the presence of receptors for SARS-COV-2 on lymphocytes.[16] The degree of lymphopenia has been described to be higher in those with severe COVID-19, which may be because of the cytokines mediated apoptosis of lymphocytes.[16] High NLR value has been associated with severity of disease illness in several studies from China.[17,18] Studies from India have also shown that lymphopenia or high NLR is seen more commonly in critically ill patients.[10,11] Ferritin was the only inflammatory marker that was significant on multivariable analysis. Similar studies from China have shown an association between ferritin and increased severity.[5,19] In our study the cutoff for ferritin was found to be 462 μg/L with a considerable AUC. However, the availability of ferritin testing facilities in primary care centers may be a cause for concern. On the other hand, NLR at a cutoff of 5.2 had a better AUC compared to ferritin and is also a simple test that is available in most primary centers. In centers where testing is easily available, and resource-limitation is not an issue, other inflammatory markers (beyond NLR and ferritin) may also be of some help in prognostication and predicting the requirement of higher levels of care.

The pandemic has tested the limits of an already overburdened healthcare system in India. Most patients in India are managed in primary care centers or make-shift centers. These centers are staffed by healthcare professionals without sufficient experience in managing critically ill patients. It is, therefore, important to have simple predictors that may suggest the requirement of critical care. We, therefore, suggest that NLR can be used for early referral to centers with critical care support.

Limitations

Our study had few limitations, mainly being a single-centre case–control study, hence postulating the same results to the general population might not be accurate. Interleukin-6 and chest imaging characters were not included in our study as it was not done in most of the mild cases.

Conclusion

Older individuals, male sex, DM, and raised inflammatory parameters (CRP, D-dimer, ferritin, NLR, and LDH) were associated with a higher incidence of severe disease. Out of these, high ferritin and NLR were independent predictors of disease severity. These parameters can be used to identify high-risk patients at resource-limited settings and refer them to tertiary care centers for better outcomes.

Orcid

Sagar S Maddani https://orcid.org/0000-0003-0700-0532
Nitin Gupta https://orcid.org/0000-0002-9687-2836
Shashikiran Umakanth https://orcid.org/0000-0001-5210-7457
Sowmya Joylin https://orcid.org/0000-0002-5112-1262
Kavitha Saravu https://orcid.org/0000-0001-6399-1129

References

1. World Health Organization. Novel coronavirus (2019-nCoV): situation report – 22. 11 February 2020. World Health Oragnization; 2020.
2. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382(18):1708–1720. DOI: 10.1056/NEJMoa2002032.
3. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City Area. JAMA 2020;323(20):2052–2059. DOI: 10.1001/jama.2020.6775.

4. Soni SL, Kajal K, Yaddanapudi LN, Malhotra P, Puri GD, Bhalla A, et al. Demographic and clinical profile of patients with COVID-19 at a tertiary care hospital in north India. Indian J Med Res 2020. DOI: 10.4103/ijmr.IJMR_2311_20.
5. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. JAMA 2020;323(13):1239–1242. DOI: 10.1001/jama.2020.2648.
6. World Health Organization. Clinical management of COVID-19: interim guidance, 27 May 2020. World Health Organization; 2020.
7. Gold JAW, Rossen LM, Ahmad FB, Sutton P, Li Z, Salvatore PP, et al. Race, Ethnicity, and Age Trends in Persons Who Died from COVID-19 – United States, May–August 2020. MMWR Morb Mortal Wkly Rep 2020;69(42):1517–1521. DOI: 10.15585/mmwr.mm6942e1.
8. Mahale N, Rajhans P, Godavarthy P, Narasimhan VL, Oak G, Marreddy S, et al. A retrospective observational study of hypoxic COVID-19 patients treated with immunomodulatory drugs in a tertiary care hospital. Indian J Crit Care Med 2020;24(11):1020–7. DOI: 10.5005/jp-journals-10071-23599.
9. Bhadade R, Harde M, deSouza R, Kasbe A, Deshpande C, Dave S, et al. Appraisal of critically ill COVID-19 patients at a dedicated COVID hospital. J Assoc Physicians India 2020;68(9):14–19. PMID: 32798339.
10. Sharma D, Dayama A, Banerjee S, Bhandhari S, Chatterjee A, Chatterjee D. To study the role of absolute lymphocyte count and RDW in COVID 19 patients and their association with appearance of symptoms and severity. J Assoc Physicians India 2020;68(8):39–42. PMID: 32738839.
11. Dosi R, Jain G, Mehta A. Clinical characteristics, comorbidities, and outcome among 365 patients of coronavirus disease 2019 at a tertiary care centre in Central India. J Assoc Physicians India 2020;68(9):20–23. PMID: 32798340.
12. Verity R, Okell LC, Dorigatti I, Winskill P, Whittaker C, Imai N, et al. Estimates of the severity of coronavirus disease 2019: a model-based analysis. Lancet Infect Dis 2020;20(6):669–677. DOI: 10.1016/S1473-3099(20)30243-7.
13. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature 2020;584(7821):430–436. DOI: 10.1038/s41586-020-2521-4.
14. Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. JAMA 2020;323(18):1775–1776. DOI: 10.1001/jama.2020.4683.
15. Danwang C, Endomba FT, Nkeck JR, Wouna DL, Robert A, Noubiap JJ. A meta-analysis of potential biomarkers associated with severity of coronavirus disease 2019 (COVID-19). Biomark Res 2020;8(1):1–3. DOI: 10.1186/s40364-020-00217-0.
16. Terpos E, Ntanasis-Stathopoulos I, Elalamy I, Kastritis E, Sergentanis TN, Politou M, et al. Hematological findings and complications of COVID-19. Am J Hematol 2020;95(7):834–847. DOI: 10.1002/ajh.25829.
17. Li X, Liu C, Mao Z, Xiao M, Wang L, Qi S, et al. Predictive values of neutrophil-to-lymphocyte ratio on disease severity and mortality in COVID-19 patients: a systematic review and meta-analysis. Crit Care 2020;24(1):647. DOI: 10.1186/s13054-020-03374-8.
18. Yang AP, Liu JP, Tao WQ, Li HM. The diagnostic and predictive role of NLR, d-NLR and PLR in COVID-19 patients. Int Immunopharmacol 2020;84:106504. DOI: 10.1016/j.intimp.2020.106504. PMID: 32304994. PMCID: PMC7152924.
19. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, 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. DOI: 10.1016/S0140-6736(20)30566-3.