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

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Abstract

Background: Covid-19 is a disease with high morbidity and mortality among elderly residents of long-term care facilities (LTCF). During an outbreak of SARS-CoV-2 infection in the LTCF an effective screening tool is essential to identify the patients at risk for severe illness and death. We explored the role of interleukin 6 (IL-6) as a predictive factor for severe disease during the outbreak of Covid-19 in one LTCF in Slovakia.

Methods: We conducted a retrospective data analysis of all laboratory-confirmed cases of COVID-19, diagnosed during the outbreak in one LTCF in Slovakia between April 11, 2020, and May 5, 2020. Within 24 hours after the diagnosis of Covid-19, clinical and laboratory screening was performed in the LTCF by trained clinicians to identify patients in need of hospitalization. Patients with oxygen saturation below 90% were immediately referred to the hospital. Patients staying in the LTCF were monitored daily and those that developed hypoxemia were transferred to the hospital. We analyzed the association between the level of IL-6 at the initial assessment and development of hypoxemia during the course of the disease and determined the cut-off of the IL-6 able to predict the development of hypoxemia requiring oxygen therapy or ventilatory support.

Results: Fifty-three patients (11 men, 42 women) with diagnosed Covid-19 were included in the analysis. 19 (53%) patients developed hypoxemia during the course of the disease. Patients with hypoxemia had significantly higher concentrations of IL-6 at initial screening. The concentration of IL-6 > 24 pg/mL predicted the development of hypoxemia with the sensitivity of 100% and specificity of 88.9%. The positive and negative predictive values were 76.9%, and 100% respectively.

Conclusions: The concentration of IL-6 > 24 pg/mL at initial assessment predicted the development of hypoxemia requiring hospitalization with excellent sensitivity and good specificity. IL-6 appears as a potential negative predictive factor for the development of the severe form of Covid-19 and might serve for early identification of patients in need of hospitalization. Further studies are needed to evaluate the robustness of the use of IL-6 as an effective screening tool for the severe course of Covid-19.

Background

Coronavirus disease 2019 (Covid-19) is a disease caused by the zoonotic novel Coronavirus called SARS-CoV-2 [1]. Covid-19 quickly spread across the globe from a place of its origin in Hubei China and pandemic was declared by WHO on March 11, 2020 [2]. Most patients with Covid-19 experience mild self-limiting disease. However, up to 20% of known cases of Covid-19 are complicated by severe pneumonia which might result in acute respiratory distress syndrome (ARDS) which causes acute hypoxemic respiratory failure [1, 3]. The overall infection fatality ratio is estimated to be below 1% [4]. The risk of death in Covid-19 is strongly associated with various risk factors, especially older age and cardiovascular comorbidities [2]. According to data from the early China epidemic, the crude case-fatality in the patients over 80 is up to 15% [5]. Elderly and highly comorbid residents of long-term care facilities (LTCF) are at high risk of Covid-19 associated morbidity and mortality [6, 7, 8]. In one well-documented outbreak in

LTCF in Washington, USA, more than half of the infected residents required hospitalization and more than one third died [8]. On the background of the ongoing pandemic, the spreading of Covid-19 in LTCF might significantly burden the local health care system and markedly contributes to mortality. Timely and effective intervention is essential to reduce morbidity and mortality during the Covid-19 outbreak in the LTCF. Such intervention consists of quick identification of cases, immediate introduction of infection control measures, initial screening, and daily monitoring of patients. An effective screening tool is essential to identify the patients at risk for severe illness and death. Such patients need close monitoring and early transfer to the hospital. Interleukin 6 (IL-6) is a potent marker of disease severity and poor outcome of Covid-19 [10, 11]. The role of systematic measurement of IL-6 at initial assessment and its ability to predict the severe course of the disease of Covid-19 patients in the LTCF is yet to be determined.

Methods

We conducted a retrospective data analysis of laboratory-confirmed cases of COVID-19, diagnosed during the outbreak in one LTCF in Slovakia between April 11, 2020, and May 5, 2020. A confirmed case of COVID-19 was defined as a positive result on real-time reverse-transcriptase–polymerase-chain-reaction assay of nasopharyngeal swab specimens for SARS-CoV-2. In our analysis, we aimed to identify laboratory markers predicting the severe course of the disease at the initial assessment.

Intervention

Within 24 hours after the diagnosis of COVID-19, clinical and laboratory screening was performed in the LTCF by trained clinicians to identify patients in need of hospitalization. The clinical initial assessment consisted of measurement of vital signs (blood pressure, heart and breath frequency) and measurement of oxygen saturation by pulse oximetry. Additionally, the venous blood was drawn to measure concentrations of serum glucose, creatinine, urea, sodium, potassium, bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), C-reactive-protein (CRP), D-dimer, IL-6 and complete blood count. After an initial assessment, daily monitoring consisting of measurement of vital signs and measurement of oxygen saturation by pulse oximetry was performed by the same clinician. The development of hypoxemia with oxygen saturation below 90% was considered as the criteria for severe disease with the need for hospitalization. Patients with oxygen saturation below 90% at the initial screening or during the daily monitoring were immediately referred to the hospital.

Biochemical analysis

Concentrations of serum glucose, creatinine, urea, sodium, potassium, bilirubin, ALT, AST, were measured using spectrophotometry (Cobas Integra 400, Roche Diagnostics, Rotkreuz, Switzerland). CRP and D-dimer were measured using immunoturbidimetry (Cobas Integra 400, Roche Diagnostics, Rotkreuz, Switzerland). Serum IL-6 concentrations were measured using an immunoassay (Elecys, Roche Diagnostics, Rotkreuz, Switzerland).

Statistical analysis

Quantitative variables are expressed as medians and 25th and 75th percentiles. Data in our cohort according to the Kolmogorov-Smirnov test were non-parametric. Medians of quantitative variables between groups were compared using the Mann-Whitney nonparametric test. Effect sizes were assessed using Cohen's d. Optimal cut off values for diagnostic test evaluation were determined using ROC analysis. Sensitivity was calculated as the number of true positive divided by true positive + false negative. Specificity was calculated as the number of true negative divided by true negative + false positive. Association of baseline serum concentration of IL-6 > 24 pg/mL with the probability of development of hypoxemia requiring oxygen therapy (HRO) was assessed using multivariate logistic regression. For statistical analysis, SPSS version 26 (International Business Machines Corporation, Armonk, NY, USA) was used.

Ethics

This study was carried out in concordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans and was approved by the local Ethical Committee of University Hospital Bratislava. The participants signed informed consent. The investigators preserved the full anonymity of all participants.

Results

During the intervention in the LTCF, 78 subjects were screened for COVID-19 and 59 patients (47 women, 12 men) had positive pharyngeal swabs for SARS-CoV-2 RNA by RT-PCR. 53 patients (90%) had blood sampling during the initial screening phase. In 6 patients, blood sampling was not performed because of technical difficulties. These patients were excluded from the study. In 53 patients (11 men, 42 women) in which blood sampling was performed, the clinical variables and the results of biochemical and blood count analysis were available for evaluation and were included in the study. 7 patients (1 man, 6 women) were diagnosed with severe disease in initial triage and were immediately transferred to a hospital within the first two days of intervention. Remaining 45 patients (10 men, 36 women) remained under observation in LTCF and were screened for severe disease and triaged on a daily basis by the intervention team. Overall, 32 patients (6 men, 26 women) were admitted. Among these patients, 19 (2 men, 17 women) had hypoxemia required oxygen therapy, 16 patients (2 men, 14 women) were admitted to ICU, and 13 patients (2 men, 12 women) died. Baseline characteristics of patients are provided in Table 1. The baseline serum concentrations of IL-6, CRP, procalcitonin, urea, creatinine, fibrinogen, AST, ALT, fasting glucose, and total bilirubin were significantly higher and lymphocyte count was significantly lower in patients who developed hypoxemia. The median of baseline serum concentrations of D-dimer and ferritin and a median total count of leukocytes were not significantly different among groups of patients with and without hypoxemia requiring oxygen therapy. Patients who developed hypoxemia requiring oxygen therapy were also significantly more comorbid according to the higher median Charlson Comorbidity

Index (Table 1). In the ROC analysis, IL-6 was identified as the best marker of hypoxemia development and the cut off of 24 pg/mL showed the best combination of sensitivity and specificity. In the group of all screened LTCF residents, baseline IL-6 concentration > 24 pg/mL predicted the development of hypoxemia with a sensitivity of 88% and specificity of 89%. PPV of 83%, and NPV of 93%. After excluding the 7 patients diagnosed with severe Covid-19 and transferred to the hospital after the initial assessment, baseline IL-6 concentration over 24 pg/mL predicted the development of hypoxemia during the daily monitoring in the LTCF with the sensitivity of 100%, specificity 89, PPV of 77%, and NPV 100% (Table 2). In multivariate analysis, baseline IL-6 concentration > 24 pg/mL was positively associated with the risk of hypoxemia development during follow up in LTCF residents after adjustment for CRP, age, gender and glomerular filtration rate (Table 3).

Table 1

Baseline characteristics of patients. Variables are provided as median (25th percentile, 75th percentile).

	No hypoxemia requiring oxygen therapy (n = 26)	Hypoxemia requiring oxygen therapy (n = 19)	p (Mann-Whitney)	Cohen d
Age (years)	81 (73, 87)	87 (80.5, 90)	0.056	0.522
SpO2	0.96 (0.95, 0.97)	0.91 (0.86, 0.94)	< 0.0001	1.563
CCI	5 (4, 6)	7 (6, 8)	< 0.05	1.038
CRP (mg/L)	8.92 (3.223, 17.943)	70.69(29.59, 142.46)	< 0.0001	1.398
IL-6 (pg/mL)	12.3 (7.3, 20.5)	43.1 (26.3, 116.7)	< 0.0001	1.880
D-dimer (mg/L)	1.215(0.558, 2.625)	1.58 (0.78, 3.43)	0.198	0.366
Fibrinogen (g/L)	3.6 (3.3, 4.18)	4.45 (3.825, 5.825)	< 0.05	0.869
Procalcitonine (ng/mL)	0.02 (0.02, 0.03)	0.132(0.048, 0.313)	< 0.0001	1.791
Ferritin (ug/L)	175.9(94.13, 429.3)	295.18 (149.79, 778.02)	0.125	0.465
AST (ukat/L)	0.355(0.29,0.533)	0.755 (0.403, 1.12)	< 0.0001	1.214
ALT (ukat/L)	0.25 (0.16, 0.37)	0.35 (0.26, 0.54)	< 0.05	0.613
Sodium (mmol/L)	140.9(137.45, 142.675)	139 (133.6, 145.6)	0.830	0.06
Potassium (mmol/L)	4.09 (3.85, 4.36)	3.71 (3.235, 4.503)	0.184	0.386
Glucose (mmol/L)	4.8 (4.2, 5.4)	5.9 (5.1, 7.1)	< 0.01	0.861
Urea (mmol/L)	6.2 (5.4, 7.5)	11 (6, 21.5)	< 0.01	0.794
Creatinine (umol/L)	74.5 (59.25, 101.25)	110.9 (73, 264)	< 0.05	0.729
Total bilirubin (umol/L)	8.75 (6.55, 11.75)	11.95(9.8, 15.4)	< 0.0001	0.728
WBC (cells/mL)	4880 (4100, 6515)	5640 (4420, 8640)	0.167	0.395

ALT - alanine aminotransferase, AST - aspartate aminotransferase, CCI - Charlson Comorbidity Index, IL-6 - interleukin 6, LBC - lymphocyte blood count, p - probability, SpO2 - oxygen saturation, WBC - white blood cell blood count.

	No hypoxemia requiring oxygen therapy (n = 26)	Hypoxemia requiring oxygen therapy (n = 19)	p (Mann-Whitney)	Cohen d
LBC (cells/mL)	1565 (1045, 2083)	860 (580, 1300)	< 0.0001	1.035
ALT - alanine aminotransferase, AST - aspartate aminotransferase, CCI - Charlson Comorbidity Index, IL-6 - interleukin 6, LBC - lymphocyte blood count, p - probability, SpO2 - oxygen saturation, WBC - white blood cell blood count.				

Table 2

Test evaluation of baseline concentration of IL-6 > 24 pg/mL for predicting the development of hypoxemia requiring oxygen therapy during follow up after excluding patients admitted to hospital during initial triage.

Statistic	Value	95% confidence interval
Sensitivity	100.00%	69.15% – 100.00%
Specificity	88.89%	70.84% – 97.65%
Disease prevalence	27.03%	13.79% – 44.12%
Positive Predictive Value	76.92%	53.42% – 90.64%
Negative Predictive Value	100.00%	
Accuracy	91.89%	78.09% – 98.30%

Table 3

Multivariate binary logistic regression analysis of the association of IL-6 > 24 pg/mL, CRP, glomerular filtration rate, gender, and age with the probability of development of hypoxemia requiring oxygen therapy during follow up.

	p	Exp(B)	95% CI of Exp(B)
IL-6 > 24 pg/mL	< 0.05	39.741	1.838–859.426
CRP	0.203	1.028	0.985–1.072
age	0.187	1.133	0.943–1.364
gender (male)	0.175	0.088	0.003–2.944
GFR	0.773	0.979	0.850–1.128
CRP - C-reactive protein, GFR - glomerular filtration rate, 95% CI – 95% confidence interval, IL-6 - interleukin 6			

Discussion

Our retrospective data analysis suggests that IL-6 is a robust predictive factor of the development of hypoxemia requiring oxygen therapy and hospitalization. The concentration of IL-6 > 24 pg/mL at the initial assessment is showing the best combination of sensitivity and specificity.

Clinical significance and implications

The prognosis of Covid-19 in the general population is favorable with an estimated infection fatality ratio below 1% [4]. However, in the elderly population, the prognosis is far worse. The risk of death in Covid-19 is increasing with advanced age and the presence of cardiovascular underlying conditions [2]. According to data from the early epidemic in Wuhan, China, the crude case-fatality in the patients over 80 is up to 15% [5]. The residents of LTCF are one of the most vulnerable populations of the Covid-19 pandemic [6, 7, 8]. The transmission of Covid-19 in LTCF might significantly burden the local health care system and markedly contributes to mortality. Timely and effective intervention is essential to reduce morbidity and mortality during the Covid-19 outbreak in the LTCF. According to the proposed guideline of response to the outbreak of Covid-19 in LTCF by Kim et al., the first phase of response should include broad testing a quick identification of cases and their clinical assessment focused on identifying patients needing immediate transfer to the hospital. In the next phase, monitoring of patients should be implemented in order to quickly identify the patients in need of hospital care [9]. Identification of patients at high risk of deterioration during the initial assessment may significantly improve the monitoring process in order to effectively allocate the resources to high-risk patients. Especially in the case of large outbreaks and limited human resources, the focus on high-risk patients might contribute to mortality reduction and improve the overall outcome of the intervention.

In our study, all patients that developed hypoxemia requiring oxygen therapy during the follow up had the baseline concentration of IL-6 over 24 pg/mL. As a screening tool, it provides excellent sensitivity with a fairly acceptable specificity over 88%. In the screening for high-risk patients in the elderly comorbid population of LTCF residents, it might identify the patients with a high risk of hypoxemia with relatively low risk of false positivity and on the other hand identify the patients with low risk for hypoxemia with great negative predictive value. This might help in the decision making for admission during the initial triage.

For the purposes of our study, we defined that the residents that developed hypoxemia requiring oxygen therapy are the cases that needed close monitoring and early transfer to the hospital. The rationale is that patients who developed hypoxemia requiring oxygen therapy are those that might benefit from the early pharmacological intervention in order to reduce mortality. According to the body of evidence on remdesivir, it improves the outcome in the patients needing conventional oxygen therapy, however, its effectiveness in the treatment of patients with more advanced disease requiring ventilatory support remains controversial [12, 13]. Another treatment that proved to be beneficial in patients requiring conventional oxygen therapy is a 10-day course of 6 mg of dexamethasone per day. In a preprint report from RECOVERY trial, it reduces the mortality by one fifth in patients requiring low flow oxygen [14]. Thus,

the patients with early disease but in the high risk of development of severe hypoxemia requiring oxygen therapy are those patients who will profit the most from close observation and rapid initiation of remdesivir and dexamethasone treatment if they develop hypoxemia requiring conventional oxygen therapy.

IL-6 and development of severe Covid-19

There is a substantial body of evidence linking the IL-6 concentration to the severity of disease and unfavorable outcome of Covid-19 [11, 15, 16]. IL-6 is produced by stromal cells and virtually all immune system cells in the lungs and its secretion is stimulated by proinflammatory cytokines. Overexpression of IL-6 is believed to have a crucial role in the incitement and propagation of the so-called cytokine storm leading to lung injury and ARDS [15]. A study by Giamarellos-Bourboulis et al. suggests that patients with severe respiratory failure in Covid-19 suffer from distinct types of immune dysregulation which are mediated by IL-6 upregulation. This dysregulation is characterized by high production of proinflammatory cytokines by monocytes and macrophages and CD4 lymphocyte depletion that contributes to the progression of inflammation of lung parenchyma [17]. An important trait of IL-6 upregulation in Covid-19 is that it precedes the development of acute lung injury that implicates its usability as an early marker of severe disease [16].

Other markers of severe disease

In our study, patients who developed hypoxemia had significantly higher serum concentrations of AST, ALT, CRP, serum glucose, creatinine, procalcitonin, and fibrinogen. These biochemical variables were identified as markers of severe disease by previous studies [18]. Medians of other well-established markers of serious disease, D-dimer and ferritin were higher in patients who developed hypoxemia, however, the differences were not statistically significant.

Prognosis of LTCF residents suffering from Covid-19

According to an epidemiologic study by McMichael et al., during the outbreak in one LTCF in Washington, USA, 54.5% of residents required hospitalization and required hospital admission and 33.7% of infected residents died [8]. In our study, we identified 59 residents with positive swabs for SARS-CoV-2. Of these patients, 32 patients (54%) were admitted to hospital which is similar to the study by McMichael et al. In our study, 13 patients (22%) died. That is less than in the study by McMichael et al., however, this difference of proportion might be attributed to potentially different age and comorbidity status of residents.

Limitations

The limitations of our study are the relatively low sample size and retrospective design. Larger prospective studies are needed to obtain more robust data and to evaluate if the examination of IL-6 during the initial assessment leads to better prognosis of LTCF residents and improves the management of the Covid-19 outbreaks in the LTCFs.

Because of the retrospective design of the study, there might be a concern of bias in the sensitivity of the diagnosis of hypoxemia between groups of hospitalized and outpatient residents. The hospitalized patients were naturally more closely monitored and therefore might be more likely to be diagnosed with hypoxemia. However, we regard this potential bias as insignificant because the outpatient residents were daily monitored for the symptoms and signs of respiratory failure, and patients suffering from dyspnea and patients with tachypnea and/or SpO2 below 90% were transferred to hospital. In normoxic patients, the bias of pulse oximetry comparing to SaO2 is regarding to be very low. It reliably identifies the patients with SaO2 below 90% and is a reliable screening tool for hypoxemia with very high negative predictive value [19, 20].

Conclusions

Baseline IL-6 concentrations over 24 pg/mL in LTCF residents suffering from Covid-19 predicts the development of hypoxemia requiring oxygen therapy with excellent sensitivity and good specificity. Patients with the IL-6 above 24 pg/mL at initial assessment seems to be at high risk of development of respiratory failure and might benefit from early hospitalization and close follow-up. Further studies are needed to evaluate the real benefits of systematic examination of IL-6 during the initial assessment and its use as predictive factor of severe disease.

Abbreviations

ALT
alanine aminotransferase
ARDS
acute respiratory distress syndrome
AST
aspartate aminotransferase
CCI
Charlson Comorbidity Index
Covid-19
Coronavirus disease 2019
IL-6
interleukin 6
LBC
lymphocyte blood count
LTCF

long term care facility

p

probability

SARS-CoV-2

severe acute respiratory distress syndrome coronavirus 2

SaO₂

oxygen saturation from arterial blood

SpO₂

oxygen saturation by pulse oximetry

WBC

white blood cell blood count.

Declarations

Ethics approval and consent to participate

This study was carried out in concordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans and was approved by the local Ethical Committee of University Hospital Bratislava. All patients or their legally authorized representatives had provided written informed consent prior to participation in this study. The investigators preserved the full anonymity of all participants.

Consent for publication

Not applicable.

Availability of data and materials

The dataset used and analyzed during this study is available from the corresponding author upon request.

Competing interests

The authors declare that they have no competing interests.

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None.

Authors' contributions

PS drafted the manuscript, co-developed the study design, and participated in the data gathering and analysis and interpretation of results. AK co-drafted the manuscript, planned the intervention, developed the study design, and participated in the data gathering and analysis and interpretation of results. JH planned the intervention and participated in the data gathering and analysis and interpretation of results. IS and RL co-drafted the manuscript and participated in the data gathering and analysis and interpretation of results. MK, BK, and AK participated in data gathering and analysis and interpretation of results. All authors have read and approved the final manuscript.

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