CANPT Score: A Tool to Predict Severe COVID-19 on Admission

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Background and Aims: Patients with critical coronavirus disease 2019 (COVID-19) have a mortality rate higher than 50%. The purpose of this study was to establish a model for the prediction of the risk of severe disease and/or death in patients with COVID-19 on admission.

Materials and Methods: Patients diagnosed with COVID-19 in four hospitals in China from January 22, 2020 to April 15, 2020 were retrospectively enrolled. The demographic, laboratory, and clinical data of the patients with COVID-19 were collected. The independent risk factors related to the severity of and death due to COVID-19 were identified with a multivariate logistic regression; a nomogram and prediction model were established. The area under the receiver operating characteristic curve (AUROC) and predictive accuracy were used to evaluate the model's effectiveness.

Results: In total, 582 patients with COVID-19, including 116 patients with severe disease, were enrolled. Their comorbidities, body temperature, neutrophil-to-lymphocyte ratio (NLR), platelet (PLT) count, and levels of total bilirubin (Tbil), creatinine (Cr), creatine kinase (CK), and albumin (Alb) were independent risk factors for severe disease. A nomogram was generated based on these eight variables with a predictive accuracy of 85.9% and an AUROC of 0.858 (95% CI, 0.823–0.893). Based on the nomogram, the CANPT score was established with cut-off values of 12 and 16. The percentages of patients with severe disease in the groups with CANPT scores <12, ≥12, and <16, and ≥16 were 4.15, 27.43, and 69.64%, respectively. Seventeen patients died. NLR, Cr, CK, and Alb were independent risk factors for mortality, and the CAN score was established to predict mortality. With a cut-off value of 15, the predictive accuracy was 97.4%, and the AUROC was 0.903 (95% CI 0.832, 0.974).

Conclusions: The CANPT and CAN scores can predict the risk of severe disease and mortality in COVID-19 patients on admission.

Keywords: SARS-CoV-2, COVID-19, severe illness, prediction, nomogram

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by severe respiratory syndrome coronavirus 2 (SARS-CoV-2), and pneumonia is the main clinical manifestation (1–3). SARS-CoV-2 is highly transmissible (4, 5), and the COVID-19 pandemic has spread to every country. With the rapid increase in the number of confirmed cases, medical resources have been inadequate (6).

As of December 30, 2020, the cumulative number of confirmed cases worldwide exceeded 80 million, and more than 1.78 million patients had died; the daily number of newly diagnosed patients is still rising. Although many clinical trials have been performed in the treatment of COVID-19 patients, so far, only dexamethasone has been validated in reducing the mortality rate of critically ill patients, and no specific medicine is available for COVID-19 (7). The demand for intensive care unit (ICU) beds, ventilators, protective equipment, other medical resources and medical staff exceed the existing supply by 10-fold (6). The early identification of patients at risk for severe disease and death, the timely initiation of interventions and admission to the ICU can prevent disease progression and reduce the mortality rate. Patients with mild COVID-19 require access to only limited medical resources for isolation and general symptomatic treatment. Therefore, it is very important to establish models predicting the prognoses of patients with COVID-19. More than 700 prognosis-related articles have been published in journals and on preprint platforms; most articles have only provided the risk factors for a poor outcome in COVID-19 patients; and ~50 prognostic models have been reported (8). Yuan et al. reported a model with good predictive efficacy [area under the receiver operating characteristic curve (AUROC) = 0.901] in predicting the risk of mortality in patients with COVID-19 using chest computed tomography (CT) scores. However, this model is not sufficiently representative and generalizable because only 27 patients from Wuhan were included (9). Other models were constructed using data only from patients in Wuhan (9–13), and many models have been presented as nomograms, which are inconvenient for clinical application and have not been verified in populations of other COVID-19 patients (12, 14–16).

Liang et al. established a model based on 1,590 COVID-19 patients from 31 provinces in China and validated this model in another 710 patients with COVID-19; the model is available on a web page (http://118.126.104.170/). The model showed good predictive ability for a poor prognosis of COVID-19 in both the development cohort and the external validation cohort (AUROC = 0.880). The following 10 variables were included the model: X-ray abnormalities, age, hemoptysis, dyspnea, unconsciousness, number of comorbidities, cancer history, neutrophil-to-lymphocyte ratio (NLR), lactate dehydrogenase (LDH) level, and direct bilirubin level; however, only the NLR, LDH level, and direct bilirubin level are biochemical indicators, which are inadequate for enabling a comprehensive evaluation of renal, heart, and coagulation function in patients with COVID-19. This model and several other models used ICU admission, invasive ventilation, and death as the composite outcome (14, 16–18), although not all patients with critical disease require ICU admission and/or invasive ventilation, and more than 50% of patients with critical disease will die (6); thus, individual models are needed for the precise prediction of severe disease or death. Wu et al. reported a model with good predictive efficacy (16) that was established based on data from 299 patients from Wuhan, China, and verified in 426 patients with COVID-19 from China, Italy, and Belgium. However, Collins et al. believed that the sample size of patients in their study was relatively small and that it was unreasonable to use 239 patients for model development and 60 patients for internal validation. The patients with a predicted risk of a poor prognosis from 21.00 to 80.00% were classified into the medium-risk group, further casting doubt regarding the basis of risk stratification in the study (19). The CALL score developed by Ji et al. includes comorbidities, lymphocytes, age, and LDH, has good predictive efficacy and is convenient for clinical use. However, the sample size in their study was relatively small, and there was no external validation (20). The NLR has been reported to be a prognostic factor in COVID-19 (21, 22); however, the NLR can only reflect the status of the immune system and is insufficient for assessing the comprehensive situation in COVID-19 patients because COVID-19 is a systemic disease (23, 24). In summary, these models have a risk of bias, and their reliability in clinical application has not been verified (8, 25). As the COVID-19 epidemic continues to spread, it is necessary to develop a reliable and clinically applicable prognostic model for COVID-19.

In this study, by comparing the demographic, clinical, and blood biochemical characteristics of COVID-19 patients with and without severe disease on admission, the risk factors for severe disease and mortality were identified, and risk prediction models for severe disease and death in COVID-19 patients were established.

MATERIALS AND METHODS

Patient Selection

This study retrospectively included patients with COVID-19 diagnosed at Shiyan Taihe Hospital, Ankang Central Hospital, Ningbo Hwamei Hospital, and Yichang Central People's Hospital from January 22, 2020 to April 15, 2020. The criteria used for the diagnosis and classification of confirmed cases of COVID-19 were provided in the "Guidance for 2019 coronavirus disease prevention, control, diagnosis and management" (26). The clinical classifications were as follow. (1) Mild: the clinical symptoms were mild, and no pneumonia manifestations were observed on imaging. (2) Moderate: patients had symptoms, such as fever and respiratory tract symptoms, and pneumonia manifestations were observed on imaging. (3) Severe: any of the following criteria were met: (1) respiratory distress, respiration rate (RR) ≥30 breaths/min; (2) pulse oxygen saturation (SpO2) ≤93% on room air at rest; or (3) arterial partial pressure of oxygen (PaO2)/oxygen concentration (FiO2) ≤300 mmHg. In regions with a high altitude (more than 1 kilometer above sea level), the PaO2/FiO2 values were adjusted based on the following: equation of PaO2/FiO2 × [atmospheric pressure (mm Hg)/760]. Patients with >50% lesion progression within 24 to 48 h on pulmonary imaging were treated as having severe cases. And (4) Critical: any of the following criteria were met: (1) respiratory failure

needing mechanical ventilation; (2) shock; or (3) other organ failure requiring monitoring and treatment in the ICU. In this study, the severe and critical cases were classified as having severe disease, while the mild and moderate cases were classified as having non-severe disease. Patients diagnosed with severe disease on admission were only included in the mortality risk analysis. This study was approved by the Medical Ethics Committee of Shiyan Taihe Hospital. The approval number is 2020KS018.

Data Collection

Clinical data pertaining to COVID-19 patients on admission were retrieved from the medical record databases of Shiyan Taihe Hospital, Ankang Central Hospital, Ningbo Hwamei Hospital, and Yichang Central People's Hospital. The data included the patients' epidemiological histories, comorbidities, vital signs (heart rate, RR, blood pressure, and body temperature), signs and symptoms (fever), laboratory tests (liver and kidney function, routine blood tests, C-reactive protein (CRP) levels, and chest CT findings), and outcome at discharge. The patients with COVID-19 who progressed to severe or critical disease during hospitalization were included in the analysis of severe disease. Survival at discharge was the final outcome of this study. The included comorbidities were hypertension, diabetes, cardiocerebrovascular disease, malignant tumor, chronic liver disease, chronic kidney disease, and chronic lung disease.

Statistical Analysis

The normally and non-normally distributed continuous variables are presented as the means ± standard deviations (SDs) and medians (interquartile ranges, IQRs), respectively. The categorical variables are presented as n (%). t-tests, chi-square tests and Mann-Whitney U-tests were used to compare the differences in various indicators between the two groups. To ensure that the variables conformed to a normal distribution to the greatest extent possible, natural logarithmic transformation was applied to the white blood cell (WBC) count, procalcitonin (PCT) level, CRP level and other variables. Then, we obtained the natural logarithm (ln) of WBC [ln (WBC)], ln (NLR), ln (PLT), ln (Alb), ln (Tbil), ln (Cr), etc. During the modeling process, variables with more than 10% missing values were excluded from the analysis, and variables with <10% missing values were addressed with multiple imputation. The independent prognostic risk factors were selected by a logistic regression analysis and included in the nomogram, which was used to establish the prediction model. For convenience in clinical application, the independent risk factors identified by the logistic regression analysis were converted into dichotomous variables with a cut-off value determined by receiver operating characteristic (ROC) curve analysis. A logistic regression was performed to determine the weight of the influence of the variables on disease progression and establish a new scoring model. The best cut-off value was determined according to the Youden index, sensitivity, specificity, predictive value, and likelihood ratio. The leave-one-out cross validation method was used for internal validation, and 1,000 bootstrap resamplings were performed. The AUROC and Hosmer-Lemeshow test were used to evaluate the predictive efficacy of the model. SPSS software, version 22.0 (SPSS, Inc., Chicago, IL, USA), was used for the data analysis. The nomogram was established using R software, version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria). A two-tailed $P < 0.05$ was considered statistically significant.

RESULTS

Baseline Characteristics of COVID-19 Patients

In total, 582 patients with COVID-19, including 202 from Shiyan Taihe Hospital, 40 from Ankang Central Hospital, 108 from Ningbo Hwamei Hospital, and 232 from Yichang Central People's Hospital, were enrolled in this study. During hospitalization, 116 patients developed severe disease, and 17 patients died. There were 466 patients with non-severe COVID-19, including 25 with mild cases and 441 with moderate cases (**Figure 1**). The median age of the patients with severe disease was significantly higher than that of the patients with non-severe disease (63.00 *vs.* 47.00, $P < 0.001$). The proportion of patients with comorbidities in the severe disease group was almost two times greater than that in the non-severe disease group (59.48 *vs.* 24.68%, $P < 0.001$). Hypertension was the most common comorbidity in the patients with COVID-19 (20.10%), followed by diabetes (9.28%) and malignant tumors (2.23%), which were more common in the patients with severe disease than those with non-severe disease (**Table 1**). Among the 582 patients with COVID-19, fever was the most common symptom (74.05%), and the incidence of fever in the patients with severe disease was higher than that in the patients with non-severe disease, although the difference was not statistically significant (80.17 *vs.* 72.53%, $P = 0.093$). However, the proportion of patients with a body temperature ≥38.5°C in the group with severe disease was significantly higher than that in the group with non-severe disease (41.38 *vs.* 22.32%, $P < 0.001$); intrapulmonary ground-glass opacities (GGOs) were observed on CT in 559 /582 (96.05%) patients with COVID-19, including all patients with severe disease, and 443/466 (95.06%) patients with non-severe disease. There was no significant difference between the two groups in terms of sex, respiration, heart rate, or blood pressure on admission (**Table 1**).

The lymphocyte (LY) count was reduced in 300/582 (51.55%) patients with COVID-19, and a reduced LY count was more common in the group with severe disease than in the group with non-severe disease (76.72 *vs.* 45.92%, $P < 0.001$). However, the group with severe disease had a significantly larger proportion of patients with elevated WBC counts, especially neutrophils (NE), than the group with non-severe disease (11.21 *vs.* 3.22%, $P < 0.001$; 23.28 *vs.* 7.73%, $P < 0.001$). Therefore, the patients with severe disease had a significantly higher NLR than those with non-severe disease (4.20 *vs.* 2.64, $P < 0.001$). The proportions of patients with reduced hemoglobin (HGB) and PLT levels were two times higher in the group with severe disease than in the group with non-severe disease (14.66 *vs.* 7.30%, $P = 0.012$; 29.31 *vs.* 13.52%, $P < 0.001$). The rates of abnormal aspartate aminotransferase (AST) and γ-glutamyl transpeptidase (GGT) levels were significantly higher in the patients with severe disease than in the patients with non-severe disease. A reduced albumin

FIGURE 1 | Flow chart of the study.
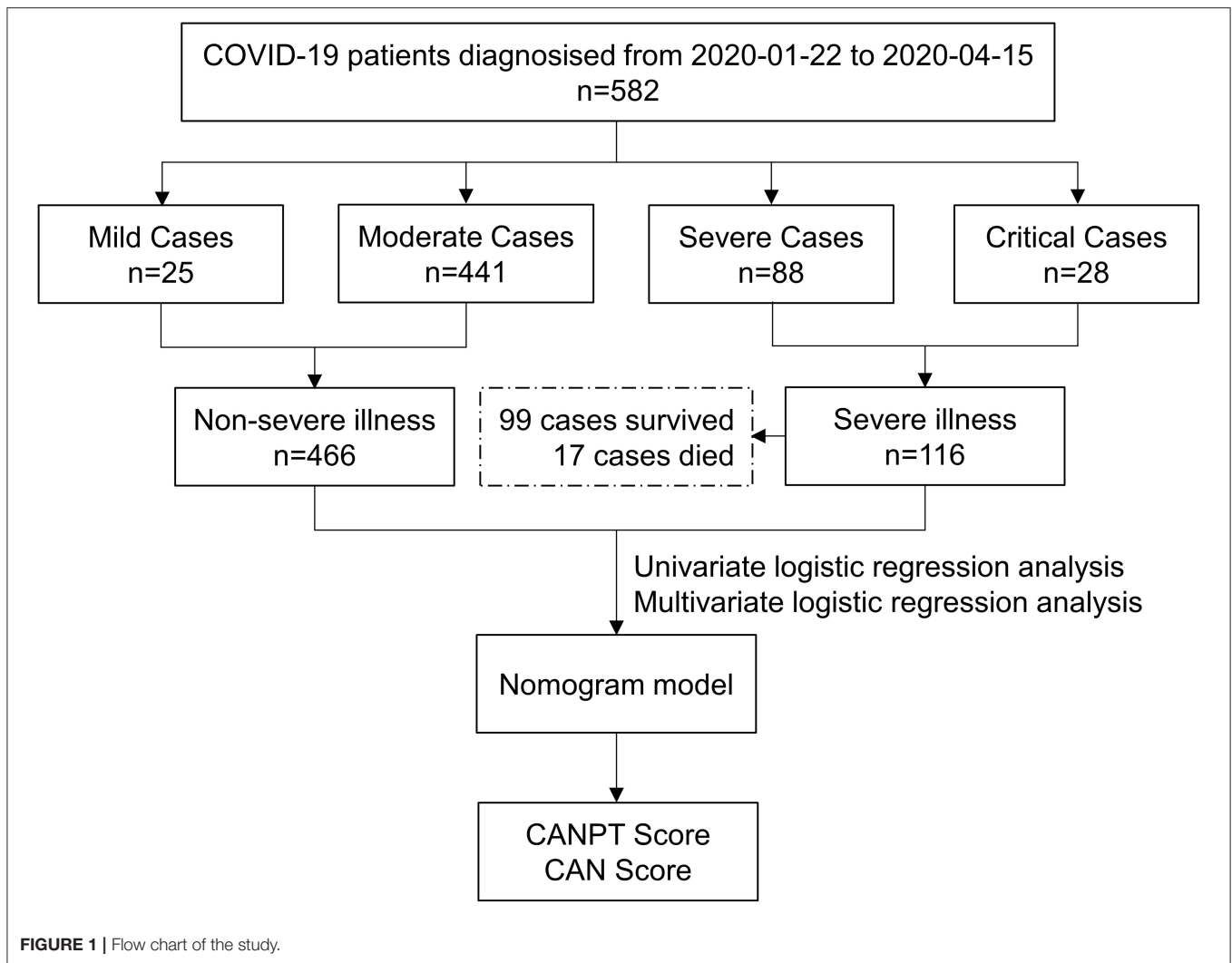
TABLE 1 | Baseline demographics and characteristics of the COVID-19 patients.

Characteristics	All patients	Severe disease	Non-severe disease	$t/z/\chi^2$ value	P-value
	n = 582	n = 116	n = 466		
Sex (male)	286 (49.1%)	62 (53.5%)	224 (48.1%)	1.08	0.300
Age, years	50.0 (36.0, 63.0)	63.0 (50.0, 71.0)	47.0 (34.0, 57.0)	−7.72	<0.001
Heart rate, beats per minute	86.0 (78.0, 97.0)	88.0 (80.0, 101.0)	85.0 (78.0, 96.0)	−1.55	0.121
Respiratory rate, breaths per minute	20.0 (18.0, 20.0)	20.0 (18.0, 21.0)	20.0 (18.0, 20.0)	−2.16	0.033
MAP, mm Hg	93.0 (87.0, 102.0)	93.0 (87.0, 102.0)	93.0 (87.0, 102.0)	0.84	0.402
Comorbidities	184 (31.6%)	69 (59.5%)	115 (24.7%)	52.04	<0.001
Hypertension	117 (20.1%)	43 (37.1%)	74 (15.9%)	25.96	<0.001
Diabetes	54 (9.3%)	24 (20.7%)	30 (6.4%)	22.41	<0.001
Malignant tumor	13 (2.2%)	7 (6.0%)	6 (1.3%)	9.58	0.002
Clinical symptoms					
Fever	431 (74.1%)	93 (80.2%)	338 (72.5%)	2.82	0.093
Highest temperature ≥38.5°C	152 (26.1%)	48 (41.4%)	104 (22.3%)	17.49	<0.001

MAP, mean arterial pressure.

TABLE 2 | Baseline blood and biochemical indices of the COVID-19 patients at baseline.

Biochemical indexes	Abnormal standard	All patients n = 582	Severe disease n = 116	Non-severe disease n = 466	t/z/χ^2 value	P-value
Routine blood tests						
White blood cell count, ×10^9/L	≥9.5	28 (4.81%)	13 (11.21%)	15 (3.22%)	12.941	<0.001
Neutrophil count, ×10^9/L	≥6.3	63 (10.82%)	27 (23.28%)	36 (7.73%)	23.268	<0.001
Lymphocyte count, ×10^9/L	≤1.1	300 (51.55%)	89 (76.72%)	214 (45.92%)	35.307	<0.001
NLR		2.86 (2.00, 4.58)	4.20 (2.50, 8.32)	2.64 (1.86, 4.18)	−6.148	<0.001
Hemoglobin, g/L	≤110	51 (8.76%)	17 (14.66%)	34 (7.30%)	6.291	0.012
Platelet count, ×10^9/L	≤125	97 (16.67%)	34 (29.31%)	63 (13.52%)	16.675	<0.001
Liver function						
Alanine aminotransferase, U/L	≥40	101 (17.35%)	24 (20.69%)	77 (16.52%)	1.124	0.289
Aspartate aminotransferase, U/L	≥40	93 (15.98%)	33 (28.45%)	60 (12.88%)	16.777	<0.001
γ-glutamyl transpeptidase, U/L	≥50	89 (16.79%)	24 (26.97%)	65 (14.74%)	7.924	0.005
Alkaline phosphatase, U/L	≥100	101 (20.74%)	23 (28.05%)	78 (19.26%)	3.205	0.073
Albumin, g/L	≤40	258 (44.33%)	83 (71.55%)	175 (37.55%)	43.502	<0.001
Total bilirubin, μmol/L	≥21	62 (10.67%)	16 (13.91%)	46 (9.87%)	1.581	0.209
Cut-off	≥11	346 (59.45%)	79 (68.10%)	267 (57.30%)	4.500	0.034
Renal function						
Blood urea nitrogen, mmol/L	≥7.6	36 (6.02%)	23 (20.00%)	16 (3.43%)	40.426	<0.001
Creatinine, μmol/L	≥104	53 (9.11%)	26 (22.41%)	27 (5.79%)	30.995	<0.001
Cut-off	≥85	153 (26.29%)	51 (43.97%)	102 (21.89%)	23.362	<0.001
Myocardium						
Creatine kinase, U/L	≥171	82 (14.14%)	30 (25.86%)	52 (11.21%)	16.419	<0.001
Cut-off	≥104	194 (33.33%)	56 (48.28%)	138 (29.61%)	14.556	<0.001
Creatine kinase-MB, U/L	≥25	13 (2.74%)	4 (3.96%)	9 (2.41%)	0.714	0.398
Lactate dehydrogenase, U/L	≥243	165 (34.96%)	56 (55.45%)	109 (29.38%)	23.722	<0.001
Coagulation function						
Prothrombin time, s	≥13	65 (16.09%)	19 (20.88%)	46 (14.70%)	1.996	0.158
Activated partial thromboplastin time, s	≥36.5	68 (16.83%)	24 (26.37%)	44 (14.06%)	7.64	0.006
International normalized ratio	≥1.5	1 (0.20%)	1 (0.94%)	0 (0.00%)	3.157	0.076
D-dimer, mg/L	≥0.25	295 (66.74%)	77 (89.53%)	218 (61.24%)	24.99	<0.001
Inflammatory indexes						
Procalcitonin, ug/L	≥0.5	5 (1.08%)	4 (4.30%)	1 (0.27%)	8.425	<0.001
C-reactive protein, mg/L	≥5	419 (72.62%)	105 (92.11%)	314 (67.82%)	27.135	<0.001
Erythrocyte sedimentation rate, mm/1 h	≥15	244 (56.74%)	54 (66.67%)	190 (54.44%)	4.003	0.045

Missing data of baseline blood and biochemical indices: variables with missing values exceeding 10% include: procalcitonin (118 cases), erythrocyte sedimentation rate (152 cases), alkaline phosphatase (95 cases), creatine kinase-MB (108 cases), lactate dehydrogenase (110 cases), prothrombin time and activated partial thromboplastin time (178 cases), and D-dimer (140 cases).
NLR, neutrophil-to-lymphocyte ratio.

(Alb) level was more common in the patients with severe disease than those with non-severe disease (71.55 *vs.* 37.55%, P < 0.001). There were larger proportions of patients with abnormal levels of blood urea nitrogen (BUN), creatinine (Cr), creatine kinase (CK), LDH, D-dimer, PCT, and CRP; activated partial thromboplastin time (APTT); and erythrocyte sedimentation rate (ESR) in the group with severe disease than in the group with non-severe disease (**Table 2**).

Independent Risk Factors for Severe COVID-19

According to univariate logistic regression analysis, 24 variables, including age, comorbidities, fever, and ln (CRP), were associated with the severity of COVID-19 and included in the multivariate

logistic regression analysis (forward likelihood method). A body temperature ≥38.5°C, ln (NLR), ln (PLT), ln (Alb), ln (Tbil), ln (Cr), and ln (CK) were independent risk factors for severe COVID-19. The risk of severe illness in the patients with a body temperature ≥38.5°C was 2.37 (95% CI, 1.39, 4.03) times that in the patients with a body temperature <38.5°C. Comorbidities and high values of ln (NLR), ln (Tbil), ln (Cr), and ln (CK), and low values of ln (PLT) and ln (Alb) were associated with an increased risk of severe COVID-19 (**Table 3**).

Predictive Nomogram for Severe COVID-19

Based on the aforementioned eight variables, a nomogram model was established to predict the risk of severe COVID-19 (**Figure 2**) with a prediction accuracy of 85.9%, a leave-one-out cross

TABLE 3 | Risk factors for severe COVID-19 and mortality.

Variable	Crude OR (95% CI)	Adjusted OR (95% CI)	P-value (Wald's test)	P-value (LR-test)
Risk factors for severe COVID-19				
Comorbidity	4.48 (2.93, 6.86)	2.69 (1.61, 4.49)	<0.001	<0.001
Temperature ≥38.5°C	2.46 (1.6, 3.77)	2.37 (1.39, 4.03)	0.002	0.002
ln (NLR)	2.75 (2.04, 3.71)	1.64 (1.13, 2.37)	0.009	0.008
ln (PLT)	0.27 (0.15, 0.48)	0.45 (0.23, 0.9)	0.024	0.023
ln (Alb)	0.00 (0.00, 0.00)	0.00 (0.00, 0.02)	<0.001	<0.001
ln (Tbil)	2.04 (1.29, 3.21)	1.92 (1.04, 3.52)	0.036	0.032
ln (Cr)	3.54 (1.96, 6.4)	2.68 (1.39, 5.17)	0.003	0.001
ln (CK)	1.86 (1.4, 2.48)	1.44 (1.03, 2.02)	0.034	0.034
Risk factors for mortality				
ln (NLR)	3.78 (2.17, 6.60)	2.67 (1.27, 5.62)	<0.001	0.01
ln (Alb)	0.01 (0.00, 0.01)	0.01 (0.00, 0.05)	<0.001	<0.001
ln (Cr)	7.28 (3.06, 17.31)	7.23 (2.89, 18.10)	<0.001	<0.001
ln (CK)	3.29 (1.93, 5.61)	3.00 (1.60, 5.61)	<0.001	<0.001

NLR, neutrophil-to-lymphocyte ratio; PLT, platelet; Alb, albumin; Tbil, total bilirubin; Cr, creatinine; CK, creatine kinase; ln, natural logarithm.

validation accuracy of 81.6%, an AUROC of 0.858 (95% CI, 0.823–0.893), and a Hosmer-Lemeshow test P-value of 0.237.

CANPT Score: A Novel Scoring Model for the Prediction of the Risk of Severe COVID-19

For convenience in clinical use, a novel scoring model was constructed based on the nomogram model and named the CANPT score, with scores ranging from 8 to 20 (**Table 4**). The AUROC of the CANPT score was 0.841 (95% CI, 0.804, 0.879), with a positive predictive value of 35.49% (95% CI, 30.23%, 41.13%), and a negative predictive value of 95.85% (95% CI, 92.81%, 97.68%) when 12 was used as the first cut-off value, and a positive predictive value of 69.64% (95% CI, 56.6%, 80.16%) and a negative predictive value of 85.36% (95% CI, 82.07%, 88.14%) when 16 was used as the second cut-off value (**Table 5**). In this study, 12/289 patients with a CANPT score <12 developed severe disease; 65/237 patients with a CANPT score ≥12 and <16 developed severe disease; and 39/56 patients with a CANPT score ≥16 developed severe disease. The actual incidence of severe disease in the COVID-19 patients with CANPT scores <12, ≥12 and <16, and ≥16 were 4.15, 27.43, and 69.64%, respectively. Thus, with cut-off values of 12 and 16, COVID-19 patients could be classified into low-risk, medium-risk, and high-risk groups with corresponding risks of developing severe COVID-19 of <5, 30, and 70%, respectively.

In this study, the CALL scores were calculated for 472 COVID-19 patients who had measurements of serum LDH levels on admission, and the predictive efficacies of the CALL score and the NLR were verified among these patients and compared with the efficacy of the CANPT score. The results showed that the AUROCs of the CANPT score, CALL score, and NLR were 0.835
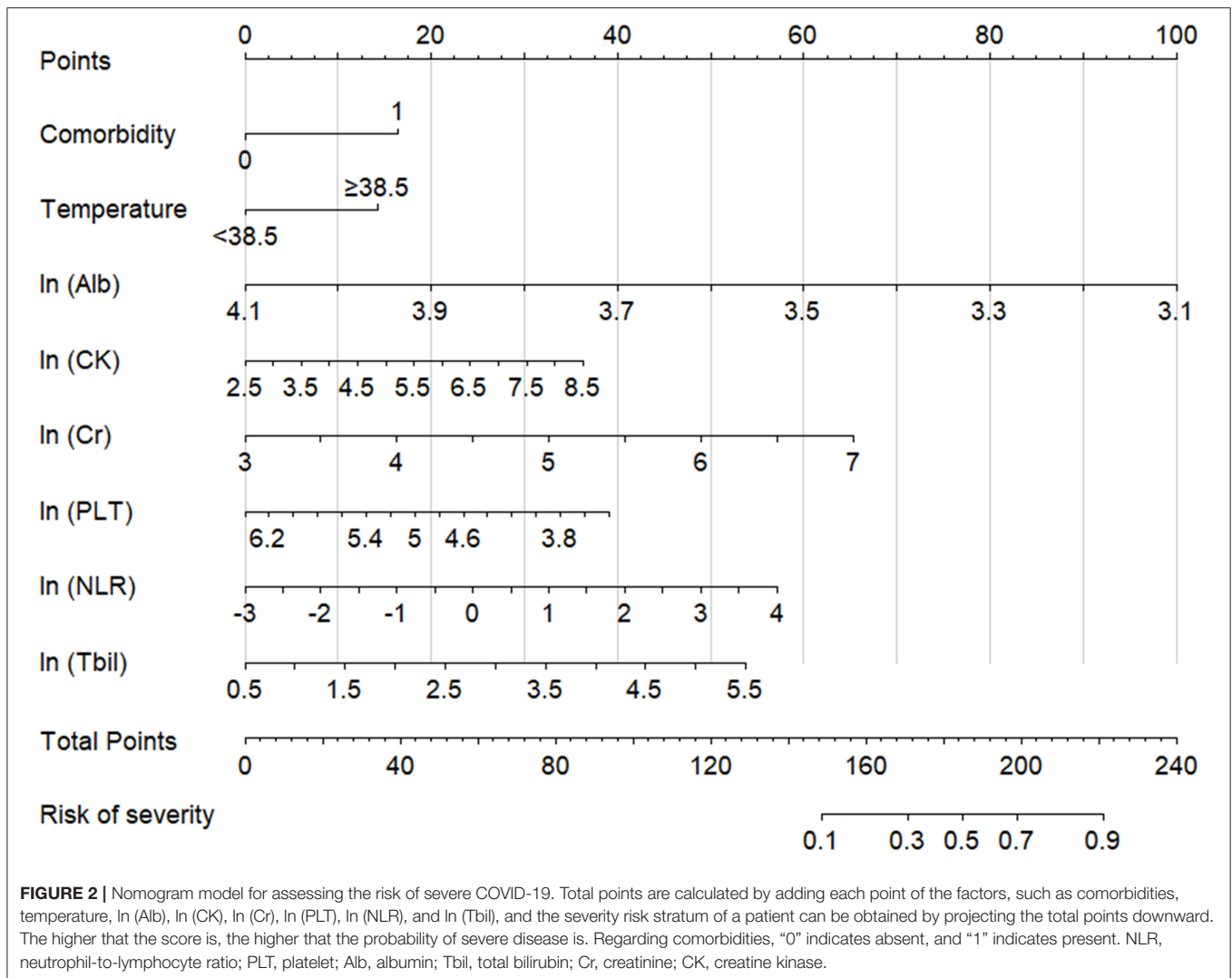
(95% CI, 0.794, 0.876), 0.795 (95% CI, 0.747, 0.844), and 0.669 (95% CI, 0.607, 0.730), respectively. The predictive performance of the CANPT score was better than that of the CALL score and NLR (**Figure 3**).

Model for the Prediction of the Risk of Mortality in COVID-19 Patients

Multivariate logistic regression analysis showed that the NLR and the levels of Alb, Cr, and CK were independent risk factors for mortality in patients with COVID-19 (**Table 3**). The CAN score was established to predict the risk of mortality in patients with COVID-19. The CAN score ranged from 4 to 19 (**Table 4**), with a prediction accuracy of 97.3%, a leave-one-out cross validation accuracy of 96.2%, an AUROC of 0.903 (95% CI, 0.832, 0.974), and a Hosmer-Lemeshow test P-value of 0.173. The cut-off value was determined by maximizing the Youden index at 15 points, with a sensitivity of 76.47% (95% CI, 52.23%, 90.95%), a specificity of 93.63% (95% CI, 91.28%, 95.38%), a positive predictive value of 26.53% (95% CI, 16.10%, 40.37%), a negative predictive value of 99.25% (95% CI, 98.01%, 99.78%), a positive likelihood ratio of 12.00 (95% CI, 11.12, 12.95), and a negative likelihood ratio of 0.25 (95% CI, 0.21, 0.29). In this study, 49/582 patients with COVID-19 had a CAN score ≥15; of these patients, 13 died. The actual mortality rates were 26.53% in the patients with a CAN score ≥15 and only 0.75% in those with a CAN score <15. Among the patients with severe disease, the actual mortality rate was 43.33% in the patients with a CAN score ≥15.

DISCUSSION

We enrolled 582 COVID-19 pneumonia patients in this study from four hospitals in three provinces, 74.57% of whom were from Hubei Province, and 25.43% of whom were from outside Hubei Province; thus, we reduced patient selection bias. Previous studies have shown that COVID-19 is a systemic disease with damage occurring not only in the lungs but also in many other systems, including the circulatory, cardiovascular, renal, gastrointestinal, endocrine, nervous, and integumentary systems (23, 24). In this study, some patients with COVID-19 had increased WBC and NE counts; increased ESRs; increased APTTs; increased levels of D-dimer, PCT, CRP, AST, GGT, BUN, Cr, CK, and LDH; decreased levels of HGB and Alb; and decreased PLT counts, further confirming the presence of multisystem damage in COVID-19 patients. Moreover, the incidence and degree of abnormalities in the above indicators in the patients with severe disease were significantly higher than those in the patients with non-severe disease, and the number of damaged systems and degree of damage were related to the severity of COVID-19. In this study, comorbidities, a body temperature ≥38.5°C, ln (NLR), ln (PLT), ln (Alb), ln (Tbil), ln (Cr), and ln (CK) were found to be independent risk factors for severe COVID-19, and the CANPT score comprehensively reflected the presence and degree of damage to the immune system, circulatory system, liver, kidneys, and heart in the patients with COVID-19, thereby accurately predicting the risk of severe disease.

FIGURE 2 | Nomogram model for assessing the risk of severe COVID-19. Total points are calculated by adding each point of the factors, such as comorbidities, temperature, ln (Alb), ln (CK), ln (Cr), ln (PLT), ln (NLR), and ln (Tbil), and the severity risk stratum of a patient can be obtained by projecting the total points downward. The higher that the score is, the higher that the probability of severe disease is. Regarding comorbidities, "0" indicates absent, and "1" indicates present. NLR, neutrophil-to-lymphocyte ratio; PLT, platelet; Alb, albumin; Tbil, total bilirubin; Cr, creatinine; CK, creatine kinase.

Current studies have confirmed that patients with severe COVID-19 develop SARS-CoV-2-related cytokine storms and systemic inflammatory response syndrome (SIRS) (27–29). SIRS often leads to dysfunction in the lungs, kidneys, liver, heart, etc., and even multiple organ failure syndrome (MOFS). Angiotensin converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2) are the receptors by which SARS-CoV-2 invades cells. In addition to the respiratory system, organs and tissues, such as the kidneys, heart, and bile duct epithelium, express ACE2/TMPRSS2 and therefore are potential target organs of SARS-CoV-2 that can be directly damaged (30, 31). Acute kidney injury (AKI) and myocardial injury have been observed in patients with critical COVID-19 (32–34). Therefore, organs, such as the kidneys, liver, and heart, can be affected by both direct damage from SARS-CoV-2 and indirect damage mediated by SIRS. Indicators of the function of these organs, such as Alb, Tbil, and Cr, were given relatively greater weight in the CANPT score to reflect that the degree of organ dysfunction plays an important role in the progression and severity of COVID-19.

Previous studies have shown that AKI is a common complication in patients with COVID-19 and that patients with kidney disease have a significantly higher risk of in-hospital mortality (35). Kidney biopsies from 17 patients with COVID-19 complicated with kidney injury did not show SARS-CoV-2 in the kidney tissue, suggesting that kidney injury in COVID-19 patients is mainly caused by SARS-CoV-2-associated SIRS, rather than direct renal damage caused by SARS-CoV-2 (36). A previous study found that the level of Cr is an independent risk factor for severe COVID-19; thus, Cr was given relatively greater weight in the CANPT score. Therefore, CANPT score could accurately reflect the extent of renal damage in COVID-19 patients early on admission.

Recent studies have shown that almost all hospitalized patients with COVID-19 have elevated levels of serum CK and LDH (28, 37, 38). Autopsies of patients who died of COVID-19 showed cardiomyocyte necrosis and monocyte infiltration (26). Persistently elevated CK indicates the occurrence and progression of myocardial injury in patients with COVID-19.

TABLE 4 | Calculation of the CANPT and CAN scores.

Variable	Adjusted OR (95% CI)	P-value (Wald's test)	Points
CANPT score			
Comorbidities			
Present	3.24 (1.98, 5.29)	<0.001	3
Absent			1
Highest temperature			
≥38.5°C	2.18 (1.30, 3.65)	0.003	2
<38.5°C			1
NLR			
≥3.7	1.90 (1.17, 3.11)	0.01	2
<3.7			1
PLT			
≥155			1
<155	1.95 (1.19, 3.18)	0.008	2
Alb			
≥38			1
<38	4.14 (2.49, 6.88)	<0.001	4
Tbil			
≥11	1.37 (0.82, 2.28)	0.229	2
<11			1
Cr			
≥85	3.13 (1.86, 5.29)	<0.001	3
<85			1
CK			
≥104	1.69 (1.03, 2.76)	0.036	2
<104			1
CAN score			
NLR			
≥7	4.92 (1.51, 16.10)	0.008	5
<7			1
Alb			
≥38			1
<38	2.50 (1.47, 4.24)	0.001	2
Cr			
≥80	8.62 (2.24, 33.24)	0.002	8
<80			1
CK			
≥106	4.34 (1.32, 14.28)	0.016	4
<106			1

NLR, neutrophil-to-lymphocyte ratio; PLT, platelet; Alb, albumin; Tbil, total bilirubin; Cr, creatinine; CK, creatine kinase.

TABLE 5 | Accuracy of the CANPT score in estimating the risk of disease progression.

Variable	Enrolled patients (n = 582)
AUROC	0.841 (0.804, 0.879)
Cut-off value (95% CI)	12
Sensitivity, %	89.66 (82.65, 94.12)
Specificity, %	59.44 (54.92, 63.81)
Positive predictive value, %	35.49 (30.23, 41.13)
Negative predictive value, %	95.85 (92.81, 97.68)
Positive likelihood ratio	2.21 (2.12, 2.31)
Negative likelihood ratio	0.17 (0.16, 0.19)
Cut-off value (95% CI)	16
Sensitivity, %	33.62 (25.66, 42.64)
Specificity, %	96.35 (94.2, 97.75)
Positive predictive value, %	69.64 (56.6, 80.16)
Negative predictive value, %	85.36 (82.07, 88.14)
Positive likelihood ratio	9.22 (8.69, 9.78)
Negative likelihood ratio	0.689 (0.671, 0.706)

AUROC, area under the receiver operating characteristic curve; CI, confidence interval.

damage (40). Abnormal coagulation function can be observed in patients with COVID-19, and almost all patients with severe COVID-19 have coagulation disorders. Several studies have shown that abnormal coagulation parameters are closely related to a poor prognosis of COVID-19 (41–46), especially D-dimer, which was not included in the modeling analysis due to the missing value of D-dimer being >10%. Previous studies have reported that the PLT count can be used as a marker of the progression of COVID-19 (47–51). In this study, a reduced PLT count was a risk factor for severe COVID-19, consistent with the results of previous studies. On the one hand, the reduced PLT count in patients with COVID-19 is due to the massive consumption of PLTs in the DIC process; autopsies of patients who died from COVID-19 showed that microthrombi formed in the pulmonary capillaries (26). On the other hand, SARS-CoV-2 can also directly infect bone marrow components, causing hematopoietic abnormalities or triggering an autoimmune response to blood cells (52, 53), further leading to a reduction in the PLT count. Therefore, the decrease in the PLT count reflects abnormal coagulation function, even DIC, in patients with COVID-19.

The presence of comorbidities is also an independent risk factor for severe COVID-19. Patients with hypertension, diabetes, structural lung disease, chronic kidney disease, etc., are more likely to develop ARDS and multiple organ dysfunction syndrome (MODS) in response to SIRS because of preexisting organ structural abnormalities and/or dysfunction (54–57). Due to the high levels of ACE2 expression on the surface, vascular endothelial cells may suffer from direct damage by SARS-CoV-2 and indirect damage due to SARS-CoV-2-associated SIRS. Patients with preexisting vascular endothelial cell damage due to diabetes, hypertension, or chronic kidney disease are predisposed to experiencing more damage to vascular endothelial cells by SARS-CoV-2, which could play a key role in the development of MOFS and severe disease (58).
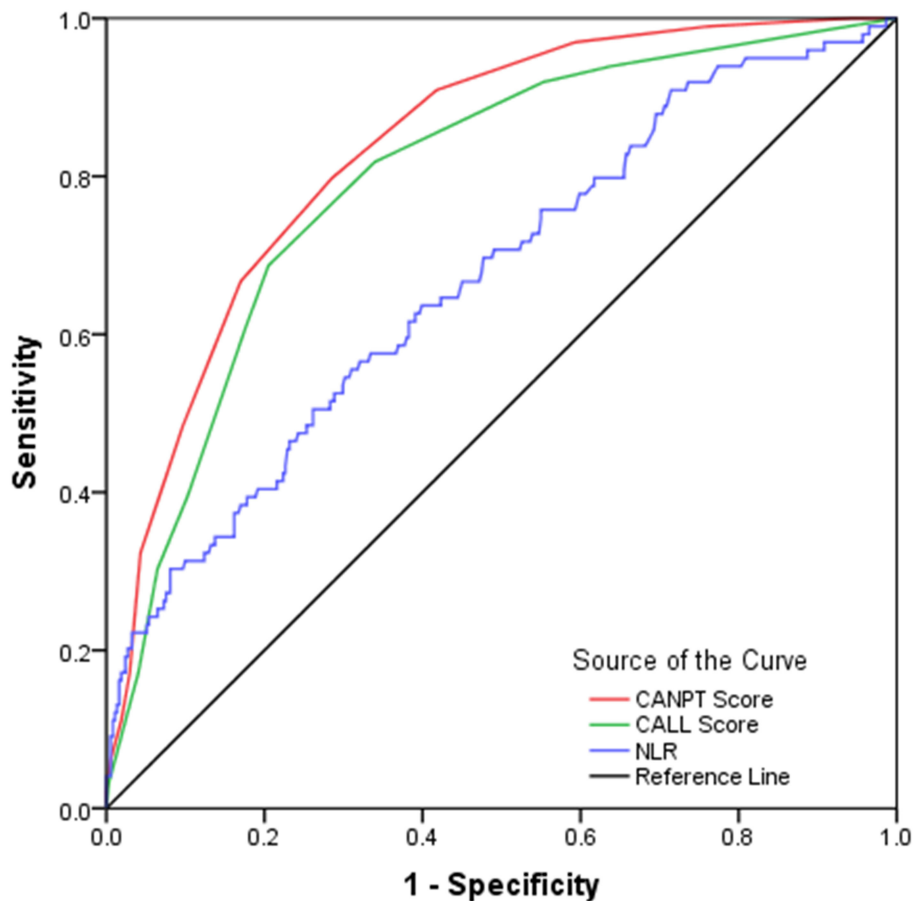
CK is a prognostic marker for severe COVID-19, and the cut-off value is less than the upper limit of normal (ULN) (39). In this study, elevated CK levels were found in 14.14% of the patients with COVID-19 and was more common in patients with severe disease than those with non-severe disease (25.86 *vs.* 11.21%, *P* < 0.001). CK was given a weight of 2 in the CANPT score, reflecting myocardial damage in patients with COVID-19.

The activation of the coagulation system is very common in inflammatory and anti-inflammatory reactions and readily leads to diffuse intravascular coagulation (DIC), which plays an important role in the occurrence and development of organ

FIGURE 3 | ROC curves of the CANPT score, CALL score, and the NLR. The area under the receiver operating characteristic curves of the CANPT score, CALL score, and the NLR were 0.835 (95% CI, 0.794, 0.876), 0.795 (95% CI, 0.747, 0.844), and 0.669 (95% CI, 0.607, 0.730), respectively. ROC, receiver operating characteristic curve; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio.

In this study, a high NLR was a risk factor for severe disease in patients with COVID-19, consistent with the results of previous studies (10, 21, 59). The elevation in the NLR is related to immune disorders in patients with COVID-19. The invasion of SARS-CoV-2 triggers cytokine storms and SIRS in the body, resulting in an increased NE count. The LY count was found to be significantly reduced in peripheral blood from patients with COVID-19 due to recruitment and translocation in the local inflammatory system, which is especially pronounced in patients with severe disease (60). Another study found that SARS-CoV-2 could promote T lymphocyte apoptosis by activating the STAT1/IRF3 pathway (61). Thus, an elevated NE count and a reduced LY count in patients with COVID-19 lead to an increase in the NLR, reflecting the degree of the immune response and SIRS in patients with COVID-19.

Fever is a common symptom in patients with COVID-19. The immune response to SARS-CoV2 leads to systemic inflammation and even SIRS, with the consequent release of endogenous pyrogens, and the severity of fever represents the severity of SIRS (62). In this study, a body temperature ≥38.5°C was found to be more common in the group with severe disease than in the group with non-severe disease and was an independent risk factor for severe COVID-19.

ARDS is a clinical characteristic of severe COVID-19 and occurs in more than 71.2% of patients with severe COVID-19 in the ICU (63). The Murray score is used to evaluate the severity of acute lung injury and the risk of ARDS. The higher the Murray score, the more severe the acute lung injury, and the higher the risk of ARDS (64). Previous studies have shown that the Alb level in patients with COVID-19 is negatively correlated with the SARS-CoV-2 load and Murray score, and the higher the SARS-CoV-2 load in patients, the more critical the patient's condition (65). Recent studies have found that a low Alb level is an independent risk factor for disease progression in patients with COVID-19 (51, 66–68). In this study, a low Alb level was an important predictor of severe disease in patients with COVID-19 and was given a weight of 4 in the CANPT score, further validating previous research.

There have been reports of severe liver damage in patients with severe COVID-19 (69–71). Chai et al. suggested that liver injury in patients with COVID-19 could be caused by SARS-CoV-2-mediated injury in bile duct cells (72). However,

SARS-CoV-2 has not been found in bile duct cells from patients who died of COVID-19, suggesting that liver damage in patients with COVID-19 is mediated by the SARS-CoV-2-associated cytokine storm and SIRS (73). Elevated ALT and AST levels suggest liver cell damage, while an elevated Tbil level indicates hepatocyte necrosis after the exclusion of bile duct obstruction or hemolysis. Several studies have found that an elevated Tbil level is significantly correlated with adverse outcomes of COVID-19 (69, 70, 74, 75); Tbil, which was given a weight of 2 in the CANPT score, reflects the severity of liver injury in patients with COVID-19.

Interestingly, the cut-off values of CK, Cr, and Tbil determined in this study were markedly lower than their ULNs. The rationale for CK, Cr, and Tbil levels being elevated is high risk for severe COVID-19, but the cut-off chosen for the CANPT score is lower than the ULN can be explained for the following reasons: (1) patients with higher values of CK, Cr, and Tbil than the cut-off levels could at high risk for according organ damage; and (2) higher values of CK, Cr, and Tbil may be resulted from an increase from much lower baseline levels due to organ injury; i.e., a significant increase in levels of CK, Cr, and Tbil could be important indicators of organ injury. The report from Qin et al. showed similar results in COVID-19 patients. In this study, cut-off values for high-sensitivity cardiac troponin I (hs-cTnI), creatine phosphokinase-MB (CK-MB), CK, and myoglobin (MYO) equivalent to ∼49% ULN and a cut-off value of N-terminal pro-brain natriuretic peptide (NT-proBNP) equivalent of ∼18.9% ULN were established for the prediction of adverse outcomes in COVID-19 patients, and patients with higher hs-cTnI, CK-MB, CK, MYO, and (NT-pro) BNP levels than the cut-off values were correlated with increased risk of death (39). Therefore, COVID-19 patients with CK, Cr, and Tbil levels higher than the cut-off values determined in this study, although within normal ranges, would still be at high risk for adverse outcomes and require more attention. Further, CANPT/CAN scoring could be helpful in identifying COVID-19 patients who are at high risk for severe disease.

In this study, <5% of the COVID-19 patients with a CANPT score <12 developed severe disease. Thus, the patients with a CANPT score <12 were considered low-risk patients, and the recommendation is to place these low-risk patients in a mobile cabin hospital or have them isolate at home with general symptomatic treatment with oral medication. In total, 27.43% of the patients with a CANPT score ≥12 and <16 developed severe disease and were considered at intermediate risk; therefore, people with a score within this range should be admitted to an isolation ward for respiratory monitoring and receive antiviral, anti-inflammatory, and symptomatic treatment. Nearly 70% of the patients with a CANPT score ≥16 developed severe disease. These patients should be considered at a high risk and should be transferred to an isolation ICU to receive comprehensive antiviral and symptomatic supportive treatment and respiratory support.

When the CAN score was used to predict the risk of mortality, only 0.75% of the patients with a CAN score <15 died, while among those with a CAN score ≥15, 26.53% of all patients, and 43.33% of the patients with severe disease eventually died. Thus, the CAN score could be used to identify patients who are at

a high risk for mortality. Patients with a CAN score <15 are relatively safe, while those with a CAN score ≥15 are at a high risk for mortality regardless of whether they have severe disease and should be treated in the ICU.

The CALL score, which considers comorbidities, the LY count, age, and the LDH level, has been reported to have good predictive efficacy and is convenient for use in clinical practice (20). Studies have also reported that the NLR is an independent predictor of poor prognosis in patients with COVID-19 (21, 22). In this study, the CANPT score was compared with the CALL score and the NLR. The predictive performance of the CANPT score was significantly superior to that of the CALL score and the NLR with a larger AUROC.

The use of comorbidities and routine indicators, including body temperature, the NLR, the PLT count, and the levels of Alb, Tbil, Cr, and CK, renders the CANPT and CAN scores easy to calculate, and these scores are efficient in predicting the risk of severe illness and death in patients with COVID-19. These scores could be used to help clinicians to identify patients at high risk for poor outcomes or mortality soon after admission. Providing intensive care to the small proportions of patients who at high risk could improve their outcomes and reduce the mortality rate, and the rational allocation of limited medical staff and equipment could alleviate the serious shortages of medical resources. There were some limitations of this study. First, the practice for identification of severe and critically ill COVID-19 might differ in different hospitals, which could bias the results of the analysis. Second, this study only included Chinese patients; thus, the performance of the CANPT score and CAN score in patients of other ethnicities must be validated. Third, only 17 of the 582 COVID-19 patients included in this study died; therefore, the CAN model might not be sufficiently accurate to predict the risk of death in COVID-19 patients. Finally, this study was a retrospective study with a sample size of 582 without external validation, and the CANPT and CAN scores must be further validated in a large sample of patients from different regions.

The CANPT and CAN scores can be used to identify patients with COVID-19 who are at a high risk for severe disease or death soon after admission, guiding patient management and the rational allocation of limited medical resources based on patient risk stratification.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: Clinical data were retrieved from the medical records databases of Shiyan Taihe Hospital, Ankang Central Hospital, Ningbo Hwamei Hospital, and Yichang Central People's Hospital. Requests to access these datasets should be directed to Yuanyuan Chen, cyy15871089714@163.com.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Medical Ethics Committee of Shiyan Taihe Hospital. The approval number is 2020KS018. Written

informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

YC and ZM designed and coordinated the research, contributed to the statistical analysis, and interpretation and the writing of the manuscript. ZM reviewed and edited the manuscript. JZ guided the data analysis. YC, HY, XZ, HH, ZJ, and SL collected the data. All authors contributed to and approved the submitted version of this manuscript.

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