ORIGINAL ARTICLE

Predictors of Severe and Critical COVID-19 in Hospitalized Hypertensive Patients

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Abstract

Introduction: The severe condition develops in every fifth patient with coronavirus disease 2019 (COVID-19). This study is aimed to assess the factors predicting severe and critical conditions in hypertensive patients with COVID-19-associated pneumonia.

Materials and methods: A total of 106 unvaccinated hypertensive patients hospitalized for COVID-19-associated pneumonia were enrolled in the study.

Results: Median body mass index (BMI) was higher in patients with severe/critical condition [30.4 (26.4–34.1) kg/m^2] than in patients with moderate condition [25.3 (23.5–29.1) kg/m^2] ($p < 0.001$). Diabetes mellitus was more prevalent in patients with severe/critical condition (40.7 vs 21.3%, $p = 0.04$). Erythrocyte sedimentation rate (ESR) was higher in patients with severe/critical condition [28.0 (14.0–34.5) vs 37.5 (24.0–46.5) mm/hour] (0.004). Patients who developed severe/critical condition were scored higher according to the community-acquired pneumonia symptom (CAP-Sym) questionnaire [30.0 (20.0–37.0) points] than patients who developed the moderate condition [22.0 (16.0–33.0) points] ($p = 0.03$). Also, ferritin level was higher in patients who developed severe/critical condition [430.5 (177.0–733.0) ng/mL] than in patients who developed the moderate condition [315.5 (169.0–396.0) ng/mL] ($p = 0.03$). BMI of ≥30 kg/m^2 increased the odds of severe/critical condition development [odds ratio (OR) = 3.83 (1.61–9.09), $p = 0.002$] and was the only independent predictor for the severe/critical condition according to the multivariate logistic regression analysis.

Conclusion: Increased BMI, diabetes mellitus, high ESR, and ferritin level at admission predict severe/critical disease in unvaccinated hypertensive patients hospitalized for COVID-19. However, only BMI of ≥30 kg/m^2 is an independent risk factor for severe/critical disease according to multivariate logistic regression analysis. CAP-Sym questionnaire may be used for the prediction of severe/critical COVID-19.

Keywords: Coronavirus disease 2019, Hospitalized, Hypertension, Predictors, Risk factors.

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first described in December 2019 and catastrophically affected the world's demographics, leading to over 6.5 million deaths.[1,2] Patients with SARS-CoV-2 infection may remain asymptomatic in the early stages; later, it may lead to severe pneumonia, respiratory distress syndrome, multi-organ failure, and even lethal outcomes.[3] The severe clinical condition develops in approximately 18.0% of patients.[4] Inhospital mortality occurs in 19.4% of patients with severe COVID-19.[5] Desaturated patients may need continuous positive airway pressure and invasive mechanical ventilation which are associated with barotraumatic events, such as pneumothorax, subcutaneous emphysema, pneumoperitoneum, and pneumomediastinum.[6] Also, plenty of long-term unfavorable effects of COVID-19 are described in patients who survived severe COVID-19.[7]

In the general population, men have an 18% higher risk of severe COVID-19 and a 50% higher risk of death than women.[8] Nearly 25.1% of patients with severe COVID-19 have at least one comorbidity, and 8.2% of patients have two or more comorbidities.[9] Chronic obstructive pulmonary disease, diabetes, hypertension, and malignancy are risk factors for critical clinical conditions.[9] There is evidence that increased D-dimer, C-reactive protein, procalcitonin, ferritin, interleukin-6 (IL-6), soluble interleukin-2 receptor (sIL-2R) levels, ESR, lymphopenia, and thrombocytopenia predicts severe COVID-19.[10–14] Well-timed discrimination of severe COVID-19 patients may facilitate appropriate management, as there is evidence that early treatment of high-risk patients may improve prognosis.[15–17]

The risk of severe condition development is twice higher in patients with arterial hypertension.[18] Patients admitted to the intensive care unit are 2.7-fold more likely to have arterial hypertension.[19] The mortality rate in hypertensive patients is 2.7-fold higher.[20] Hypertensive patients are older and are more likely to have comorbidities.[21] As arterial hypertension significantly impacts clinical outcomes in COVID-19 patients, assessment of

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severe clinical condition predictors in hypertensive patients is important to improve the efficacy of the treatment and the patient's prognosis.

Aim

This study is aimed to assess the factors predicting severe and critical clinical conditions in hypertensive hospitalized patients with COVID-19-associated pneumonia.

Materials and Methods

Participants

A total of 106 hypertensive patients hospitalized for COVID-19-associated pneumonia from March to June 2021 were enrolled in the study. All enrolled patients were not vaccinated for COVID-19.

Variables

Pneumonia was confirmed with chest computed tomography or chest X-ray. Coronavirus SARS-CoV-2 as an etiological factor of pneumonia was confirmed with either polymerase chain reaction or enzyme-linked immunosorbent assay test with the assessment of immunoglobulin M level.

The diagnosis of arterial hypertension was established in accordance with the criteria of the 2018 European Society of Cardiology guideline.[22] Pneumonia severity was assessed in accordance with the confusion, uremia, respiratory rate, BP, age ≥ 65 years (CURB-65) score.[23] Patients' symptoms were assessed using the CAP-Sym questionnaire.[24]

Coronavirus disease 2019 (COVID-19)—associated pneumonia severity was assessed according to the protocol of medical care for treatment of COVID-19.[25] A severe clinical condition was considered in the presence of at least one of the following characteristics—respiratory rate of ≥30 breaths/minute, oxygen saturation of ≤93%, and pulmonary infiltrates occupying >50% of the lung area. The critical condition was defined in the presence of at least one of the followings—acute respiratory distress syndrome, sepsis, altered consciousness, and multiple organ dysfunction syndrome.

A total of 46 (43.4%) patients had a severe clinical condition and 13 (12.3%) patients had a critical clinical condition. In 47 (44.3%) patients, the clinical condition was labeled as moderate.

Besides the conventional laboratory tests (total blood count, urinalysis, fasting glucose, and biochemical profile), IL-6, ferritin, and sIL-2R levels were measured.

Inclusion Criterion

- Pneumonia associated with COVID-19 in a hospitalized hypertensive patient.

Exclusion Criteria

- Pregnancy.
- Age of <18 years.
- Moderate and severe cognitive decline.
- Acute myocardial infarction.
- Acute phase of ischemic stroke and transient ischemic attack.
- Acute phase of intracerebral hemorrhage.
- Active cancer.
- Active gastrointestinal bleeding.
- Stage 5 chronic kidney disease.

Setting

This was a prospective single centre study and was conducted in Ivano-Frankivsk Central City Hospital and Ivano-Frankivsk City Hospital No 1.

Sampling

Each patient (who met the inclusion criterion and none of the exclusion criteria) hospitalized from March to June 2021 was proposed to be a participant in the study.

Ethics Statement

A consent form was signed by each prospective participant before recruitment into the study. All of the procedures in the study met bioethical standards according to the Helsinki Declaration. The study was approved by the Bioethical Commission of Ivano-Frankivsk National Medical University, Ivano-Frankivsk, Ivano-Frankivsk Oblast, Ukraine.

Statistical Analysis

Statistical processing of the study results was performed using the software Statistica 10 and Microsoft Excel and an online calculator Stats.Blue.[26] Shapiro–Wilk test was performed to establish the type of distribution. Descriptive statistics for data with the normal distribution are presented as the mean with standard deviation (SD) (mean ± SD). The median and interquartile range [Me (Q1–Q3)] was calculated for data with the abnormal distribution. Categorical data are presented as counts and percentages. The *t*-test was used for the comparison of two variables with the normal distribution. Mann–Whitney *U* test was performed to compare variables with the abnormal distribution. Fisher's exact test was used for the comparison of two categorical variables. Also, the OR with a 95% confidence interval (CI) was calculated. Multivariate logistic regression was used. The null hypothesis suggested that there is no statistical significance. If the *p*-value was <0.05, the null hypothesis was rejected; if the *p*-value was ≥0.05, the null hypothesis was accepted, which is common in biomedical studies.

Results

A total of 46 (43.4%) patients had a severe clinical condition and 13 (12.3%) patients had a critical clinical condition. In 47 (44.3%) patients, the clinical condition was labeled as moderate.

The main clinical parameters at the moment of hospital admission in patients who developed moderate and severe/critical clinical conditions are shown in Table 1. BMI was higher in patients with severe/critical clinical condition ($p < 0.001$). History of diabetes mellitus was more prevalent in patients with severe/critical clinical condition ($p = 0.04$). Patients who developed severe/critical clinical condition had higher CURB-65 ($p = 0.02$) and CAP-Sym questionnaire ($p = 0.03$) scores at the moment of hospital admission. Laboratory parameters at the moment of hospital admission in patients who developed moderate and severe/critical clinical conditions are shown in Table 2. Also, patients in severe/critical clinical condition had higher total leukocyte count ($p = 0.02$), segmented neutrophil percentage ($p = 0.03$), ESR ($p = 0.004$), fasting capillary glucose ($p = 0.002$), aspartate aminotransferase ($p = 0.04$), alanine aminotransferase ($p = 0.006$), and activated partial prothrombin time (APPT) ($p = 0.03$) at the moment of hospital admission. Ferritin level at the moment of hospital admission was significantly higher in patients with severe/critical clinical condition ($p = 0.03$). sIL-2R and IL-6 levels at the

moment of hospital admission were lower in patients in moderate clinical condition; however, statistical significance was not met.

Univariate analysis of risk factors for the development of the severe/critical condition is shown in Table 3. Therefore, risk factors for the development of the severe/critical condition during hospital stay include BMI of ≥30 kg/m^2, history of diabetes mellitus, CURB-65 score of >1, CAP-Sym score of ≥30, ESR of ≥35 mm/hour, ferritin level of >350 ng/mL.

Multivariate logistic regression analysis showed that BMI is an independent risk factor for the development of severe/critical clinical condition (Table 4).

Multivariate logistic regression analysis of the laboratory predictors of severe/critical condition development is shown in Table 5. Levels of ferritin of >350 ng/mL, sIL-2R of >6 ng/mL, and IL-6 of >48 pg/mL at the moment of hospital admission failed to show independent risk factors

Statins and antihypertensive agents prescribed to patients with moderate and severe/critical clinical conditions are listed in Table 6. There was no statistically significant difference in statin and antihypertensive therapy in patients with moderate and severe/critical conditions.

Discussion

Our study showed that among hypertensive patients, the elderly were not associated with a higher prevalence of severe/critical clinical condition development. Similar results showed the study performed by Sun et al.; there was no significant difference in age between patients with severe COVID-19 and the ones with moderate COVID-19.[27] However, the study performed by Zhao et al. showed that age was an independent predictor of severe COVID-19.[28]

Espiritu et al. reports an association between BMI abnormalities and odds of severe/critical COVID-19,[29] which corresponds to our data that high BMI is more prevalent in patients with severe/critical clinical condition.

Our study showed that diabetes mellitus was more prevalent in patients in severe/critical clinical condition. Our data corresponds to the results of the meta-analysis performed by Shang et al. that showed an association of diabetes mellitus with an increased risk of the severe condition and a higher mortality rate.[30]

Our data showed that the CURB-65 score of >1 predicts severe/critical clinical condition, which corresponds to the results of the study performed in China that showed CURB-65 might serve as a useful prognostic marker in COVID-19 patients.[31]

Our study showed that ferritin level at the moment of hospital admission was significantly higher in patients with severe/critical clinical condition. This data corresponds to the results of the meta-analysis that confirmed an association between high serum ferritin levels and severe COVID-19.[32]

Serum IL-6 and sIL-2R levels in our study were somewhat higher in patients with severe/critical COVID-19, but statistical significance

Table 1: The main clinical parameters at the moment of hospital admission in patients who developed moderate and severe/critical clinical conditions

Parameter	*Patients with moderate condition (n = 47)*	*Patients with severe/critical condition (n = 59)*	*p-value*
Patients' characteristics			
Age, years	67.6 ± 2.7	69.0 ± 2.0	0.43
BMI, kg/m^2	25.3 (23.5–29.1)	30.4 (26.4–34.1)	<0.001
Male gender	20 (42.6%)	21 (35.6%)	0.55
Comorbidities			
Prior myocardial infarction	6 (12.8%)	7 (11.9%)	1.0
Prior stroke	4 (8.5%)	5 (8.5%)	1.0
History of diabetes mellitus	10 (21.3%)	24 (40.7%)	0.04
Atrial fibrillation	5 (10.6%)	6 (10.2%)	1.0
Severe valvular heart disease	3 (6.4%)	1 (1.7%)	0.32
Hypothyroidism	1 (2.1%)	5 (8.4%)	0.22
Complaints at the hospital admission			
Cough	36 (76.6%)	51 (86.4%)	0.21
Breathlessness	22 (46.8%)	45 (76.3%)	0.002
Fatigue	38 (80.9%)	54 (91.5%)	0.15
Leg pain	21 (44.7%)	29 (49.2%)	0.70
Back pain	22 (46.8%)	16 (27.1%)	0.04
Headache	17 (36.2%)	15 (25.4%)	0.29
Insomnia	28 (59.6%)	39 (66.1%)	0.55
Taste disorders	10 (21.3%)	13 (22.0%)	1.0
Smell disorders	10 (21.3%)	11 (18.6%)	0.81
CURB-65 and CAP-Sym scores at the moment of hospital admission			
CURB-65 score	1.0 (0.0–1.0)	1.0 (0.0–2.0)	0.02
CAP-Sym questionnaire	22.0 (16.0–33.0)	30.0 (20.0–37.0)	0.03

Note: Data are presented as either absolute number (%), mean value (CI) for variables with a normal distribution, or median value (lower and upper quartiles) for variables with an abnormal distribution. BMI, body mass index

Table 2: Laboratory parameters at the moment of hospital admission in patients who developed moderate and severe/critical clinical conditions

Parameter	*Patients with moderate condition (n = 47)*	*Patients with severe/critical condition (n = 59)*	*p-value*
Erythrocytes, 10^{12}/L	4.6 (4.1–4.9)	4.6 (4.2–5.0)	0.80
Hemoglobin, gm/L	129.0 (120.0–140.0)	131.0 (121.0–142.0)	0.86
Leukocytes, 10^9/L	5.4 (4.3–7.1)	7.2 (5.0–9.8)	0.02
Band neutrophils, %	5.0 (3.0–8.0)	4.0 (3.0–7.0)	0.53
Segmented neutrophils, %	68.5 (60.0–76.0)	74.0 (65.0–81.0)	0.03
Lymphocytes, %	19.0 (15.0–24.0)	16.0 (10.5–22.0)	0.057
Monocytes, %	4.0 (2.0–6.0)	4.0 (2.5–6.0]	0.72
Platelets, 10^9/L	187.0 (141.0-283.5)	204.0 (160.0–245.0)	0.69
ESR, mm/hour	28.0 (14.0–34.5)	37.5 (24.0–46.5)	0.004
Fasting glucose, mmol/L	5.6 (5.2–6.6)	6.9 (5.7–9.5)	0.002
Total protein, gm/L	72.0 (64.5–76.3)	68.0 (62.7–73.7)	0.35
Total bilirubin, µmol/L	10.2 (8.4–13.4)	9.9 (8.4–13.1)	0.80
Aspartate aminotransferase, IU/L	24.8 (16.2–36.7)	32.0 (21.9–39.5)	0.04
Alanine aminotransferase, IU/L	22.8 (14.4–34.4)	28.1 (23.4–46.4)	0.006
Creatinine, µmol/L	95.4 (86.7–104.6)	100.2 (86.0–117.0)	0.25
Blood urea nitrogen, mmol/L	5.6 (4.9–7.1)	6.8 (5.0–8.0)	0.052
Total cholesterol, mmol/L	4.82 ± 0.39	4.83 ± 0.38	0.97
Prothrombin index, %	104.0 (96.4–111.0)	103.0 (87.5–112.5)	0.58
APPT, seconds (s)	22.7 (21.3–24.2)	25.5 (22.1–28.5)	0.03
Fibrinogen, gm/L	4.9 (4.2–5.9)	5.2 (4.7–6.4)	0.31
Ferritin, ng/mL	315.5 (169.0–396.0)	430.5 (177.0–733.0)	0.03
sIL-2R, ng/mL	5.59 (4.29–7.30)	6.29 (4.68–9.46)	0.15
IL-6, pg/mL	37.8 (13.6–74.4)	52.6 (19.1–110.8)	0.13

Note: Data are presented as either mean value (CI) for variables with a normal distribution or median value (lower and upper quartiles) for variables with an abnormal distribution. APPT, activated partial prothrombin time; ESR, erythrocyte sedimentation rate; IL-6, interleukin-6; sIL-2R, soluble interleukin-2 receptor

Table 3: Univariate analysis of risk factors for the development of the severe/critical condition

Risk factor	*OR*	*95% CI*	*p-value*
Age of ≥70-year-old	1.28	0.59–2.76	0.528
BMI ≥ 30.0 kg/m^2	3.83	1.61–9.09	0.002
History of diabetes mellitus	2.54	1.06–6.06	0.036
CURB-65 score >1	7.67	1.66–35.52	0.009
CAP-Sym score ≥ 30	2.44	1.09–5.47	0.030
Total leukocyte count ≥ 10.0 × 109 /L	2.67	0.88–8.07	0.081
Lymphocyte percentage <19.0%	1.95	0.89–4.28	0.096
ESR ≥ 35.0 mm/hour	4.11	1.52–11.12	0.005
Aspartate aminotransferase ≥40.0 IU/L	1.59	0.60–4.19	0.351
Alanine aminotransferase ≥40.0 IU/L	2.64	0.99–7.01	0.052
APPT > 35.0 s	6.80	0.34–134.27	0.208
Fibrinogen > 4.0 gm/L	0.92	0.29–2.87	0.885
Ferritin > 350.0 ng/mL	2.42	1.09–5.35	0.030
sIL-2R > 6.0 ng/mL	1.49	0.69–3.23	0.307
IL-6 > 48.0 pg/mL	1.91	0.88–4.17	0.104

APPT, activated partial prothrombin time; BMI, body mass index; CI, confidence interval; ESR, erythrocyte sedimentation rate; IL-6, interleukin-6; OR, odds ratio; sIL-2R, soluble interleukin-2 receptor

was not met. Many studies showed that increased IL-6 level is associated with severe disease and adverse outcomes.[33–35] In patients aged ≥60-year-old, a high sIL-2R level was associated with mortality.[36] However, the study conducted by Liu et al., showed that the IL-6 level predicts a severe disease but not mortality.[37] Also, sIL-2R levels were associated with a prolonged duration of illness.[38] sIL-2R levels at the moment of hospital admission and in dynamic may reflect COVID-19 severity and predict severe respiratory failure.[12]

The controversies between our study and the studies mentioned above may be explained by differences in populations. Our study included only hospitalized hypertensive patients with COVID-19.

Table 4: Multivariate logistic regression analysis of risk factors for the development of the severe/critical clinical condition

Variable	*Coefficient*	*SE*	*p-value*	*OR*	*95% CI*
Age of ≥70-year-old	0.0165	0.4843	0.9728	1.0166	(0.3935, 2.6266)
BMI ≥ 30.0 kg/m^2	1.1569	0.4842	0.0169	3.1801	(1.2312, 8.2140)
History of diabetes mellitus	0.5571	0.5108	0.2755	1.7456	(0.6414, 4.7506)
CURB-65 score > 1	1.5117	0.8671	0.0813	4.5343	(0.8287, 24.8098)
CAP-Sym score > 30	0.8338	0.4564	0.0677	2.3021	(0.9410, 5.6315)

BMI, body mass index; CI, confidence interval; OR, odds ratio; SE, standard error

Table 5: Multivariate logistic regression analysis of the laboratory predictors of severe/critical clinical condition development

Variable	*Coefficient*	*SE*	*p-value*	*OR*	*95% CI*
Ferritin > 350.0 ng/mL	0.8202	0.4400	0.0623	2.2710	(0.9587, 5.3797)
sIL-2R > 6.0 ng/mL	–0.0376	0.4404	0.9320	0.9631	(0.4063, 2.2833)
IL-6 > 48.0 pg/mL	0.4480	0.4158	0.2813	1.5653	(0.6928, 3.5362)

CI, confidence interval; IL-6, interleukin-6; OR, odds ratio; SE, standard error; sIL-2R, soluble interleukin-2 receptors

Table 6: Statins and antihypertensive agents prescribed to enrolled patients

Medications	*Patients with moderate condition (n = 47)*	*Patients with severe/critical condition (n = 59)*	*p-value*
Statins	15 (31.9%)	14 (23.7%)	0.39
ACEi	28 (59.6%)	31 (52.5%)	0.56
ARB	13 (27.7%)	20 (33.9%)	0.53
Diuretics	20 (42.6%)	25 (42.4%)	1.00
CCB	14 (29.8%)	24 (40.7%)	0.31
β-blockers	16 (34.0%)	22 (37.3%)	0.84
MRA	1 (2.1%)	7 (11.9%)	0.07

ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CCB, calcium channel blockers; MRA, mineralocorticoid receptor antagonists

None of the enrolled patients had a mild clinical condition. Each participant had pulmonary involvement confirmed radiologically.

Further perspectives include an assessment of lethal outcome predictors in hypertensive hospitalized patients and CAP-Sym questionnaire validation for COVID-19-associated pneumonia.

Conclusion

Increased BMI, diabetes mellitus, high ESR, and ferritin level at admission predict severe/critical disease in unvaccinated hypertensive patients hospitalized for COVID-19. However, only a BMI of ≥30 kg/m^2 is an independent risk factor for severe/critical disease according to multivariate logistic regression analysis. The CAP-Sym questionnaire may be used for the prediction of severe/critical COVID-19.

Limitations

Our study has some limitations within which the findings need to be interpreted carefully. First, our study was limited by the number of participants. Second, our study included only unvaccinated patients. Third, all patients were hospitalized for pneumonia confirmed by a radiological study, and none of the patients had a mild clinical course.

References

1. 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. DOI: 10.1016/S0140-6736(20)30183-5
2. Center for Systems Science and Engineering. John Hopkins University COVID-19 Dashboard by the Center for Systems Science and. Engineering (CSSE). Available at: https://www.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6.
3. Hernandez Acosta RA, Esquer Garrigos Z, Marcelin JR, et al. COVID-19 pathogenesis and clinical manifestations. Infect Dis Clin North Am 2022;36(2):231–249. DOI: 10.1016/j.idc.2022.01.003
4. Hu Y, Sun J, Dai Z, et al. Prevalence and severity of coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis. J Clin Virol 2020;127:104371. DOI: 10.1016/j.jcv.2020.104371
5. Assal HH, Abdel-hamid HM, Magdy S, et al. Predictors of severity and mortality in COVID-19 patients. Egypt J Bronchol 2022;16(1):18. DOI:10.1186/s43168-022-00122-0
6. Sen KK, Dubey R, Mohanty SS, et al. Spectrum of barotraumatic events in COVID-19 patients on high-resolution computed tomography. Indian J Respir Care 2022;11(1):67–70. DOI: 10.4103/ijrc.ijrc_115_21
7. Joshee S, Vatti N, Chang C. Long-term effects of COVID-19. Mayo Clin Proc 2022;97(3):579–599. DOI: 10.1016/j.mayocp.2021.12.017
8. Pijls BG, Jolani S, Atherley A, et al. Demographic risk factors for COVID-19 infection, severity, ICU admission and death: a meta-analysis of 59 studies. BMJ Open 2021;11(1):e044640. DOI: 10.1136/bmjopen-2020-044640
9. Guan WJ, Liang WH, Zhao Y, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur Respir J 2020;55(5):2000547. DOI: 10.1183/13993003.00547-2020
10. Del Sole F, Farcomeni A, Loffredo L, et al. Features of severe COVID-19: a systematic review and meta-analysis. Eur J Clin Invest 2020;50(10):e13378. DOI: 10.1111/eci.13378
11. Bozkurt FT, Tercan M, Patmano G, et al. Can ferritin levels predict the severity of illness in patients with COVID-19? Cureus 2021;13(1):e12832. DOI: 10.7759/cureus.12832

12. Gatselis NK, Lygoura V, Lyberopoulou A, et al. Soluble IL-2R levels at baseline predict the development of severe respiratory failure and mortality in COVID-19 patients. Viruses 2022;14(4):787. DOI: 10.3390/v14040787
13. Toori KU, Qureshi MA, Chaudhry A. Lymphopenia: a useful predictor of COVID-19 disease severity and mortality. Pak J Med Sci 2021;37(7):1984–1988. DOI: 10.12669/pjms.37.7.4085
14. Zeng F, Huang Y, Guo Y, et al. Association of inflammatory markers with the severity of COVID-19: a meta-analysis. Int J Infect Dis 2020;96:467–474. DOI: 10.1016/j.ijid.2020.05.055
15. Tam AR, Zhang RR, Lung KC, et al. Early treatment of high-risk hospitalized COVID-19 patients with a combination of interferon beta-1b and remdesivir: a phase 2 open-label randomized controlled trial. Clin Infect Dis 2022;ciac523. DOI: 10.1093/cid/ciac523
16. Gupta A, Gonzalez-Rojas Y, Juarez E, et al. Early treatment for COVID-19 with SARS-CoV-2 neutralizing antibody sotrovimab. N Engl J Med 2021;385(21):1941–1950. DOI: 10.1056/NEJMoa2107934
17. Alexander PE, Armstrong R, Fareed G, et al. Early multidrug treatment of SARS-CoV-2 infection (COVID-19) and reduced mortality among nursing home (or outpatient/ambulatory) residents. Med Hypotheses 2021;153:110622. DOI: 10.1016/j.mehy.2021.110622
18. Pranata R, Lim MA, Huang I, et al. Hypertension is associated with increased mortality and severity of disease in COVID-19 pneumonia: a systematic review, meta-analysis and meta-regression. J Renin Angiotensin Aldosterone Syst 2020;21(2):1470320320926899. DOI: 10.1177/1470320320926899
19. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020;323(11):1061–1069. DOI: 10.1001/jama.2020.1585
20. Chen J, Liu Y, Qin J, et al. Hypertension as an independent risk factor for severity and mortality in patients with COVID-19: a retrospective study. Postgrad Med J 2022;98(1161):515–522. DOI: 10.1136/postgradmedj-2021-140674
21. Mughal M, Gandhi H, Okoh A, et al. Is hypertension (HTN) an independent risk factor for mortality in COVID-19 patients? J Am Coll Cardiol 2021;77(18):3068. DOI: 10.1016/S0735-1097(21)04423-5
22. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J 2018;39(33):3021–3104. DOI: 10.1093/eurheartj/ehy339
23. Lim WS, van der Eerden MM, Laing R, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax 2003;58(5):377–382. DOI: 10.1136/thorax.58.5.377
24. Lamping DL, Schroter S, Marquis P, et al. The community-acquired pneumonia symptom questionnaire: a new, patient-based outcome measure to evaluate symptoms in patients with community-acquired pneumonia. Chest 2002;122(3):920–929. DOI: 10.1378/chest.122.3.920
25. Ministerstvo Okhorony Zdorovia Ukrainy. Derzhavnyi Ekspertnyi Tsentr. Protokol «Nadannia medychnoi dopomohy dlia likuvannia koronavirusnoi khvoroby (COVID-19)». Available at: https://www.dec.gov.ua/wp-content/uploads/2021/01/2021_01_kn_covid-19.pdf [accessed 22, July, 2022].
26. Online Statistics Suite [Internet]. Stats.Blue. Available from: https://stats.blue/ [accessed 23, July, 2022].
27. Sun C, Xue M, Yang M, et al. Early prediction of severe COVID-19 in patients by a novel immune-related predictive model. mSphere 2021;6(5):e0075221. DOI: 10.1128/mSphere.00752-21
28. Zhao Q, Yuan Y, Zhang J, et al. Early predictors of severe COVID-19 among hospitalized patients. J Clin Lab Anal 2022;36(2):e24177. DOI: 10.1002/jcla.24177
29. Espiritu AI, Reyes NGD, Leochico CFD, et al. Body mass index and its association with COVID-19 clinical outcomes: findings from the Philippine CORONA study. Clin Nutr ESPEN 2022;49:402–410. DOI: 10.1016/j.clnesp.2022.03.013
30. Shang L, Shao M, Guo Q, et al. Diabetes mellitus is associated with severe infection and mortality in patients with COVID-19: a systematic review and meta-analysis. Arch Med Res 2020;51(7):700–709. DOI: 10.1016/j.arcmed.2020.07.005
31. Guo J, Zhou B, Zhu M, et al. CURB-65 may serve as a useful prognostic marker in COVID-19 patients within Wuhan, China: a retrospective cohort study. Epidemiol Infect 2020;148:e241. DOI: 10.1017/S0950268820002368
32. Kaushal K, Kaur H, Sarma P, et al. Serum ferritin as a predictive biomarker in COVID-19. a systematic review, meta-analysis and meta-regression analysis. J Crit Care 2022;67:172–181. DOI: 10.1016/j.jcrc.2021.09.023
33. Coomes EA, Haghbayan H. Interleukin-6 in COVID-19: a systematic review and meta-analysis. Rev Med Virol 2020;30(6):1–9. DOI: 10.1002/rmv.2141
34. Sanli DET, Altundag A, Kandemirli SG, et al. Relationship between disease severity and serum IL-6 levels in COVID-19 anosmia. Am J Otolaryngol 2021;42(1):102796. DOI: 10.1016/j.amjoto.2020.102796
35. Sabaka P, Koščálová A,Straka I, et al. Role of interleukin 6 as a predictive factor for a severe course of COVID-19: retrospective data analysis of patients from a long-term care facility during Covid-19 outbreak. BMC Infect Dis 2021;21(1):308. DOI: 10.1186/s12879-021-05945-8
36. Kaya H, Kaji M, Usuda D. Soluble interleukin-2 receptor levels on admission associated with mortality in coronavirus disease 2019. Int J Infect Dis 2021;105:522–524. DOI: 10.1016/j.ijid.2021.03.011
37. Liu X, Wang H, Shi S, et al. Association between IL-6 and severe disease and mortality in COVID-19 disease: a systematic review and meta-analysis. Postgrad Med J 2021;0:1–9. DOI: 10.1136/postgradmedj-2021-139939
38. Ma A, Zhang L, Ye X, et al. High levels of circulating IL-8 and soluble IL-2R Are associated with prolonged illness in patients with severe COVID-19. Front Immunol 2021;12:626235. DOI: 10.3389/fimmu.2021.626235