Research Article | Internal Medicine

Prognostic Value of Serum Interleukin-6 Level in Hypertensive Patients with COVID-19-Associated Pneumonia

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Abstract

Background. An interleukin-6 (IL-6) is a proinflammatory cytokine which plays an important role in COVID-19-associated hyperinflammation.

Aim. This study aimed to assess the predictive ability of serum IL-6 levels for the development of severe/critical clinical conditions, a hypoxemic state requiring supplemental oxygen, and lethal outcomes in patients with COVID-19-associated pneumonia and arterial hypertension (AH).

Materials and Methods. One hundred and thirty-five unvaccinated patients hospitalized for COVID-19-associated pneumonia were enrolled in the study. AH was diagnosed in 78.5% of cases. Pneumonia was confirmed radiologically. SARS-COV-2 as an etiological factor was confirmed by either PCR or ELISA. In addition to conventional laboratory tests, IL-6, ferritin, and soluble interleukin-2 levels were measured.

Results. Among AH patients, the median levels of IL-6 were higher in non-survivors (95.1 [37.8–158.8] pg/mL) as compared to survivors (39.5 [13.6–81.1] pg/mL) (p = 0.04). Among AH patients, the median serum level of IL-6 was 98.3 [37.8–158.8] pg/mL in critically ill patients, 41.7 [11.8–83.4] pg/mL in severely ill patients, 37.8 [13.6–74.4] pg/mL in moderately ill patients (p = 0.051). The median serum level of IL-6 was lower at the time of discharge (6.5 [2.0–21.5] pg/mL) as compared to that on admission (43.2 [16.1–92.0] pg/mL) (p < 0.001). IL-6 level failed to predict severe/critical condition (AUC = 0.59, p = 0.13) and the need for supplemental oxygen (AUC = 0.61, p = 0.06); however, it might be used for the prediction of the lethal outcome (AUC = 0.69, p = 0.03). The cut-off value of IL-6 level for lethal outcome prediction of 91.0 pg/mL showed a sensitivity of 58.3% and a specificity of 78.7%. Patients with IL-6 levels > 91.0 pg/mL on admission had higher odds of lethal outcomes (OR = 4.87 [1.40–16.92], p = 0.01).

Conclusions. Serum IL-6 level on admission did not show significant predictive ability for severe/critical conditions and hypoxemic states requiring supplemental oxygen in AH patients. However, serum IL-6 levels on admission were higher in non-survivors and might be used for the prediction of lethal outcomes with a cut-off value of 91.0 pg/mL in AH patients.

Keywords

COVID-19; Interleukin-6; Hypertension; Pneumonia; Predictive Value

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Introduction

A novel coronavirus as a causal agent of severe acute respiratory syndrome was first described in December 2019 in China [1]. Afterwards this virus was named SARS-CoV-2 and spread rapidly worldwide causing a pandemic. According to the World Health Organization (WHO) reports, as of 23 June 2022, there were almost 540 million confirmed cases of COVID-19, including over 6.3 million deaths globally [2]. One of the most common manifestations of COVID-19 is pneumonia which may progress into acute respiratory distress syndrome [3, 4].

Severe COVID-19 cases are associated with hyperinflammation, leading to macrophage activation syndrome [5]. The devastating effect of immune dysregulation is considered to play a critical role in the deterioration of the patient's condition [6]. In fatal cases, COVID-19 was found to lead to the hyperactivation of cytotoxic T-cells with high concentrations of cytotoxic granules [7]. An interleukin-6

(IL-6) is a proinflammatory cytokine that activates T- and B-cells [8]. IL-6 level rises in macrophage activation syndrome, as the cytokine is released by alveolar macrophages upon lung infection [9].

Lower IL-6 levels were found to be associated with a milder clinical course of COVID-19 [10]. Patients with complicated COVID-19 have 2.9-fold higher IL-6 levels than those with uncomplicated disease [11]. IL-6 level may predetermine the disease progression and is found to be significantly higher in non-survivors [12, 13]. An abrupt increase in the circulating IL-6 level was found in deceased patients [14].

IL-6 level as a predictor of severe disease and in-hospital death has been widely studied. IL-6 levels are higher in non-survivors as compared to survivors [15]. Furthermore, IL-6 level is found to be an independent prognostic factor for COVID-19 severity and mortality [16]. It should be noted that the presence of comorbidity or chronic diseases may potentially impact COVID-19 progression [17]. Thus, 49.7% of patients hospitalized for COVID-19 have arterial hypertension (AH) [18], which is associated with a 2-fold increase in mortality rate and incidence of severe COVID-19 [19]. The assessment of the association between IL-6 levels and lethal outcomes in AH patients is important, as an early intensive strategy may improve the patients' prognosis. Thus, the assessment of the predictive value of IL-6 level for the prediction of the severe clinical condition and hypoxemic state requiring supplemental oxygen in AH patients is meaningful.

This study **aimed** to assess the predictive ability of serum IL-6 levels for severe/critical clinical condition development, a hypoxemic state requiring supplemental oxygen, and lethal outcomes in patients with COVID-19-associated pneumonia and AH.

Materials and Methods

Study Design
This was a single-centre, prospective clinical study conducted in the Ivano-Frankivsk Central City Hospital and the Ivano-Frankivsk City Hospital No. 1. The patients were enrolled between March and June 2021.

Study Population
One hundred and thirty-five adult patients hospitalized for COVID-19-associated pneumonia were enrolled in the study. All patients were not vaccinated for COVID-19. A total of 106 (78.5%) patients had AH.

The main characteristics of patients enrolled in the study are shown in Table 1.

Table 1. The main characteristics of enrolled patients.

Parameter	Patients with AH (n=106)	Patients without AH (n=29)	p
Age, years†	68.4±1.7	59.1±4.9	<0.01
BMI, kg/m^2†	28.7±1.1	28.4±1.9	0.74
Male gender	41 (38.7%)	12 (41.4%)	0.79
CURB-65§	1.0 [0.0–1.0]	1.0 [0.0–1.0]	0.22

Notes: BMI – body mass index;
† Mean with standard deviation (Mean ± SD)
§ Median with interquartile range (Me [Q1–Q3])

Diagnostic Statements
Pneumonia was confirmed by chest computed tomography or chest X-ray. Coronavirus SARS-CoV-2 as an etiological agent of pneumonia was confirmed with either polymerase chain reaction (PCR) or ELISA test, with the assessment of immunoglobulin M (IgM) level.

The diagnosis of AH was made in accordance with the criteria of the 2018 European Society of Cardiology guidelines [20]. Pneumonia severity was assessed in accordance with the CURB-65 score [21, 22].

The severity of COVID-19-associated pneumonia was assessed according to the Protocol of Medical Care for Treatment of Coronavirus Disease (COVID-19) [23]. A severe clinical condition was defined in the presence of at least one of the following characteristics: respiratory rate $\geq$ 30 breaths per minute; oxygen saturation $\leq$ 93%; pulmonary infiltrates involving > 50% of the lung area. The critical condition was defined in the presence of at least one of the following signs: acute respiratory distress syndrome; sepsis; altered consciousness; multiple organ dysfunction syndrome.

Disease severity of all enrolled patients is shown in Fig. 1.

In addition to conventional laboratory tests (complete blood count, urinalysis, fasting glucose, biochemical profile), levels of IL-6 (IL E-3200 Interleukin-6, "Novamedline", ELISA test), soluble IL-2 receptors (30166211, sInterleukin-2-Receptor, "IVSet", ELISA test), and ferritin
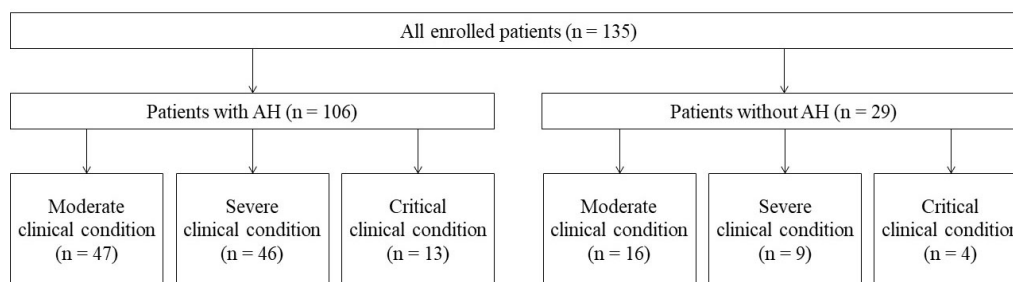

Figure 1. Clinical condition of enrolled patients.

(L2KFE2, Immulite 2000 Ferritin, "Siemens", ELISA test) were measured. A PCR test and ELISA test with the assessment of IgM level (in patients with negative PCR test) were performed as well.

Patient Management
All patients were treated in accordance with the Protocol of Medical Care for Treatment of Coronavirus Disease (COVID-19) [23]. All patients received corticosteroids and either low-molecular-weight heparin or unfractionated heparin.

Statistical Analysis
Statistical processing of the study results was performed using the software Statistica 10, MedCalc, and MS Excel. The Shapiro-Wilk test was used to evaluate the distribution of variables. Descriptive statistics for data with non-normal distribution are presented as the median and interquartile range (Me [Q1–Q3]). Mean with standard deviation (Mean ± SD) was calculated for descriptive statistics for data with normal distribution. The Mann-Whitney U test, the Kruskal-Wallis test with the post-hoc Dunn's test, the Wilcoxon signed-rank test, the Chi-square test, the Odds ratio (OR), and the Spearman's rank correlation analysis were used. A p-value < 0.05 was considered significant.

Results

The median level of IL-6 at the time of admission in AH patients did not significantly differ from that in patients without AH (Table 2). However, serum soluble interleukin-2 receptor (sIL-2R) level was higher in AH patients. Among AH patients, there was no statistically significant difference in IL-6 serum levels in terms of clinical condition (moderate – 37.8 [13.6–74.4] pg/mL, severe – 41.7 [11.8–83.4] pg/mL, critical – 98.3 [37.8–158.8] pg/mL; p = 0.051).

Table 2. Specific biomarkers in enrolled patients.

Parameter	Patients with AH (n=106)	Patients without AH (n=29)	p
IL-6, pg/mL	43.2 [16.1-92.0]	47.2 [10.0-92.4]	0.61
sIL-2R, ng/mL	5.87 [4.51-8.16]	4.99 [3.56-6.14]	0.04
Ferritin, ng/mL	349.0 [176.0-572.5]	349.0 [189.0-746.5]	0.92

There was no statistically significant difference in IL-6 levels among AH patients in terms of gender (males – 30.7 [12.7–83.9] pg/mL, females – 50.6 [20.0–93.6] pg/mL; p = 0.24) and hypoxemic state (the need for supplemental oxygen – 63.5 [20.0–110.8] pg/mL, no need for supplemental oxygen – 37.0 [10.8–68.4] pg/mL; p = 0.06).

The lethal outcome was observed in 12 (11.3%) AH patients. Fig. 2 presents serum IL-6 levels in survivors and non-survivors with AH and all enrolled patients on admission.
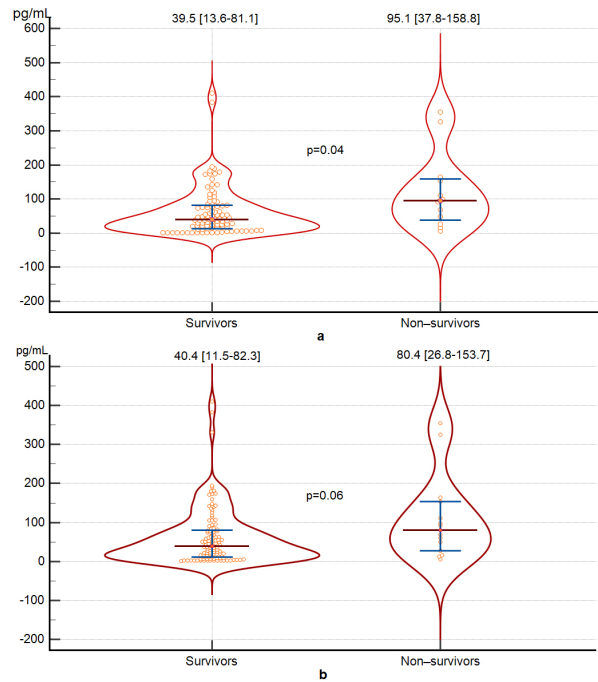

Figure 2. Serum IL-6 levels in survivors and non-survivors with arterial hypertension (a) and all enrolled patients (b) on admission.

At the time of discharge, in survivors, the median level of IL-6 was 6.5 [2.0–21.5] pg/mL in patients with AH and 18.2 [2.0–37.2] pg/mL in patients without AH (p = 0.39). Serum IL-6 level was significantly lower in AH patients at the time of discharge as compared to that on admission (p < 0.001); however, this was not statistically significant in patients without AH (p = 0.07).

There was a moderate positive correlation between IL-6 and ferritin levels (r = 0.35, p < 0.001) in AH patients. In AH patients, there was no correlation between the levels of IL-6 and sIL-2R (r = 0.18, p = 0.07). In patients without AH, IL-6 level did not correlate with ferritin level (r = -0.17, p = 0.39) and sIL-2Rs (r = -0.26, p = 0.18).

The predictive abilities of IL-6 level for the development of severe and critical clinical conditions, supplemental oxygen requirement, and in-hospital lethal outcomes in AH patients on admission are shown in Table 3 and receiver operating characteristic (ROC) curves are presented in Fig. 3-5.

IL-6 serum level failed to predict severe/critical clinical condition (Area Under the Curve (AUC) = 0.585, p = 0.13) and hypoxemic state requiring supplemental oxygen (AUC = 0.606, p = 0.06). There was acceptable discrimination (AUC = 0.688, p = 0.03) of IL-6 serum levels in the prediction of lethal outcomes. However, the Youden index was 0.37 indicating the inability of serum IL-6 level to predict the lethal outcome. The cut-off value of IL-6 level of > 91.0 pg/mL showed a sensitivity of 58.3% and a specificity of 78.7%. Patients with such IL-6 levels at the time of admission had higher odds of lethal outcomes (OR = 4.87 [1.40–16.92], p = 0.01).

Table 3. Predictive ability of serum IL-6 level for the development of severe/critical clinical conditions, a hypoxemic state requiring supplemental oxygen, and lethal outcomes in patients with arterial hypertension.

| IL-6 level	Sensitivity, %	Specificity, %	Positive Predictive Value, %	Negative Predictive Value, %
Development of severe/critical clinical conditions				
≥6.0 pg/mL	84.8	17.0	56.2	47.1
≥24.0 pg/mL	71.2	38.3	59.2	51.4
≥48.0 pg/mL	54.2	61.7	64.0	51.8
≥64.0 pg/mL	45.8	74.5	69.2	52.2
≥100.0 pg/mL	27.1	85.1	69.6	48.2
Development of hypoxemic state requiring supplemental oxygen				
≥6.0 pg/mL	86.0	17.9	48.3	58.8
≥24.0 pg/mL	74.0	39.3	52.1	62.9
≥48.0 pg/mL	58.0	62.5	58.0	62.5
≥64.0 pg/mL	50.0	75.0	64.1	62.7
≥100.0 pg/mL	28.0	83.9	60.9	56.6
In-hospital lethal outcome				
≥6.0 pg/mL	91.6	17.0	12.4	94.1
≥24.0 pg/mL	83.3	35.1	14.1	94.3
≥48.0 pg/mL	75.0	56.4	18.0	94.6
≥64.0 pg/mL	66.7	67.0	20.5	94.0
≥100.0 pg/mL	41.7	80.9	21.7	91.6
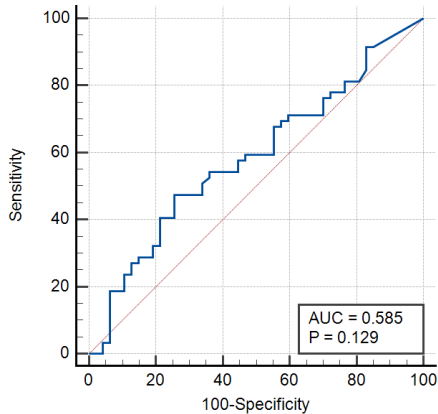
Figure 3. ROC curve of IL-6 serum level on admission for prediction of severe/critical clinical condition in patients with arterial hypertension.
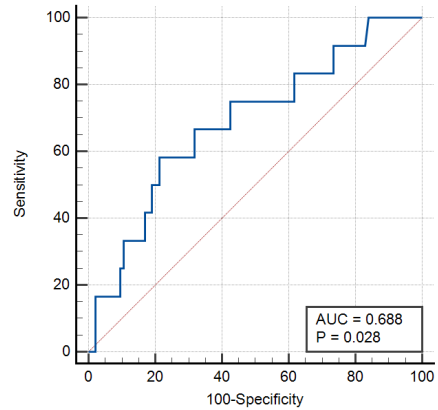

Figure 5. ROC curve of IL-6 serum level on admission for prediction of in-hospital lethal outcome in patients with arterial hypertension.
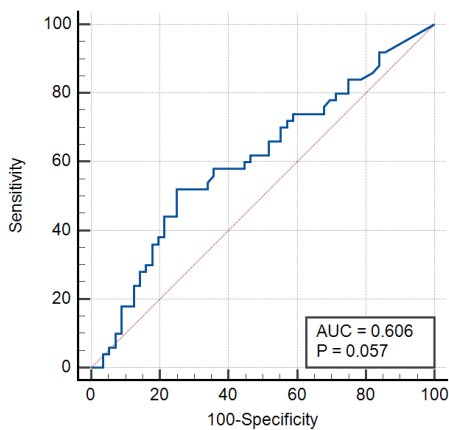

Figure 4. ROC curve of IL-6 serum level on admission for prediction of hypoxemic state requiring supplemental oxygen in patients with arterial hypertension.

Discussion

Our study showed that IL-6 level was higher in non-survivors. Multiple studies showed similar results. In a study of Guirao *et al.*, higher levels of IL-6 were associated with severe COVID-19 course, mechanical ventilation requirements in the intensive care unit (ICU), and mortality [24]. The cut-off value of serum IL-6 levels of 35 pg/mL was proposed; both the risk of mortality (OR = 20.00, p = 0.0001) and ICU admission (OR = 12.75, p = 0.005) increased in patients with IL-6 level above this cut-off point [24]. Another study showed that non-survivors had higher IL-6 levels than survivors; the optimal cut-off value of IL-6 level was considered as 30.95 pg/mL [25]. Population with elevated IL-6 had a higher mortality rate (28.2% vs 5%; p = 0.0001, OR = 7.47) [26].

A study by Zhou *et al.* showed that elevated IL-6 levels were associated with an increase in the incidence of critical cases, acute respiratory distress syndrome, mechanical ven-

tilation rate, and mortality [27]. Serum IL-6 concentration is an independent predictor of the lethal outcome; the optimal cut-off value for predicting the lethal outcome is 26.09 pg/mL [27].

Our study showed some tendency towards an increase in serum IL-6 level on admission with clinical condition worsening in AH patients, although statistical significance was not achieved. According to Zhou *et al.* a higher level of IL-6 predicted a more severe clinical condition [28]. In a study by Sun *et al.*, IL-6 levels were higher in patients with severe COVID-19 and non-severe disease [29]. A meta-analysis conducted by Mojtabavi *et al.* showed that patients with severe COVID-19 had 23.1 pg/mL higher IL-6 as compared to patients with non-severe COVID-19 [30].

Liu *et al.* reported that IL-6 level might be an independent risk factor for disease severity and in-hospital mortality [31]. However, among ICU patients, IL-6 failed to predict clinical outcomes in terms of survivors vs. non-survivors [32].

Sabaka *et al.* reported a significant predictive ability of IL-6 level (AUC = 0.911, p = 0.0001), with high sensitivity (100.0%), specificity (88.9%), positive predictive value (76.9%), and negative predictive value (100.0%) of the cut-off value > 24 pg/mL in the prediction of the development of hypoxemia requiring supplemental oxygen [33]. In our study, the values for the development of severe or critical clinical conditions (AUC = 0.585, p = 0.13) and hypoxemia requiring supplemental oxygen (AUC = 0.606, p = 0.06) were significantly lower. These differences may be explained by differences in disease severity at the time of recruitment in these studies. Our study studied the predictive ability of IL-6 level in AH patients only, while a study by Sabaka *et al.* included ambulatory patients, among whom, 54.2% of patients were hospitalized [33].

In addition, a study conducted by Gao *et al.* showed acceptable discrimination of IL-6 levels for severe COVID-19 (AUC = 0.795, p < 0.001) [34]. Broman *et al.* supported these results and concluded that IL-6 was one of the strongest predictors of severity in patients hospitalized for COVID-19 [35]. Gorham *et al.* demonstrated the predictive ability of IL-6 level for ICU mortality (AUC = 0.73, p = 0.01) similar to data from our study [36]. A study conducted by Aykal *et al.* showed an important role of this marker as a predictor of severe clinical condition in patients with COVID-19 [37]. This study showed that patients with severe condition had higher IL-6 levels than patients with moderate and mild conditions. The AUC for IL-6 level as a predictor of severe clinical condition was 0.864 (p < 0.001) [37].

A model using both IL-6 and IL-10 suggested by Dhar *et al.* showed high predictive ability for severe COVID-19 (AUC = 0.957; accuracy 91.7%), whereas IL-6 (AUC = 0.821; accuracy 77.8%) and IL-10 (AUC = 0.878; accuracy 80.6%) taken individually showed far lower predictive ability [38].

Yamamoto *et al.* found that IL-6 level on day 3 after admission had satisfactory discrimination ability for mortality in critically ill patients (AUC = 0.766; p < 0.001) [39]. IL-6 level showed somewhat lover discriminative ability

in hospitalized patients (AUC = 0.74, p < 0.0001), according to a study by Laguna-Goya *et al.* [40]. However, a meta-analysis conducted by Liu *et al.* showed no predictive ability of IL-6 level for mortality (AUC = 0.531 with a sensitivity of 0.15 and a specificity of 0.73) [41]. Our study showed a lower discriminative ability of IL-6 level for the prediction of lethal outcomes (AUC = 0.688, p = 0.03, Youden index = 0.37).

There is a wide range of optimal cut-off values for lethal outcome prediction. Avila-Nava *et al.* reported that the optimal cut-off value was 30.95 pg/mL with a Youden index of 0.57 and for each 100 pg/mL the probability of lethal outcomes increased by 10% [25], whereas according to the research by Mandel *et al.*, the optimal cut-off value was 163.4 pg/mL with a sensitivity of 91.7% and a specificity of 57.6% [42]. Milenkovic *et al.* reported that the optimal cut-off value of IL-6 for lethal outcome prediction was 74.98 pg/mL [43]. Our study showed the optimal cut-off point of 91.0 pg/mL for the prediction of in-hospital mortality in AH patients.

Dynamic IL-6 changes may predict lung injury in COVID-19 and guide future treatment of patients [31]. Serum levels of post-tocilizumab IL-6 showed a good predictive ability to discriminate survivors from non-survivors (AUC = 0.815, p = 0.02) [44]. Galván-Román *et al.* showed that early administration of tocilizumab for patients with high IL-6 levels is associated with improved oxygenation [45]. Targeting IL-6 levels with tocilizumab reduces the mortality rate in patients with COVID-19 [46]. Anti-IL-6 signaling agents in addition to standard care reduced the mortality rate in COVID-19 [47].

There was a correlation between serum levels of IL-6 and ferritin (r = 0.64, p = 0.0001) [48]. Chen at el. reported no correlation between IL-6 level and sIL-2Rs [49]. Our correlation analysis demonstrated similar results.

Our research study significantly differs from the studies listed above as we studied the predictive ability of serum IL-6 levels in AH patients, while other studies included the general population. The results of our research may be extrapolated on patients hospitalized for COVID-19-associated pneumonia suffering from AH only. Measurement of IL-6 level on admission is important as high levels predict in-hospital lethal outcome. This enables categorizing patients with high IL-6 levels as a high-risk group requiring meticulous monitoring of clinical condition.

Limitations

Our study has some limitations; therefore, the findings need to be interpreted carefully: firstly, our study was limited by the number of participants; secondly, our study included unvaccinated patients only, which means that the results of the study cannot be extrapolated to the general population; thirdly, no patient with mild condition was included in this study as all enrolled patients were hospitalized with COVID-19-associated pneumonia.

Conclusions

Serum IL-6 level on admission did not show significant predictive ability for severe/critical conditions and hypox-

emic states requiring supplemental oxygen in AH patients. However, serum IL-6 levels on admission were higher in non-survivors and might be used for the prediction of lethal outcomes with a cut-off value of 91.0 pg/mL in AH patients.

Ethical Statement & Informed Consent

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

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of Interest

The authors declare that no conflicts exist.

Financial Disclosure

The authors declared no financial support.

References

[1] Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. New England Journal of Medicine. 2020;382(8):727–733. Available from: https://doi.org/10.1056/NEJMoa2001017

[2] WHO. WHO COVID-19 dashboard [Internet]. World Health Organization. 2022 [cited 2022 June 24]. Available from: https://covid19.who.int/

[3] Churruca M, Martínez-Besteiro E, Couñago F, Landete P. COVID-19 pneumonia: a review of typical radiological characteristics. World Journal of Radiology. 2021;13(10):327–343. Available from: https://doi.org/10.4329/wjr.v13.i10.327

[4] Gibson PG, Qin L, Puah SH. COVID-19 acute respiratory distress syndrome (ARDS): clinical features and differences from typical pre-COVID-19 ARDS. Medical Journal of Australia. 2020;213(2):54-56.e1. Available from: https://doi.org/10.5694/mja2.50674

[5] McGonagle D, Sharif K, O'Regan A, Bridgewood C. The role of cytokines including interleukin-6 in COVID-19 induced pneumonia and macrophage activation syndrome-like disease. Autoimmunity Reviews. 2020;19(6):102537. Available from: https://doi.org/10.1016/j.autrev.2020.102537

[6] Wang Y, Perlman S. COVID-19: inflammatory profile. Annual Review of Medicine. 2022;73(1):65–80. Available from: https://doi.org/10.1146/annurev-med-042220-012417

[7] Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. The Lancet Respiratory Medicine. 2020;8(4):420–422. Available from: https://doi.org/10.1016/S2213-2600(20)30076-X

[8] Vatansever HS, Becer E. Relationship between IL-6 and COVID-19: to be considered during treatment. Future Virology. 2020;15(12):817–822. Available from: https://doi.org/10.2217/fvl-2020-0168

[9] Otsuka R, Seino K. Macrophage activation syndrome and COVID-19. Inflammation and Regeneration. 2020;40:19. Available from: https://doi.org/10.1186/s41232-020-00131-w

[10] Sanli DET, Altundag A, Kandemirli SG, Yildirim D, Sanli AN, Saatci O, et al. Relationship between disease severity and serum IL-6 levels in COVID-19 anosmia. American Journal of Otolaryngology. 2021;42(1):102796. Available from: https://doi.org/10.1016/j.amjoto.2020.102796

[11] Coomes EA, Haghbayan H. Interleukin-6 in Covid-19: a systematic review and meta-analysis. Reviews in Medical Virology. 2020;30(6):1–9. Available from: https://doi.org/10.1002/rmv.2141

[12] Santa Cruz A, Mendes-Frias A, Oliveira AI, Dias L, Matos AR, Carvalho A, et al. Interleukin-6 is a biomarker for the development of fatal severe acute respiratory syndrome coronavirus 2 pneumonia. Frontiers in Immunology. 2021;12:613422. Available from: https://doi.org/10.3389/fimmu.2021.613422

[13] Chang Y, Bai M, You Q. Associations between Serum Interleukins (IL-1β, IL-2, IL-4, IL-6, IL-8, and IL-10) and disease severity of COVID-19: a systematic review and meta-analysis. Abdalla SS, editor. BioMed Research International. 2022;2022:1–15. Available from: https://doi.org/10.1155/2022/2755246

[14] Jafrin S, Aziz MdA, Islam MS. Elevated levels of pleiotropic interleukin-6 (IL-6) and interleukin-10 (IL-10) are critically involved with the severity and mortality of COVID-19: an updated longitudinal meta-analysis and systematic review on 147 studies. Biomarker Insights. 2022;17:117727192211066. Available from: https://doi.org/10.1177/11772719221106600

[15] Tian W, Jiang W, Yao J, Nicholson CJ, Li RH, Sigurslid HH, et al. Predictors of mortality in hospitalized COVID-19 patients: A systematic review and meta-analysis. Journal of Medical Virology. 2020;92(10):1875–1883. Available from: https://doi.org/10.1002/jmv.26050

[16] Halim C, Mirza AF, Sari MI. The association between TNF-α, IL-6, and Vitamin D levels and COVID-19 severity and mortality: a systematic review and meta-analysis. Pathogens. 2022;11(2):195. Available from: https://doi.org/10.3390/pathogens11020195

[17] Sanyaolu A, Okorie C, Marinkovic A, Patidar R, Younis K, Desai P, et al. Comorbidity and its impact on patients with COVID-19. SN Comprehensive Clinical Medicine. 2020;2(8):1069–1076. Available from: https://doi.org/10.1007/s42399-020-00363-4

[18] Garg S, Kim L, Whitaker M, O'Halloran A, Cummings C, Holstein R, et al. Hospitalization rates and characteristics of patients hospitalized with laboratory-confirmed coronavirus disease 2019 — COVID-NET, 14 States, March 1–30, 2020. MMWR Morbidity and Mortality Weekly Report. 2020;69(15):458–464. Available from: https://doi.org/10.15585/mmwr.mm6915e3

[19] Pranata R, Lim MA, Huang I, Raharjo SB, Lukito AA. Hypertension is associated with increased mortality and severity of disease in COVID-19 pneumonia: a systematic review, meta-analysis and meta-regression. Journal of the Renin-Angiotensin-Aldosterone System. 2020;21(2):147032032092689. Available from: https://doi.org/10.1177/1470320320926899

[20] Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. European Heart Journal. 2018;39(33):3021–3104. Available from: https://doi.org/10.1093/eurheartj/ehy339

[21] Lim WS. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax. 2003;58(5):377–382. Available from: https://doi.org/10.1136/thorax.58.5.377

[22] Guo J, Zhou B, Zhu M, Yuan Y, Wang Q, Zhou H, et al. CURB-65 may serve as a useful prognostic marker in COVID-19 patients within Wuhan, China: a retrospective cohort study. Epidemiology and Infection. 2020;148:e241. Available from: https://doi.org/10.1017/S0950268820002368

[23] Ministerstvo Okhorony Zdorovia Ukrainy. Derzhavnyi Ekspertnyi Tsentr. Protokol "Nadannia medychnoi dopomohy dlia likuvannia koronavirusnoi khvoroby (COVID-19)". 2021 [cited 2022 Jul 1]. Available from: https://www.dec.gov.ua/wp-content/uploads/2021/01/2021_01_kn_covid-19.pdf

[24] Guirao JJ, Cabrera CM, Jiménez N, Rincón L, Urra JM. High serum IL-6 values increase the risk of mortality and the severity of pneumonia in patients diagnosed with COVID-19. Molecular Immunology. 2020;128:64–68. Available from: https://doi.org/10.1016/j.molimm.2020.10.006

[25] Avila-Nava A, Cortes-Telles A, Torres-Erazo D, López-Romero S, Chim Aké R, Gutiérrez Solis AL. Serum IL-6: A potential biomarker of mortality among SARS-CoV-2 infected patients in Mexico. Cytokine. 2021;143:155543. Available from: https://doi.org/10.1016/j.cyto.2021.155543

[26] Nguyen N, Nguyen H, Ukoha C, Hoang L, Patel C, Ikram FG, et al. Relation of interleukin-6 levels in COVID-19 patients with major adverse cardiac events. Baylor University Medical Center Proceedings. 2021;35(1):6–9. Available from: https://doi.org/10.1080/08998280.2021.1961571

[27] Zhou J, He W, Liang J, Wang L, Yu X, Bao M, et al. Association of interleukin-6 levels with morbidity and mortality in patients with coronavirus disease 2019 (COVID-19). Japanese Journal of Infectious Diseases. 2021;74(4):293–298. Available from: https://doi.org/10.7883/yoken.JJID.2020.463

[28] Zhou Y-Z, Teng X-B, Han M-F, Shi J-F, Li C-X, Zhang X-H, et al. The value of PCT, IL-6, and CRP in the early diagnosis and evaluation of COVID-19. Eur Rev Med Pharmacol Sci. 2021;25(2):1097-1100. Available from: https://doi.org/10.26355/eurrev_202101_24680

[29] Sun H, Guo P, Zhang L, Wang F. Serum interleukin-6 concentrations and the severity of COVID-19 pneumonia: a retrospective study at a single center in Bengbu City, Anhui Province, China, in January and February 2020. Medical Science Monitor. 2020;26:e926941. Available from: https://doi.org/10.12659/MSM.926941

[30] Mojtabavi H, Saghazadeh A, Rezaei N. Interleukin-6 and severe COVID-19: a systematic review and meta-analysis. European Cytokine Network. 2020;31(2):44–49. Available from: https://doi.org/10.1684/ecn.2020.0448

[31] Liu Z, Li J, Chen D, Gao R, Zeng W, Chen S, et al. Dynamic Interleukin-6 Level changes as a prognostic indicator in patients with COVID-19. Frontiers in Pharmacology. 2020;11:1093. Available from: https://doi.org/10.3389/fphar.2020.01093

[32] Acharya S, Kumar S, Talwar D, Raisinghani N, Madaan S, Hulkoti V, et al. Interleukin 6 and Its correlation with COVID-19 in terms of outcomes in an intensive care unit of a rural hospital: a cross-sectional study. Indian Journal of Critical Care Medicine. 2022;26(1):39–42. Available from: https://doi.org/10.5005/jp-journals-10071-24075

[33] Sabaka P, Koščálová A, Straka I, Hodosy J, Lipták R, Kmotorková B, 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 Infectious Diseases. 2021;21:308. Available from: https://doi.org/10.1186/s12879-021-05945-8

[34] Gao Y, Li T, Han M, Li X, Wu D, Xu Y, et al. Diagnostic utility of clinical laboratory data determinations for patients with the severe COVID-19. Journal of Medical Virology. 2020;92(7):791–796. Available from: https://doi.org/10.1002/jmv.25770

[35] Broman N, Rantasärkkä K, Feuth T, Valtonen M, Waris M, Hohenthal U, et al. IL-6 and other biomarkers as predictors of severity in COVID-19. Annals of Medicine. 2021;53(1):410–412. Available from: https://doi.org/10.1080/07853890.2020.1840621

[36] Gorham J, Moreau A, Corazza F, Peluso L, Ponthieux F, Talamonti M, et al. Interleukin-6 in critically ill COVID-19 patients: a retrospective analysis. PLOS ONE. 2020;15(12):e0244628. Available from: https://doi.org/10.1371/journal.pone.0244628

[37] Aykal G, Esen H, Seyman D, Çalışkan T. Could IL-6 predict the clinical severity of COVID-19? Turkish Journal of Biochemistry. 2021;46(5):499–507. Available from: https://doi.org/10.1515/tjb-2021-0020

[38] Dhar SK, K Vishnupriyan, Damodar S, Gujar S, Das M. IL-6 and IL-10 as predictors of disease severity in COVID-19 patients: results from meta-analysis and regression. Heliyon. 2021;7(2):e06155. Available from: https://doi.org/10.1016/j.heliyon.2021.e06155

[39] Yamamoto R, Sasaki J, Shibusawa T, Nakada T, Mayumi T, Takasu O, et al. Accuracy for mortality prediction with additive biomarkers including interleukin-6 in critically ill patients: a multicenter prospective observational study. Critical Care Explorations. 2021;3(4):e0387. Available from: https://doi.org/10.1097/CCE.0000000000000387

[40] Laguna-Goya R, Utrero-Rico A, Talayero P, Lasa-Lazaro M, Ramirez-Fernandez A, Naranjo L, et al. IL-6–based mortality risk model for hospitalized patients with COVID-19. Journal of Allergy and Clinical Immunology. 2020;146(4):799-807.e9. Available from: https://doi.org/10.1016/j.jaci.2020.07.009

[41] Liu X, Wang H, Shi S, Xiao J. Association between IL-6 and severe disease and mortality in COVID-19 disease: a systematic review and meta-analysis. Postgraduate Medical Journal. 2022;98:871-879. Available from: https://doi.org/10.1136/postgradmedj-2021-139939

[42] Mandel M, Harari G, Gurevich M, Achiron A. Cytokine prediction of mortality in COVID19 patients. Cytokine. 2020;134:155190. Available from: https://doi.org/10.1016/j.cyto.2020.155190

[43] Milenkovic M, Hadzibegovic A, Kovac M, Jovanovic B, Stanisavljevic J, Djikic M, et al. D-dimer, CRP, PCT, and IL-6 levels at admission to ICU can predict in-hospital mortality in patients with COVID-19 pneumonia. Oxidative Medicine and Cellular Longevity. 2022;2022:1–9. Available from: https://doi.org/10.1155/2022/8997709

[44] Quartuccio L, Sonaglia A, Pecori D, Peghin M, Fabris M, Tascini C, et al. Higher levels of IL-6 early after tocilizumab distinguish survivors from nonsurvivors in COVID-19 pneumonia: a possible indication for deeper targeting of IL-6. Journal of Medical Virology. 2020;92(11):2852–2856. Available from: https://doi.org/10.1002/jmv.26149

[45] Galván-Román JM, Rodríguez-García SC, Roy-Vallejo E, Marcos-Jiménez A, Sánchez-Alonso S, Fernández-Díaz C, et al. IL-6 serum levels predict severity and response to tocilizumab in COVID-19: an observational study. Journal of Allergy and Clinical Immunology. 2021;147(1):72-80.e8. Available from: https://doi.org/10.1016/j.jaci.2020.09.018

[46] Castelnovo L, Tamburello A, Lurati A, Zaccara E, Marrazza MG, Olivetti M, et al. Anti-IL6 treatment of serious COVID-19 disease. Medicine. 2021;100(1):e23582. Available from: https://doi.org/10.1097/MD.0000000000023582

[47] Han Q, Guo M, Zheng Y, Zhang Y, De Y, Xu C, et al. Current evidence of interleukin-6 signaling inhibitors in patients with COVID-19: a systematic review and meta-analysis. Frontiers in Pharmacology. 2020;11:615972. Available from: https://doi.org/10.3389/fphar.2020.615972

[48] Farid E, Sridharan K, Alsegai OA, Khawaja SA, Mansoor EJ, Teraifi NA, et al. Utility of inflammatory biomarkers in patients with COVID-19 infections: Bahrain experience. Biomarkers in Medicine. 2021;15(8):541–549. Available from: https://doi.org/10.2217/bmm-2020-0422

[49] Chen LYC, Biggs CM, Jamal S, Stukas S, Wellington CL, Sekhon MS. Soluble interleukin-6 receptor in the COVID-19 cytokine storm syndrome. Cell Reports Medicine. 2021;2(5):100269. Available from: https://doi.org/10.1016/j.xcrm.2021.100269

Appendix 1

Comorbidities and drugs received by hypertensive and non-hypertensive patients before hospitalization.

Parameter	Patients with AH (n=106)	Patients without AH (n=29)	p
Comorbidities			
Diabetes mellitus	34 (32.1%)	3 (10.3%)	0.02
History of myocardial infarction	13 (12.3%)	0 (0.0%)	0.047
Heart failure with a reduced ejection fraction	0 (0.0%)	2 (6.9%)	0.01
Heart failure with a mid-range ejection fraction	5 (4.7%)	1 (3.4%)	0.77
Complete heart block	1 (0.9%)	0 (0.0%)	0.60
Atrial fibrillation	11 (10.4%)	5 (17.2%)	0.31
Dilated cardiomyopathy	0 (0.0%)	1 (3.4%)	0.06
Severe valvular heart disease	4 (3.8%)	2 (6.9%)	0.47
Hypothyroidism	6 (5.7%)	2 (6.9%)	0.48
History of ischemic stroke	8 (7.5%)	2 (6.9%)	0.91
History of intracranial hemorrhage	1 (0.9%)	0 (0.0%)	0.60
Systemic lupus erythematosus	1 (0.9%)	0 (0.0%)	0.60
Medications received before hospitalization			
ACE inhibitors	48 (45.3%)	0 (0.0%)	<0.01
Angiotensin receptor blockers	31 (29.2%)	0 (0.0%)	<0.01
Diuretics	35 (33.0%)	3 (10.3%)	0.02
Beta-blockers	39 (36.8%)	5 (17.2%)	0.047
Calcium channel blockers	34 (32.1%)	0 (0.0%)	<0.01
Statins	21 (19.8%)	0 (0.0%)	0.01

Note: ACE – angiotensin-converting enzyme.