Therapeutics and Clinical Risk Management

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Prognostic Factors and Clinical Prediction Score for Progressive Respiratory Failure in Severe COVID-19 Pneumonia Patients Treated with Tocilizumab: A Multicenter Study

Nantakarn Pongtarakulpanit[1], Kulapong Jayanama[2], Phichayut Phinyo[3], Waravudh Naothavorn[2], Siripat Nuprom[2], Dhanesh Pitidhammabhorn[2], Pipat Ngammisri[2], Pintip Ngamjanyaporn[1], Vichayhud Suthichatchawan[4], Lerkiat Wicharit[5], Kanin Thammavaranucupt[2]

[1]Division of Allergy, Immunology and Rheumatology, Department of Medicine, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; [2]Chakri Naruebodindra Medical Institute, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Samut Prakan, Thailand; [3]Center for Clinical Epidemiology and Clinical Statistics, Department of Family Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand; [4]Department of Medicine, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; [5]Boromarajonani College of Nursing, Nakhon Ratchasima, Faculty of Nursing, Praboromarajchanok Institute, Nakhon Ratchasima, Thailand

Correspondence: Kanin Thammavaranucupt, Chakri Naruebodindra Medical Institute, Faculty of Medicine Ramathibodi Hospital, Mahidol University, 111 Moo 14, Bang Pla, Bang Phli, Samut Prakan, 10540, Thailand, Tel +66817210571, Email kanin.tha@mahidol.ac.th

Purpose: A proportion of COVID-19 pneumonia patients develop respiratory failure despite tocilizumab administration. This retrospective cohort study aimed to identify prognostic factors associated with progressive respiratory failure within 14 days among patients with severe COVID-19 pneumonia treated with Tocilizumab and to describe treatment outcomes.

Patients and Methods: Patients with severe COVID-19 pneumonia were assessed, and their demographic, clinical, laboratory data, and prior treatment were collected on the day of tocilizumab administration. A multivariable Cox proportional hazard model was employed to identify prognostic factors.

Results: Of the 109 patients, 32 (29.4%) progressed to respiratory failure. We identified the following independent prognostic factors for progressive respiratory failure: pulse oximetry saturation to fraction of inspired oxygen ratio (SpO_2/FiO_2) ≤ 160 (HR 2.97, 95% CI 1.41–6.23, P = 0.004), estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m^2 (HR 3.21, 95% CI 1.23–8.39, P = 0.017), and serum potassium ≤ 4 mmol/L (HR 2.82, 95% CI 1.38–5.80, P = 0.005). A predictive model based on these factors effectively stratified the risk of progressive respiratory failure (area under the curve = 0.72, 95% CI 0.63–0.80). Patients experiencing progressive respiratory failure had poor clinical outcomes, with a mortality rate of 62.5%, compared to 0.0% in the non-respiratory failure group (p < 0.001).

Conclusion: In severe COVID-19 pneumonia patients treated with Tocilizumab, low SpO_2/FiO_2 ratio, low eGFR, and relatively low serum potassium were independent predictors for progressive respiratory failure. This simple clinical score may help identify high-risk patients early, though external validation is required before routine implementation.

Keywords: interleukin-6 blockade, immunomodulatory therapy, risk stratification, clinical outcomes, survival analysis

Introduction

Hypoxic respiratory failure in patients with COVID-19 is associated with an excessive systemic inflammatory response. Interleukin-6 (IL-6) is a key driver of this hyperinflammatory process, contributing to endothelial dysfunction, impaired oxygen exchange, and progression to respiratory failure. Tocilizumab, an IL-6 receptor blocker, is approved to treat several autoimmune inflammatory diseases. According to the RECOVERY trial,[1] COVID-19 patients with hypoxia and systemic inflammation treated with Tocilizumab were less likely to reach the composite endpoint of mechanical

Received: 15 September 2025
Accepted: 12 December 2025
Published: 22 December 2025

ventilation or death. A meta-analysis of randomized clinical trials (RCTs) confirmed that Tocilizumab decreased the risk of mechanical ventilation.[2] Current World Health Organization (WHO) guideline recommends treatment with IL-6 receptor blockers in patients with severe and critical COVID-19.[3]

Despite treatment with Tocilizumab, a portion of patients continue to have disease progression. The reported absolute risk of progression to invasive mechanical ventilation or death was 27% in RCTs.[4] For endotracheal intubation, the reported risk was 6.2–15.4% in RCTs and 0.0–33.3% in cohort studies.[2] Several studies have attempted to identify prognostic markers among patients treated with tocilizumab; however, findings have been heterogeneous. De Biasi et al demonstrated that specific immune-cell signatures could differentiate responders from non-responders to IL-6 inhibition, while Masotti et al and Pagkratis et al reported clinical and biochemical predictors associated with poor outcomes in tocilizumab-treated patients.[5–7] Nevertheless, these studies primarily focused on immunologic or biochemical markers rather than simple bedside clinical parameters.

Medical early warning scores, such as the National Early Warning Score 2 (NEWS2), NEWS2 adding age as a variable, and COVID-19 severity index, are sensitive methods for predicting short-term deterioration of patients with COVID-19 in general.[8–10] However, their performance in patients treated with tocilizumab remains uncertain.[11,12] Recent studies in patients treated with tocilizumab have focused on immune biomarkers and early-warning constructs, but dedicated prognostic tools for this subgroup remain scarce.[13,14]

We conducted this retrospective cohort study to identify prognostic factors associated with progressive respiratory failure requiring mechanical ventilation in severe COVID-19 pneumonia patients treated with Tocilizumab and to characterize their clinical outcomes. We also proposed a prediction model to stratify the risk of progressive respiratory failure in these patients.

Materials and Methods

Study Design and Participants

We conducted a multicenter retrospective study from June 2022 to February 2023. Recruited patients were admitted to Chakri Naruebodindra Medical Institute or Ramathibodi Hospital from April 2021 to May 2022. Both hospitals are affiliated with the Faculty of Medicine Ramathibodi Hospital, Mahidol University, Thailand, and share similar COVID-19 treatment protocols. To minimize selection bias, all consecutive eligible patients during the study period were included. Both hospitals followed identical institutional treatment protocols based on national and RECOVERY-aligned guidelines. Inclusion criteria included age > 18 years, diagnosis of COVID-19 based on reverse transcriptase polymerase chain reaction (RT-PCR), and severe COVID-19 pneumonia (new infiltration on chest radiograph without other explainable causes and oxygen saturation <92% on room air or signs of severe respiratory distress) treated with Tocilizumab in hospital ward or intensive care unit settings. Exclusion criteria were intubation before tocilizumab administration and terminal illness receiving palliative care.

Indication for tocilizumab administration was in accordance with the RECOVERY trial:[1] patients with hypoxia (oxygen saturation <92% on room air or requiring oxygen therapy) and evidence of systemic inflammation (elevated C-reactive protein or IL-6).

Data Collection and Study Endpoint

We reviewed electronic medical records and collected data for the recruited patients from admission day until discharge. On tocilizumab administration day, baseline data, including demographic, clinical, laboratory data, and treatment of COVID-19, were obtained. Patients' clinicals were classified through the WHO ordinal clinical severity scale.[15] The primary endpoint was progressive respiratory failure, defined as the need for invasive mechanical ventilation within 14 days after tocilizumab administration. Escalation to high-flow nasal cannula or noninvasive ventilation was not considered an endpoint. For patients with do-not-intubate (DNI) status, death attributable to respiratory failure within 14 days was classified as an event. The other clinical outcomes after tocilizumab administration, including acute kidney injury, venous thromboembolism, cardiovascular complications, infection, inotropic drug use, length of hospital stay, and death, were determined at discharge. Serious infections were defined as infections requiring intravenous antibiotics,

prolonging hospitalization, or resulting in death. All secondary outcomes were adjudicated through detailed chart review by attending physicians and independently cross-checked by two investigators to ensure accuracy and consistency. Missing laboratory values were not imputed. Outliers were verified against original medical records to ensure accuracy.

Candidate Predictors for Progressive Respiratory Failure

All variables collected on tocilizumab administration day were explored for their statistical significance and were considered candidate predictors for a clinical prediction score. However, these variables were prespecified based on clinical plausibility and prior literature, and univariate screening was performed only to identify candidates for multivariable modeling to reduce the risk of data-driven overfitting. For continuous data, the optimal cut-off values for predicting were determined by calculating the area under the receiver operative characteristic curve (AuROC) and the Youden index. Because these cut-offs were derived from the same dataset used for model development, there may be potential information leakage, and this limitation has been acknowledged.

Sample Size and Statistical Analysis

Because the outcome of interest (progressive respiratory failure) occurred infrequently, a formal sample size calculation was not feasible. Therefore, all consecutive eligible patients during the study period were included to maximize statistical power and minimize selection bias. Descriptive statistics were used to present the demographic, clinical, laboratory data, and treatment variables. Categorical data were compared using the Chi-Square test or Fischer's exact test as appropriate. To compare normally distributed and non-normally distributed continuous data, the independent *t*-test and Mann–Whitney test were applied, respectively. Continuous variables were dichotomized before modeling to facilitate bedside clinical applicability, despite the acknowledged potential reduction in statistical power. We selected variables for a multivariable Cox proportional hazards model using forward stepwise selection. The proportional hazards assumption was tested using Schoenfeld residuals and was not violated. Then, we identified prognostic factors for progressive respiratory failure from significant clinical factors.

The clinical prediction score for progressive respiratory failure was developed using significant clinical factors from multivariable Cox regression analysis. With 32 events and three variables in the final model, the events-per-variable ratio remained above the recommended minimum of 10. Score performance was evaluated in terms of discrimination using AuROC and calibration using a calibration plot. Internal validation was performed using bootstrap resampling with 500 replicates. For each replicate, the model was refitted in the bootstrap sample and evaluated in the original dataset to estimate optimism. The apparent AUC of the final model was 0.715 (range 0.533, 0.846). The optimism-corrected AUC was calculated as the apparent AUC minus the average optimism across bootstrap samples. The final optimism-corrected AUC was 0.72. P value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS Statistics version 22 (IBM, Armonk, NY, USA) and Stata version 17.0 (StataCorp LP, College Station, TX, USA).

Ethical Considerations

This study was approved by the Human Research Ethics Committee, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Thailand (COA. No. MURA2021/1062). The informed consent requirement was waived by the Ethics Committee because of the retrospective design of the study. This study complied with the Declaration of Helsinki, and all patient data were anonymized before analysis to ensure confidentiality.

Results

A total of 109 eligible patients were recruited into the study: 54 patients from Chakri Naruebodindra Medical Institute, 41 patients from Ramathibodi Hospital, and 14 patients received initial treatment from Ramathibodi Hospital and then transferred to Chakri Naruebodindra Medical Institute. A flow diagram summarizing patient screening and eligibility is shown in Figure 1. The mean ± standard deviation (SD) age of the participants was 60.3 ± 14.2 years. There was a slight male predominance (51.4%). Body mass index (BMI) was high among participants, with a median (interquartile range, IQR) of 26.8 (24.0–31.2) kg/m^2. The majority of patients (79.5%) did not receive COVID-19 immunization (Table 1). A single dose of Tocilizumab was administered intravenously to 86.2% of the patients; the remaining individuals

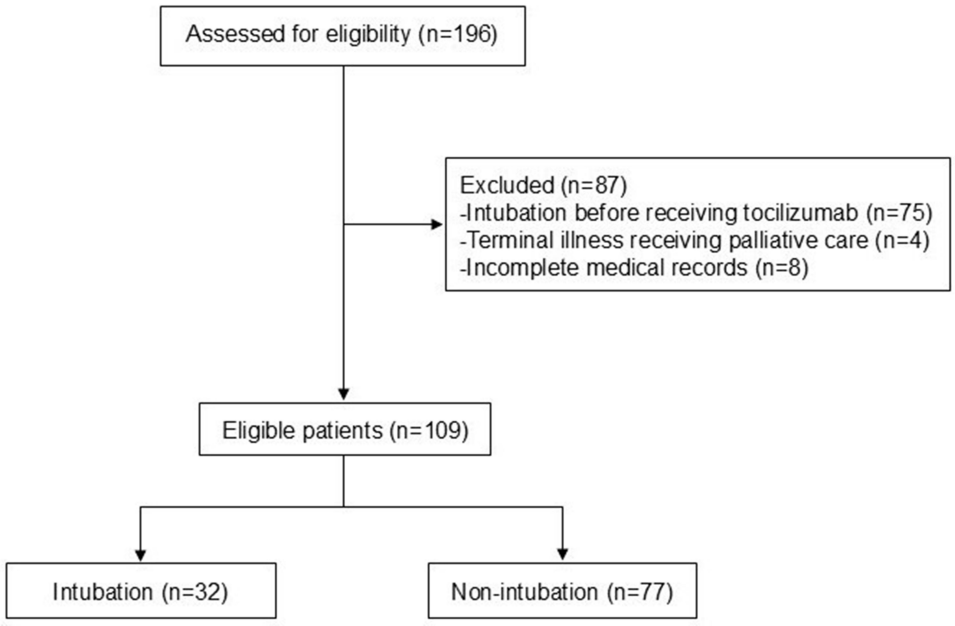

Figure 1 Flow diagram of patient selection for the study.

received two infusions. Tocilizumab was given in doses ranging from 400 to 800 mg (7.6 ± 1.2 mg/kg/dose). The median COVID-19 illness duration (number of days from symptom onset to the administration of Tocilizumab) was nine days (IQR 7–11 days). Of the 109 patients, 32 (29.4%) progressed to respiratory failure requiring mechanical ventilation within 14 days after tocilizumab administration. The median time to respiratory failure was two days after tocilizumab administration (range 1–12 days) (Figure 2). The median length of hospital stay was 17 days (range 3–92 days).

Table 1 Demographic Data, Clinical Settings, Laboratory Features, and Previous Treatment of Severe COVID-19 Pneumonia Patients on Tocilizumab Administration Day

Characteristics (n=109)	**Values n (%), mean ± SD, or median (IQR)**
Demographic Data	
Age (years)	60.3 ± 14.2
Male (%)	56 (51.4)
BMI (kg/m^2)	26.8 (24.0–31.2)
Comorbidity (%)	67 (61.5)
Chronic lung disease	5 (4.6)
Diabetes mellitus	36 (33.0)
Hypertension	51 (46.8)
Chronic kidney disease (CKD)	14 (12.8)
CKD stage ≤ 3	11 (10.1)
Coronary artery disease	7 (6.4)
Cerebrovascular disease	7 (6.4)

(*Continued*)

Table 1 (Continued).

Characteristics (n=109)	**Values n (%), mean ± SD, or median (IQR)**
Cancer	7 (6.4)
Autoimmune disease	4 (3.7)
COVID19 vaccination (n =103) (%)	21 (20.4)
Clinical settings	
COVID-19 illness duration (days)	9.0 (7.0–11.0)
SpO_2/FiO_2 ratio	163.3 (118.8–240.0)
Respiratory rate/min	23.0 (20.0–27.0)
Respiratory support (%)	
None	1 (0.9)
Oxygen by nasal prongs	17 (15.6)
Oxygen by mask	2 (1.8)
High-flow oxygen	71 (65.1)
Noninvasive ventilation	18 (16.5)
WHO Ordinal Clinical Severity Scale (%)	
3: hospitalized, no oxygen therapy	1 (0.9)
4: hospitalized, oxygen mask or nasal prongs	18 (16.5)
5: hospitalized, noninvasive mechanical ventilation or high-flow nasal cannula	90 (82.6)
Laboratory features	
WBC ($\times 10^6/mm^3$)	10.5 ± 4.4
Platelet ($\times 10^6/mm^3$)	248.4 ± 85.7
IL-6 (n = 90) (pg/mL)	43.6 (18.2–75.2)
C-reactive protein (mg/L)	76.4 (45.4–133.0)
Lactate dehydrogenase (U/L)	402.0 (307.5–527.5)
eGFR ($mL/min/1.73m^2$)	94.5 (74.8–102.7)
eGFR < 60 $mL/min/1.73m^2$	15 (13.8)
Sodium (mmol/L)	135.8 ± 3.4
Potassium (mmol/L)	4.2 ± 0.5
Chloride (mmol/L)	100.6 ± 4.6
Bicarbonate (mmol/L)	23.1 ± 3.3
Previous treatment	
IV methylprednisolone (mg)	500.0 (250.0–1000.0)
Remdesivir (%)	36 (33.0)

(*Continued*)

https://doi.org/10.2147/TCRM.S567679

Table 1 (Continued).

Characteristics (n=109)	Values n (%), mean ± SD, or median (IQR)
Prophylactic anticoagulant (%)	98 (89.9)
Baricitinib (%)	8 (7.3)
Tofacitinib (%)	7 (6.4)

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; IL, interleukin; IQR, interquartile range; IV, intravenous; SD, standard deviation; SpO2/FiO2 ratio, pulse oximetry saturation to fraction of inspired oxygen ratio; WBC, white blood cell count; WHO, World Health Organization.

Comparison of Demographic Data, Clinical Settings, Laboratory Data, and Previous Treatment

Older age (P = 0.034), receiving Tocilizumab in early of the disease course (P = 0.003), low pulse oximetry saturation to fraction of inspired oxygen ratio (SpO_2/FiO_2) (P = 0.009), high serum sodium (P = 0.036), and low serum potassium (P = 0.046) on tocilizumab administration day were associated with progression to respiratory failure requiring mechanical ventilation in severe COVID-19 pneumonia patients (Table S1). Vaccination status was evaluated in the univariate analysis but was not retained in the final multivariable model because it was not significantly associated with progressive respiratory failure. Complete univariate comparisons of baseline demographic, clinical, and laboratory variables between patients with and without progressive respiratory failure are presented in Supplementary Table 1.

Independent Predictors for Progressive Respiratory Failure

We performed multivariable Cox regression analyses to identify the potential poor prognostic factors for progressive respiratory failure. After adjusting for age and sex, the independent predictors of progressive respiratory failure were SpO_2/FiO_2 ratio ≤ 160 (HR 2.972, 95% CI 1.417–6.231, P=0.004), eGFR < 60 mL/min/1.73m^2 (HR 3.214, 95% CI 1.232–8.388, P= 0.017), and serum potassium ≤ 4.0 mmol/L (HR 2.824, 95% CI 1.375–5.797, P=0.005) (Table 2).

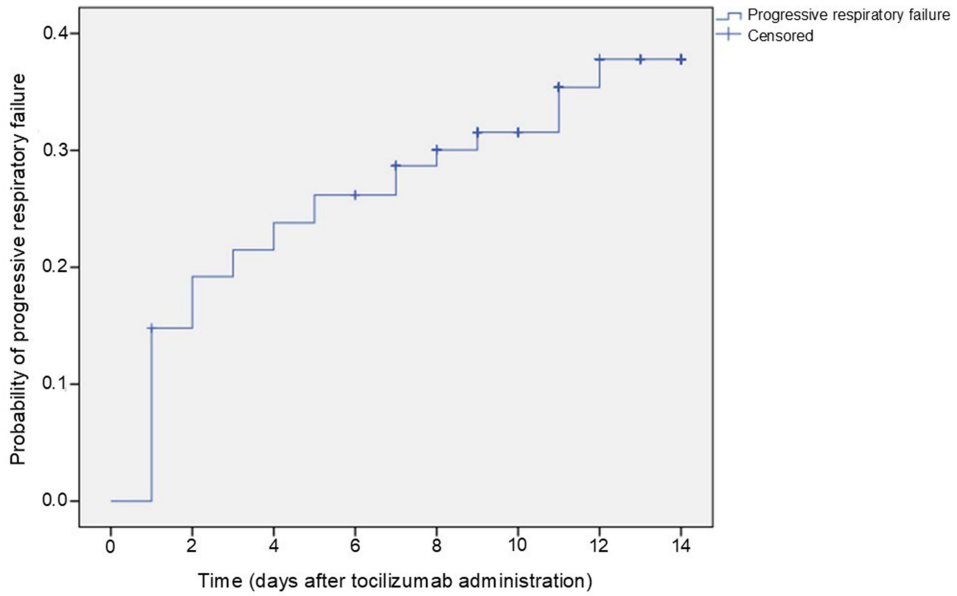

Figure 2 Probability of progressive respiratory failure after tocilizumab administration comparison of demographic data, clinical settings, laboratory data, and previous treatment.

Table 2 The Predictors of Progressive Respiratory Failure in Severe COVID-19 Pneumonia Patients Treated with Tocilizumab

Parameters	Multivariable Cox-regression Analysis		
	HR	95% CI	P value
Age (years)	1.016	0.998–1.054	0.262
Male (%)	1.391	0.667–2.905	0.379
SpO_2/FiO_2 ratio ≤ 160	2.972	1.417–6.231	**0.004**
eGFR < 60 mL/min/1.73m^2	3.214	1.232–8.388	**0.017**
Potassium ≤ 4.0 mmol/L	2.824	1.375–5.797	**0.005**

Note: P < 0.05: significant (shown in bold).
Abbreviations: eGFR, estimated glomerular filtration rate; HR, hazard ratio; SpO_2/FiO_2 ratio, pulse oximetry saturation to fraction of inspired oxygen ratio.

Although older age and earlier administration of tocilizumab were significant in univariate analyses, these variables did not remain significant after multivariable adjustment.

Prediction Model for Progressive Respiratory Failure

The final prediction model for progressive respiratory failure in severe COVID-19 pneumonia treated with Tocilizumab was based on three independent prognostic factors, SpO2/FiO2 ratio ≤ 160, eGFR < 60 mL/min/1.73m^2, and serum potassium ≤ 4 mmol/L. Each independent predictor in the multivariable model was assigned a specific score derived from the multivariate Cox's proportional hazard regression coefficient. The regression coefficient of each item was divided by the lowest coefficient and then rounded up to the nearest integer to develop a scoring system. The prediction score was defined as the number of prognostic factors for progressive respiratory failure (score of +1 for each). The scoring scheme had a total score ranging from 0 to 3. The AUC for the score was 0.72 (95% CI 0.63–0.80) (Figure 3), demonstrating good discriminative ability. Since we intended to use the score to screen patients at high risk of progressive respiratory failure, we chose the score cut-off point of 1 (sensitivity of 93.8% and specificity of 35.1%). The sensitivity and

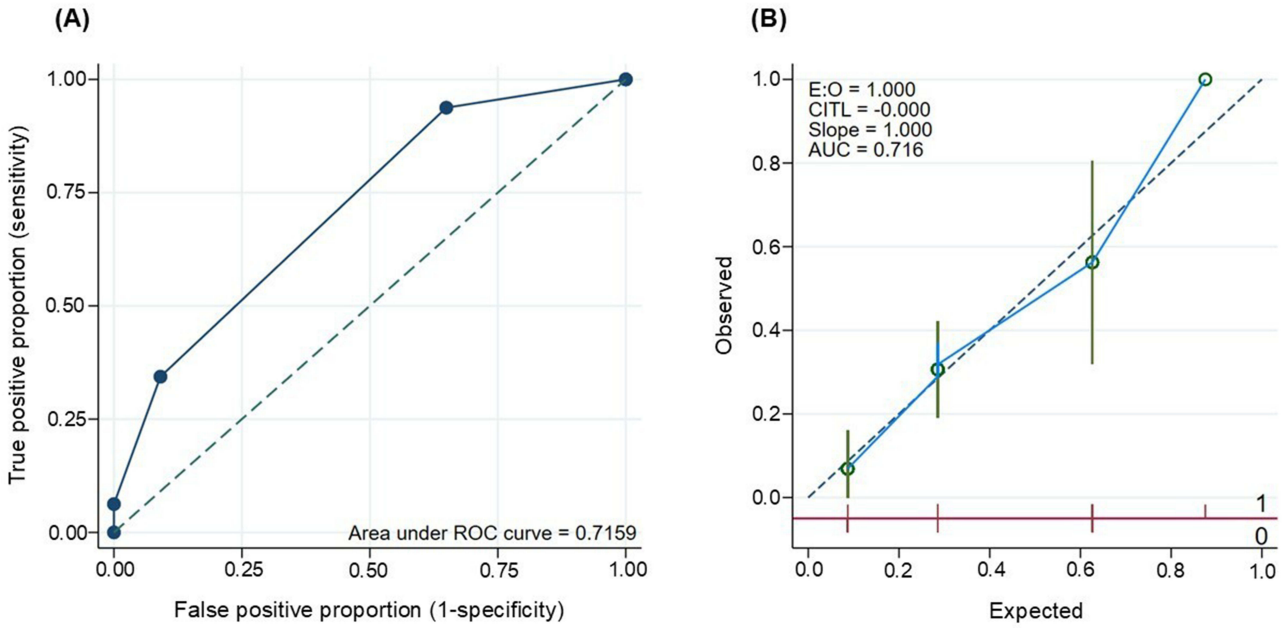

Figure 3 Discriminative ability based on the area under the receiver operative characteristic curve (AuROC) for the prediction model (**A**) and model calibration (**B**).

https://doi.org/10.2147/TCRM.S567679

Table 3 Clinical Outcomes

Parameters n (%), or median (IQR)	All Patients (n = 109)	Respiratory Failure Patients (n = 32)	Non-Respiratory Failure Patients (n = 77)	P value
Acute kidney injury (%)	24 (22.0)	14 (43.8)	10 (13.0)	**<0.001**
Thrombosis (%)	10 (9.2)	7 (21.9)	3 (3.9)	**0.007**
Cardiovascular complications (%)	8 (7.3)	6 (18.8)	2 (2.6)	**0.008**
Secondary infection (%)	32 (29.4)	26 (81.3)	6 (7.8)	**<0.001**
Inotropic drug use (%)	19 (17.4)	18 (56.3)	1 (1.3)	**<0.001**
Length of hospital stay (days)	17.0 (12.5–25.0)	24.5 (11.3–33.8)	16.0 (13.0–21.0)	0.054
Death (%)	20 (18.3)	20 (62.5)	0 (0.0)	**<0.001**

Note: P < 0.05: significant (shown in bold).
Abbreviation: IQR, interquartile range.

specificity for each cut-off point are depicted in the Table S2. All mortality events occurred among patients who developed progressive respiratory failure. Higher risk-score categories showed a clear increase in the likelihood of respiratory failure, supporting the score's clinical relevance; however, mortality was not analyzed separately by score category due to small subgroup sizes.

Clinical Outcomes After Tocilizumab Administration

The overall mortality of severe COVID-19 pneumonia patients treated with Tocilizumab was 18.3% (20 patients). Causes of death were COVID-19 pneumonia with multi-organ failure (12 patients), secondary infection (7 patients), and pulmonary embolism (1 patient). Intubated patients were likely to have poor clinical outcomes, including acute kidney injury, venous thromboembolism, cardiovascular complications, infection, inotropic drug use during admission, and death (Table 3). A total of 48 secondary infections occurred among 32 patients (29.4%). Bacterial pneumonia was the most common infection, followed by urinary tract infection, primary bacteremia, cytomegalovirus infection, and invasive pulmonary aspergillosis. Serious infections occurred in 29 patients (26.6%).

Discussion

Our retrospective cohort focuses on prognostic factors of progressive respiratory failure in severe COVID-19 pneumonia treated with Tocilizumab from April 2021 to May 2022. The patients received standard doses of Tocilizumab at the median duration of 9 days since COVID-19 symptom onset, similar to the individuals from the RECOVERY trial.[1] The rates of respiratory failure and mortality observed in our cohort were comparable to those reported in previous studies.[2,4] We found that SpO_2/FiO_2 ratio ≤ 160, eGFR < 60 mL/min/1.73m^2, and serum potassium ≤ 4.0 mmol/L were independent predictors of respiratory failure.

The SpO_2/FiO_2 ratio correlates well with PaO_2/FiO_2 and is practical for risk assessment, especially where arterial blood gas measurements are not readily available. A SpO_2/FiO_2 ratio of 235 corresponds with a PaO_2/FiO_2 of 200, utilized to define acute respiratory distress syndrome.[16] In hospitalized COVID-19 patients, Kim et al[17] found that the SpO_2/FiO_2 ratio predicted high-flow nasal cannula (HFNC) failure with subsequent respiratory failure. The median SpO_2/FiO_2 ratio was 160 (120–186) in the HFNC failure group, the same number as the cut-off from the ROC curve analysis in the current study. Lu et al[18] reported a strong association between a sharply decreased SpO_2/FiO_2 ratio and mortality risk of severe and critically ill patients with COVID-19. The SpO_2/FiO_2 ratio threshold ≤ 160 determined in this study could be used to identify severe COVID-19 pneumonia patients treated with Tocilizumab at risk of respiratory failure.

Chen et al[19] demonstrated that renal insufficiency (eGFR < 60 mL/min/1.73m^2) on admission independently predicted poor prognosis (composite endpoint of intensive care unit admission, invasive ventilation, or death) among COVID-19 inpatients. Renal dysfunction has been consistently associated with worse outcomes in COVID-19.[20,21] Our study

showed that eGFR < 60 mL/min/1.73m^2 was an independent predictor for respiratory failure in severe COVID-19 pneumonia treated with Tocilizumab, supporting the previous findings.

Hypokalemia is a frequent electrolyte abnormality in COVID-19 and has been associated with greater disease severity in previous studies.[22–24] Proposed mechanisms include RAAS dysregulation and physiologic stress responses triggered by SARS-CoV-2 infection.[25] In our cohort, serum potassium ≤4.0 mmol/L was independently associated with progressive respiratory failure. However, this association should not be interpreted as causal; hypokalemia may reflect underlying neurohormonal activation, systemic stress, or illness severity rather than directly contributing to respiratory deterioration.[26] Given its potential cardiac implications and its common occurrence in severe COVID-19, maintaining serum potassium above 4.0 mmol/L remains clinically prudent.[27]

Masotti et al[6] reported prognostic factors of poor outcomes (combination of mortality and/or intensive care unit admission with endotracheal intubation) in tocilizumab-treated patients with severe respiratory failure from COVID-19: age ≥ 65 years, procalcitonin ≥ 0.14 ng/mL, room-air pulse oximetry oxygen saturation ≤ 90% and chest computed tomography (CT) ground glass opacity ≥ 50% at admission. For prognostic factors specific to progressive respiratory failure, Pagkratis et al[7] reported PaO_2/FiO_2 ratio at admission and lactate dehydrogenase on the day of tocilizumab treatment as predictors of respiratory failure. Overall, these prior reports align with our observations and reinforce the relevance of early physiologic and biochemical indicators in patients receiving tocilizumab.

Mussini et al[28] developed a score to estimate the risk of progressing to mechanical ventilation and death in tocilizumab-treated COVID-19 patients. Female gender, day-4 C-reactive protein value above the median, day-4 platelet value above the median, and day-4 PaO_2/FiO_2 ratio value above the median were used to generate the risk score. The accuracy of the score was very good (AUC 0.8). However, this score focused on composite outcomes and required median laboratory data values. In the current study, we proposed a new risk prediction model for respiratory failure in severe COVID-19 pneumonia treated with Tocilizumab. This score relies on readily available bedside parameters and may help flag patients who require intensified monitoring after tocilizumab. Higher scores can guide clinicians toward earlier reassessment or escalation of care, although the model is intended to complement clinical judgment.

This study has several limitations. First, the small sample size and retrospective design introduce the possibility of information bias and limit the robustness of the findings. Missing data on COVID-19 vaccination status and serum IL-6 levels, as well as the unavailability of PaO_2/FiO_2 measurements and chest CT severity scoring, constrained the comprehensiveness of our analyses. Second, selection bias may be present because only patients who received tocilizumab were included, and confounding by indication may have occurred if patients selected for tocilizumab differed systematically from those who did not receive it. Third, the prediction model has not undergone external validation, which restricts its generalizability. Finally, although the lower cutoff point enhances sensitivity, its limited specificity reduces the model's usefulness as a standalone triage tool. Future studies with larger cohorts and external validation are needed to confirm these findings and refine the predictive score.

Conclusion

In this retrospective cohort of patients with severe COVID-19 pneumonia treated with tocilizumab, independent predictors of respiratory failure were a SpO_2/FiO_2 ratio ≤160, an eGFR <60 mL/min/1.73 m^2, and a serum potassium ≤4.0 mmol/L. These readily available parameters may help clinicians identify patients at higher risk of progressive respiratory failure and support decisions regarding monitoring intensity and ICU planning. We also proposed a simple, clinically applicable prediction score based on these variables; however, its current use should be considered preliminary until it has been validated in independent cohorts. Future research should focus on validating and refining this score, as well as on comparing its performance with that of existing early warning tools in patients receiving IL-6 receptor blockade.

Acknowledgments

We are grateful to our colleagues at Chakri Naruebodindra Medical Institute and Ramathibodi Hospital, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Thailand, for their care of the patients.

Disclosure

The authors report no conflicts of interest in this work.

References

1. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet*. 2021;397(10285):1637–1645. doi:10.1016/s0140-6736(21)00676-0
2. Luo L, Luo T, Du M, Mei H, Hu Y. Efficacy and safety of tocilizumab in hospitalized COVID-19 patients: a systematic review and meta-analysis. *J Infect*. 2022;84(3):418–467. doi:10.1016/j.jinf.2021.11.013
3. Therapeutics and COVID-19: living guideline. World Health Organization. Available from: WHO/2019-nCoV/therapeutics/2023.1. Accessed December 15, 2025.
4. Shankar-Hari M, Vale CL, Godolphin PJ, et al; Group WHOREAfC-TW. Association between administration of IL-6 antagonists and mortality among patients hospitalized for COVID-19: a meta-analysis. *JAMA*. 2021;326(6):499–518. doi:10.1001/jama.2021.11330
5. De Biasi S, Mattioli M, Meschiari M, et al. Prognostic immune markers identifying patients with severe COVID-19 who respond to tocilizumab. *Front Immunol*. 2023;14:1123807. doi:10.3389/fimmu.2023.1123807
6. Masotti L, Landini G, Panigada G, et al. Predictors of poor outcome in tocilizumab treated patients with Sars-CoV-2 related severe respiratory failure: a multicentre real world study. *Int Immunopharmacol*. 2022;107:108709. doi:10.1016/j.intimp.2022.108709
7. Pagkratis K, Chrysikos S, Antonakis E, et al. Predictors of mortality in tocilizumab-treated severe COVID-19. *Vaccines*. 2022;10(6). doi:10.3390/vaccines10060978
8. Zhang K, Zhang X, Ding W, et al. The prognostic accuracy of national early warning score 2 on predicting clinical deterioration for patients with COVID-19: a systematic review and meta-analysis. *Front Med*. 2021;8:699880. doi:10.3389/fmed.2021.699880
9. Liao X, Wang B, Kang Y. Novel coronavirus infection during the 2019–2020 epidemic: preparing intensive care units-the experience in Sichuan Province, China. *Intensive Care Med*. 2020;46(2):357–360. doi:10.1007/s00134-020-05954-2
10. Huespe I, Carboni Bisso I, Di Stefano S, Terrasa S, Gemelli NA, Las Heras M. COVID-19 Severity Index: a predictive score for hospitalized patients. *Med Intensiva*. 2022;46(2):98–101. doi:10.1016/j.medine.2020.12.002
11. Nuñez-Ramos JA, Forero Illera E, Quintero Barrios JL, et al. Prognostic factors in hospitalized COVID-19 patients at the start of the pandemic in Colombia: a Retrospective Cohort Study. *Cureus*. 2021;13(5):e14865. doi:10.7759/cureus.14865
12. Sines BJ, Jakharia KK, Lu CH, et al. Validation of the age, neutrophil to lymphocyte ratio, C reactive protein score on 28 day mortality in the National COVID cohort collaborative. *Sci Rep*. 2025;15(1):28254. doi:10.1038/s41598-025-08822-5
13. Tom J, Bao M, Tsai L, et al. Prognostic and predictive biomarkers in patients with coronavirus disease 2019 treated with tocilizumab in a randomized controlled trial. *Crit Care Med*. 2022;50(3):398–409. doi:10.1097/ccm.0000000000005229
14. Kılıç Ö, Tecer D, Kaya MN, Çınar M, Yılmaz S. Can the early warning score (ANDC) predict tocilizumab efficacy in patients with COVID-19 cytokine storm? *Eur J Rheumatol*. 2025;12(1):1–6. doi:10.5152/eurjrheum.2025.24048
15. Blueprint WRD. COVID-19 Therapeutic Trial Synopsis. 2020. Available from: https://www.who.int/publications/i/item/covid-19-therapeutic-trial-synopsis. Accessed January 28, 2023.
16. Rice TW, Wheeler AP, Bernard GR, Hayden DL, Schoenfeld DA, Ware LB. Comparison of the Sp o 2 /F io 2 Ratio and the Pa o 2 /F io 2 ratio in patients with acute lung injury or ARDS. *Chest*. 2007;132(2):410–417. doi:10.1378/chest.07-0617
17. Kim JH, Baek AR, Lee SI, et al. ROX index and SpO2/FiO2 ratio for predicting high-flow nasal cannula failure in hypoxemic COVID-19 patients: a multicenter retrospective study. *PLoS One*. 2022;17(5):e0268431. doi:10.1371/journal.pone.0268431
18. Lu X, Jiang L, Chen T, et al. Continuously available ratio of SpO(2)/FiO(2) serves as a noninvasive prognostic marker for intensive care patients with COVID-19. *Respir Res*. 2020;21(1):194. doi:10.1186/s12931-020-01455-4
19. Chen K, Lei Y, He Y, et al. Clinical outcomes of hospitalized COVID-19 patients with renal injury: a multi-hospital observational study from Wuhan. *Sci Rep*. 2021;11(1):15205. doi:10.1038/s41598-021-94570-1
20. Li X, Zhong X, Wang Y, Zeng X, Luo T, Liu Q. Clinical determinants of the severity of COVID-19: a systematic review and meta-analysis. *PLoS One*. 2021;16(5):e0250602. doi:10.1371/journal.pone.0250602
21. Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature*. 2020;584(7821):430–436. doi:10.1038/s41586-020-2521-4
22. Yin J, Yuan N, Huang Z, et al. Assessment of hypokalemia and clinical prognosis in Patients with COVID-19 in Yangzhou, China. *PLoS One*. 2022;17(7):e0271132. doi:10.1371/journal.pone.0271132
23. Chen D, Li X, Song Q, et al. Assessment of hypokalemia and clinical characteristics in patients with coronavirus disease 2019 in Wenzhou, China. *JAMA Network Open*. 2020;3(6):e2011122. doi:10.1001/jamanetworkopen.2020.11122
24. Moreno PO, Leon-Ramirez JM, Fuertes-Kenneally L, et al. Hypokalemia as a sensitive biomarker of disease severity and the requirement for invasive mechanical ventilation requirement in COVID-19 pneumonia: a case series of 306 Mediterranean patients. *Int J Infect Dis*. 2020;100:449–454. doi:10.1016/j.ijid.2020.09.033
25. Noori M, Nejadghaderi SA, Sullman MJM, et al. How SARS-CoV-2 might affect potassium balance via impairing epithelial sodium channels? *Mol Biol Rep*. 2021;48(9):6655–6661. doi:10.1007/s11033-021-06642-0
26. Tajbakhsh A, Gheibi Hayat SM, Taghizadeh H, et al. COVID-19 and cardiac injury: clinical manifestations, biomarkers, mechanisms, diagnosis, treatment, and follow up. *Expert Rev Anti Infect Ther*. 2021;19(3):345–357. doi:10.1080/14787210.2020.1822737
27. Macdonald JE, Struthers AD. What is the optimal serum potassium level in cardiovascular patients? *J Am Coll Cardiol*. 2004;43(2):155–161. doi:10.1016/j.jacc.2003.06.021
28. Mussini C, Cozzi-Lepri A, Menozzi M, et al. Development and validation of a prediction model for tocilizumab failure in hospitalized patients with SARS-CoV-2 infection. *PLoS One*. 2021;16(2):e0247275. doi:10.1371/journal.pone.0247275