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ORIGINAL RESEARCH

Risk Factors and Nomogram Prediction Model for Healthcare-Associated Infections (HAIs) in COVID-19 Patients

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Background: To identify risk factors for acquiring HAIs in COVID-19 patients and establish visual prediction model.

Methods: Data was extracted from Xinglin Hospital Infection Monitoring System to analyze COVID-19 patients diagnosed between December 1, 2022, and March 1, 2023. Univariate and multivariate analyses were conducted to identify risk factors. Predictive signature was developed by selected variables from lasso, logistic regression, and their intersection and union. Models were compared using DeLong's *t*-tests. Likelihood ratio (LR) and Youden's index was used to evaluate the predictive performance. Nomogram was constructed using optimal variables ensemble, prediction accuracy was evaluated using AUC, DCA and calibration curve.

Results: Total of 739 patients met the criteria, of which 53 (7.2%) were HAIs. NSAIDs, surgery, fungi and MDRO detected, hormone drugs and LYMR were independent risk factors. Lasso model screened seven variables, and logistic model identified six risk factors. Union model performed the best with the maximum of the Youden's index is 0.703, the sensitivity is 95.6%, the specificity is 74.7%, the LR is 3.778. The best AUC of union model is 0.953 (0.928–0.978), and the accuracy is 87.5%. DCA indicated that the union model provided the best net benefits and calibration curve demonstrated good predictive agreement.

Conclusions: HAIs prediction in COVID-19 patients is feasible and beneficial to improve prognosis. Physicians can use this nomogram to identify high-risk COVID-19 populations for HAIs and tailor follow-up strategies.

Keywords: risk factors, healthcare-associated infection, COVID-19, nomogram, prediction model

Background

Coronaviruses are a subclass of the coronaviruses family that cause respiratory infections in mammals and avifauna.[1,2] Symptoms and tropism caused by coronavirus vary depending on the host species.[3] It causes symptoms in humans that are asymptomatic or accompanied by fever, cough and shortness of breath.[4,5] However, especially in the elderly and immunocompromised, coronavirus infection can lead to severe acute pneumonia and even death.[6] In 2019, the novel coronavirus infection (2019-nCoV, or SARS-CoV-2) caused the Coronavirus Disease-2019 (COVID-19) became epidemic worldwide.[7] On 11 March 2020, the World Health Organization (WHO) declared that SARS-CoV-2 had caused global spread and triggered a pandemic. At the beginning of December 2022, the Chinese government issued an overall plan for the implementation of "Classified and treated as a Category B infectious disease" for SARS-CoV-2.

Hospital-acquired infections (HAIs) pose significant and ongoing challenge in healthcare settings, leading to prolonged hospital stays, increased antimicrobial resistance, higher morbidity and mortality rates, and substantial costs for healthcare systems. It is critical to recognize the impact of HAIs as a secondary infection and its development of antibiotic resistance on COVID-19 patients. Recent research[8] focused on inpatient adults diagnosed with COVID-19 in

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Wuhan, China, revealing that half of non-survivors had secondary infections, with almost all receiving antibiotic treatment. A survey at Barcelona Hospital in Spain found 74 bacterial infections in 72 of 989 adult patients hospitalized more than 48 hours with COVID-19.[9] Joint survey analysis by Rawson et al[10] of the United States and China found that 8% of 806 COVID-19 patients had bacterial or fungal infections, much higher than the average infection rate of 5% among the general patients. Similarly, 16% (109 cases) of 712 hospitalized COVID-19 patients in Valladolid, Spain, were reported bacterial or fungal infection or both.[11]

HAIs are preventable incidents that result in significantly worse prognosis among hospitalized patients and seriously squeeze social medical resources.[12] According to WHO, the prevalence of HAI ranges from 5.7% to 19.1% in developing countries and from 3.5% to 12% in developed countries. However, these estimates may only represent a fraction of the actual prevalence due to under-reporting in many countries.[13] While previous researches have extensively examined the diagnosis, treatment, risk factors associated with COVID-19, including age, CT features, vaccines, symptoms, and medical interventions,[14] there is a notable gap in research focusing on the risk factors for acquiring HAIs in patients with COVID-19. Therefore, it is crucial for clinicians to identify the epidemiological significances and risk factors of HAIs in patients with COVID-19. Moreover, although several scoring systems have been established to predict the COVID-19 patients' prognosis, few are applicable to HAIs. It is essential to establish effective prediction models through large-scale cohorts and advanced modeling techniques to determine the predictors of HAIs. Visualization prediction using nomogram has shown promising results in predicting individualized prognosis in recent studies.[15–17]

In this study, confirmed COVID-19 patients during the rapid increase period in China (from December 1, 2022 to March 1, 2023) were selected to examine the predictive signatures. Patients who meet inclusion criteria and their clinical features and test results were used to identify the risk factors. Nomogram was constructed using prognostic factors screened based on logistic regression and lasso regression methods to assess the risk of HAIs in each individual. Overall, our findings highlight the feasible predictive clinical features and risk factors of acquiring HAIs in COVID-19 patients, offering practical predictive tools for clinical application and help clinicians to tailor follow-up treatment strategies.

Methods and Materials

Data Source

Clinical HAIs data was extracted from the Xinglin Hospital Infection Real-time Monitoring System (NIS, Xinglin Information Technology Co., Ltd., Hangzhou). NIS program is an intelligent early warning strategy system, based on the logic of hospital sense diagnosis, which realizes a monitoring system that does not rely on clinicians to report and automatically warns suspected hospital-sensed cases. Patients diagnosed with COVID-19 (U07.100×001 or 002) in the First Affiliated Hospital of Nanjing Medical University from December 1, 2022 to March 1, 2023 and possessed positive follow-up record were included as primary cases. Inclusion criteria are as follows: (1) detection of confirmed COVID-19 patients by real-time PCR or antigen testing; (2) age >18 years old; (3) the duration of hospitalization >48 hours; (4) patients were admitted to the hospital with a clear diagnosis of COVID-19. Patients were diagnosed with the COVID-19 after hospitalization, expectant mother, nucleic acid results had turned negative at admission and those with incomplete clinical data were excluded. All data were de-identified, and all protocols were approved by the Institutional Review Committee of the First Affiliated Hospital of Nanjing Medical University, and informed consent was obtained from all patients.

Patients Enrollment

A total of 798 confirmed COVID-19 patients were screened in the NIS system between December 1, 2022 and March 1, 2023, among which 59 cases were excluded which does not meet the diagnostic criteria of COVID-19. Patients who with a stay of less than 48 hours (n=32), were younger than 18 years (n=2), nuclei acid results had turned negative at admission (n=1), and did not have complete clinical data (n=2) were excluded. Moreover, expectant mother (n=22) was also excluded. Ultimately, 739 cases from NIS system were accepted into cohort as shown in Figure 1.

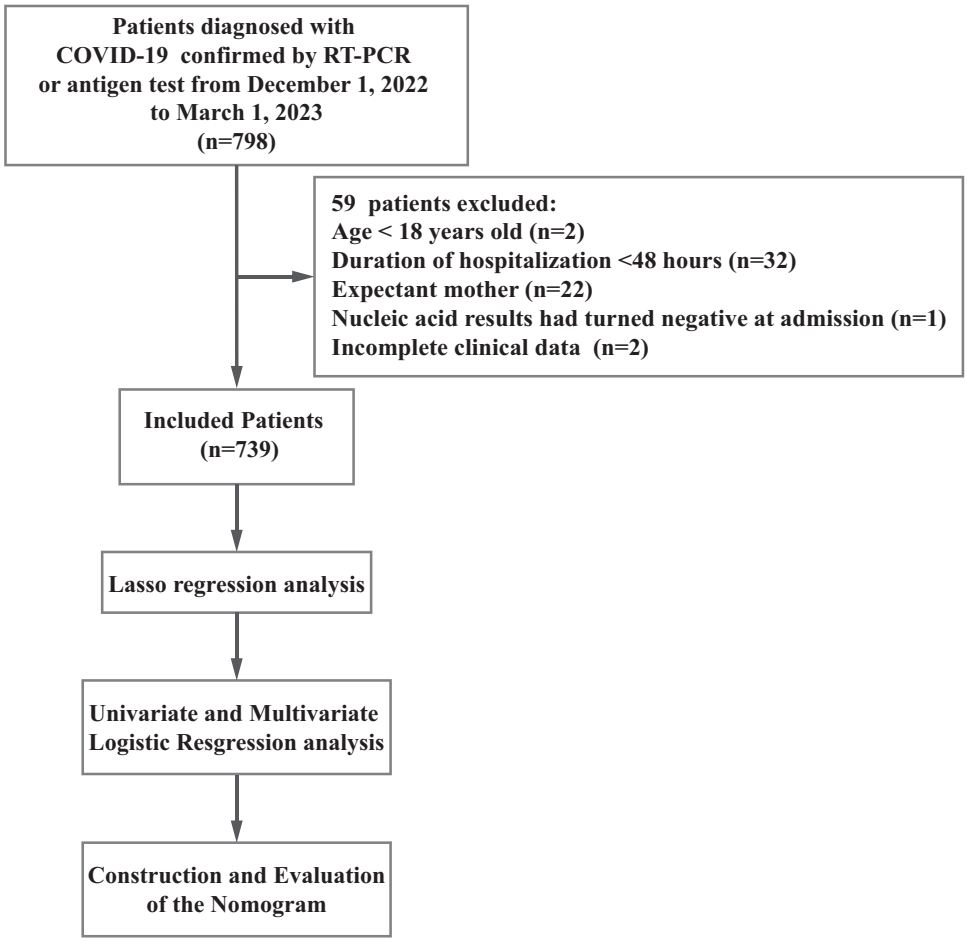

Figure 1 Inclusion and exclusion criteria of COVID-19 patients.

Variables Definition

We selected valuable variables based on previous relevant studies and clinical experience for detailed definitions in the NIS and inpatient system manually. Basic information mainly included age, gender, inpatient department. The second part is the therapeutic measures received by the patient including whether to receive antiviral treatment and the drugs used (Azvudine or Paxlovid), non-steroidal anti-inflammatory drugs (NSAIDs), hormone drugs, immunosuppressive drugs, biological agents, anticoagulant, antibiotics and blood transfusion. Variables in the third section primarily reflect the patient's underlying disease prior to hospitalization as shown in Table 1. It describes the ability to detect micro-organisms, including fungi and MDRO in the fourth section. Section five are the results of the patient's first laboratory tests after admission, including complete blood count, coagulation function, and blood biochemistry. The last three remaining component variables were "three catheters" monitoring (ventilator supporting, CVC and urinary catheter intubation days), prior surgical history (surgery) and whether or not they were transferred to the ICU during hospitalization (be referral to ICU). Age (20–40, 41–60, 61–80, >80), ventilator supporting days, CVC days and urinary catheter intubation days (0, 1–7, 8–30, >30) were transformed into categorical variables in logistic regression analyses. The main outcome was confirmed cases of HAIs.

Statistical Analyses

Continuous variables were compared using either the Mann–Whitney *U*-test or *t*-test, along with the corresponding nonparametric test. Categorical variables were compared using the chi-square test or Fisher's exact test. Univariate and multivariate logistic regression analyses were applied to estimate the relationship between variables and HAIs in the whole cohort. Variable

Table 1 Demographic and Clinical Characteristics of COVID-19 Patients with Healthcare-Associated Infections

Variables	Total (n = 739)	Hospital Acquired Infections (n =53)	Non-hospital Acquired Infections (n = 686)	Standardize Difference (95% CI)	P value
Basic Information					
Age, Median±SD	72.55 ± 15.60	72.25 ± 14.59	72.57 ± 15.68	0.02 (−0.26, 0.30)	0.615
Gender, n (%)				0.01 (−0.27, 0.29)	0.945
Female	220 (29.77)	16 (30.19)	204 (29.74)		
Male	519 (70.23)	37 (69.81)	482 (70.26)		
Inpatient department, n (%)				1.35 (1.07, 1.64)	<0.001
Internal medicine department	316 (42.76)	10 (18.87)	306 (44.61)		
Surgical department	136 (18.40)	1 (1.89)	135 (19.68)		
ICU	164 (22.19)	37 (69.81)	127 (18.51)		
Geriatrics	69 (9.34)	5 (9.43)	64 (9.33)		
Emergency Department	54 (7.31)	0 (0.00)	54 (7.87)		
Treatment Strategies					
Antiviral treatment, n (%)				0.17 (−0.11, 0.45)	0.232
No	305 (41.27)	26 (49.06)	279 (40.67)		
Yes	434 (58.73)	27 (50.94)	407 (59.33)		
Azvudine, n (%)				0.15 (−0.13, 0.43)	0.291
No	423 (57.24)	34 (64.15)	389 (56.71)		
Yes	316 (42.76)	19 (35.85)	297 (43.29)		
Paxlovid, n (%)				0.10 (−0.18, 0.37)	0.486
No	637 (86.20)	44 (83.02)	593 (86.44)		
Yes	102 (13.80)	9 (16.98)	93 (13.56)		
Non-steroidal anti-inflammatory drugs, n (%)				0.14 (−0.14, 0.42)	0.302
No	507 (68.61)	33 (62.26)	474 (69.10)		
Yes	232 (31.39)	20 (37.74)	212 (30.90)		
Hormone Drugs, n (%)				0.38 (0.10, 0.66)	0.006
No	212 (28.69)	24 (45.28)	188 (27.41)		
Yes	527 (71.31)	29 (54.72)	498 (72.59)		
Immunosuppressive drugs, n (%)				0.27 (−0.01, 0.55)	0.166
No	715 (96.75)	53 (100.00)	662 (96.50)		
Yes	24 (3. 25)	0 (0.00)	24 (3.50)		
Biological agents, n (%)				0.13 (−0.15, 0.41)	0.307
No	682 (92.29)	47 (88.68)	635 (92.57)		
Yes	57 (7.71)	6 (11.32)	51 (7.43)		
Anticoagulant therapy, n (%)7.71				0.03 (−0.25, 0.31)	0.832
No	303 (41.00)	21 (39.62)	282 (41.11)		
Yes	436 (59.00)	32 (60.38)	404 (58.89)		
Antibiotics, n (%)				0.40 (0.12, 0.68)	0.04
No	51 (6.90)	0 (0.00)	51 (7.43)		
Yes	688 (93.10)	53 (100.00)	635 (92.57)		
Blood transfusion, n (%)				0.60 (0.32, 0.88)	<0.001
No	600 (81.19)	30 (56.60)	570 (83.09)		
Yes	139 (18.81)	23 (43.40)	116 (16.91)		
Underlying Disease Prior to Hospitalization					
Hypertension, n (%)				0.08 (−0.20, 0.36)	0.562
No	363 (49.12)	24 (45.28)	339 (49.42)		
Yes	58 (7.85)	29 (54.72)	29 (54.72)		

(*Continued*)

Table 1 (Continued).

Variables	Total (n = 739)	Hospital Acquired Infections (n =53)	Non-hospital Acquired Infections (n = 686)	Standardize Difference (95% CI)	P value
Tumor, n (%)				0.17 (−0.11, 0.45)	0.199
No	642 (86.87)	43 (81.13)	599 (87.32)		
Yes	97 (13.13)	10 (18.87)	87 (12.68)		
Diabetes, n (%)				0.04 (−0.24, 0.32)	0.785
No	546 (73.88)	40 (75.47)	506 (73.76)		
Yes	193 (26.12)	13 (24.53)	180 (26.24)		
COPD or Chronic bronchitis, n (%)				0.04 (−0.24, 0.32)	0.794
No	618 (83.63)	45 (84.91)	573 (83.53)		
Yes	121 (16.37)	8 (15.09)	113 (16.47)		
CAD, n (%)				0.45 (0.17, 0.73)	0.011
No	619 (83.76)	51 (96.23)	568 (82.80)		
Yes	120 (16.24)	2 (3.77)	118 (17.20)		
Microbial Detection Capability					
Fungi Detected or Not, n (%)				1.31 (1.02, 1.60)	<0.001
No	529 (71.58)	11 (20.75)	518 (75.51)		
Yes	210 (28.42)	42 (79.25)	168 (24.49)		
MDRO Detected or Not, n (%)				1.29 (1.01, 1.58)	<0.001
No	647 (87.55)	21 (39.62)	626 (91.25)		
Yes	92 (12.45)	32 (60.38)	60 (8.75)		
Laboratory Results at Admission					
Complete Blood Count					
WBC ($\times 10^9$/L)	8.34 ± 7.36	8.98 ± 4.76	8.29 ± 7.53	0.11 (−0.17, 0.39)	0.134
NEUTR (%)	77.44 ± 15.95	80.01 ± 13.10	77.24 ± 16.15	0.19 (−0.09, 0.47)	0.322
LYMR (%)	13.48 ± 11.61	10.41 ± 6.85	13.71 ± 11.88	0.34 (0.06, 0.62)	0.133
Platelet ($\times 10^9$/L)	180.05 ± 88.44	172.89 ± 84.47	180.03 ± 88.07	0.08 (−0.20, 0.36)	0.563
Hb (g/L)	113.33 ± 24.43	72.25 ± 14.59	114.23 ± 24.08	0.48 (0.20, 0.76)	<0.001
Coagulation Function					
D-dimer (mg/L)	15.55 ± 86.65	4.96 ± 9.36	17.01 ± 91.97	0.18 (−0.10, 0.47)	0.481
Blood Biochemistry					
BNP (pg/mL)	3421.35 ± 6985.75	3644.68 ± 6992.21	3389.83 ± 6978.71	0.04 (−0.25, 0.33)	0.186
BUN (mmol/L)	20.22 ± 32.17	30.58 ± 76.83	19.45 ± 26.15	0.19 (−0.10, 0.48)	0.074
Cr (μmol/L)	97.70 ± 129.90	122.10 ± 190.89	94.92 ± 122.26	0.17 (−0.12, 0.46)	0.236
ALT (U/L)	27.97 ± 43.95	25.72 ± 26.79	28.06 ± 45.20	0.06 (−0.22, 0.35)	0.63
AST (U/L)	73.47 ± 122.72	82.92 ± 149.06	72.65 ± 121.24	0.08 (−0.21, 0.36)	0.335
UA (μmol/L)	294.57 ± 156.08	251.78 ± 153.74	296.67 ± 154.48	0.29 (−0.02, 0.60)	0.014
eGFR (mL/min/1.73m^2)	70.95 ± 33.69	69.00 ± 33.16	71.24 ± 33.77	0.07 (−0.25, 0.38)	0.698
LDH (U/L)	329.41 ± 223.98	389.38 ± 255.43	327.60 ± 226.79	0.26 (−0.05, 0.56)	0.103
TBIL (μmol/L)	13.43 ± 24.95	23.04 ± 44.71	12.81 ± 23.25	0.29 (−0.01, 0.59)	0.184
DBIL (μmol/L)	5.86 ± 11.20	13.08 ± 29.88	5.42 ± 8.57	0.35 (0.04, 0.65)	0.127
IBIL (μmol/L)	6.74 ± 6.46	10.21 ± 15.97	6.52 ± 5.26	0.31 (0.01, 0.61)	0.175
TP (g/L)	60.88 ± 7.51	60.96 ± 7.76	60.84 ± 7.51	0.02 (−0.28, 0.31)	0.783
Albumin (g/L)	31.54 ± 4.91	31.85 ± 4.68	31.50 ± 4.91	0.07 (−0.23, 0.37)	0.859
Globulin (g/L)	31.54 ± 4.91	29.08 ± 8.06	29.37 ± 6.06	0.04 (−0.26, 0.34)	0.926
"Three Catheters" Monitoring					
Ventilator supporting days	3.00 ± 9.67	16.15 ± 23.17	1.98 ± 6.75	0.83 (0.55, 1.11)	<0.001
CVC days	5.52 ± 12.85	23.00 ± 27.27	4.17 ± 9.80	0.92 (0.64, 1.20)	<0.001
Urinary catheter intubation days	5.81 ± 12.40	22.94 ± 25.46	4.49 ± 9.59	0.96 (0.68, 1.24)	<0.001

(*Continued*)

Table 1 (Continued).

Variables	Total (n = 739)	Hospital Acquired Infections (n =53)	Non-hospital Acquired Infections (n = 686)	Standardize Difference (95% CI)	P value
Surgery, n (%)				0.63 (0.35, 0.91)	<0.001
No	693 (93.78)	39 (73.58)	654 (95.34)		
Yes	46 (6.22)	14 (26.42)	32 (4.66)		
Be referral to ICU, n (%)				116 (16.91%)	<0.001
No	543 (73.48)	15 (28.30)	528 (76.97)		
Yes	196 (26.52)	38 (71.70)	158 (23.03)		

Abbreviations: CI, Confidence Interval; ICU, Intensive Care Unit; COPD, Chronic obstructive pulmonary disease; CAD, Coronary artery disease; MDRO, Multiple Drug Resistant Organism; WBC, White Blood cell; NEUTR, Neutrophil ratio; LYMR, Lymphocyte ratio; Hb, Hemoglobin; BNP, Brain natriuretic peptide; BUN, Blood urea nitrogen; Cr, Creatinine; ALT, Alanine transaminase; AST, Glutamate aminotransferase; UA, Uric acid; eGFR, Estimated glomerular filtration rate; LDH, Lactate dehydrogenase; TBIL, Total bilirubin; DBIL, Direct bilirubin; IBIL, Indirect bilirubin; TP, Total protein; CVC, Central venous catheter.

filtering was performed using the least absolute shrinkage and selection operator (Lasso) binary logistic regression model. Models were divided into four groups: lasso model, logistic model, the union of lasso and logistic model, and the intersection of two models. Differences in predictive accuracy were measured by the area under the Receiver Operator Characteristic (ROC) curve (AUC) of nomograms constructed from variables screened by different models. The AUC of four models were compared using DeLong's test. Likelihood ratio (LR) and Youden's index indicated that the probability of a correct judgment as positive and was used to evaluate the predictive performance of model. Decision curve analysis (DCA) was conducted to evaluate clinical net benefits. Based on the results of the union of lasso and logistic regression analysis, a nomogram was constructed and visualized to predict the probability of Healthcare-Associated Infections (HAIs) in COVID-19 patients. Calibration curve was utilized to assess the consistency of the prediction, while the Hosmer–Lemeshow type $\chi 2$ statistic was applied to the entire dataset. Duplicate and missing values were processed using R software. Statistical analysis was conducted using SPSS (Standard version 24.0, Chicago, IL, USA) and R software (Version 4.3.1, http://www.r-project.org). P values less than 0.05 for two-sided tests were deemed statistically significant.

Results

Comparison of Baseline Characteristic Between HAIs and Non-HAIs Group

Totally 739 patients diagnosed between December 1, 2022 and March 1, 2023 were eligible and enrolled in the dataset (Figure 1). Table 1 depicted the clinical characteristics of COVID-19 patients with or without HAIs. The HAIs group eventually included 53 patients, and the non-HAIs group had 686 patients. All patients were over 18 years, the mean age of total was 72.55 years old. Age and gender were evenly distributed between the HAIs and non-HAIs group. Most of the HAIs patients (69.81%) comes from ICU and the number of patients from internal medicine (18.87%) ranked second. However, the incidence of HAIs in patients from geriatric (1.89%), surgical (9.43%), and emergency departments (0%) is relatively low. Among total COVID-19 patients, 58.73% received antiviral treatment, with Azvudine and Paxloivid accounting for 42.76% and 13.8%, respectively. Drug treatments included NSAIDs like aspirin or celecoxib (31.39%), hormone drugs such as methylprednisolone (71.31%), immunosuppressive drugs like baritinib, cyclophosphamide, cyclosporine (3.25%), biological agents including gamma globulin (7.71%), anticoagulant therapy (59%), and antibiotics (93.1%)

Among all patients, 26.52% were eventually transferred to the ICU, with 71.70% of patients in the HAIs group being transferred. It is important to highlight that all HAI patients who were hospitalized received antibiotics, while none were administered immunosuppressants. In terms of medication, patients with HAIs were treated with NSAIDs (37.74%), hormone drugs (54.72%), immunosuppressants (0%), biological agents (11.32%), and anticoagulants (60.38%). Additionally, 50.94% of HAIs patients underwent antiviral treatment, with Azvudine and Paxlovid representing 35.85% and 16.98% of these cases, respectively.

The average days in HAIs patients of ventilator supporting, central venous catheterization and urinary catheter incubation were 16.15, 23 and 22.94, respectively. The time of HAIs patients of using ventilator (P<0.001), CVC (P<0.001) and urinary catheter (P<0.001) were longer in HAI group, and the difference was statistically significant. Laboratory tests at admission of HAIs patients showed a significant decrease in hemoglobin (Hb, P<0.001) and uric acid (UA, P=0.014) compared to the non-HAIs group. In addition, the number of HAIs patients with blood transfusion (P<0.001), transfer to the ICU (P<0.001), surgery (P<0.001), and using of antibiotics (P=0.04) were higher than the non-HAIs group.

The chronic disease histories of patients with HAIs and non-HAIs were compared. Among the total patients, the proportions with hypertension, tumor, diabetes, COPD or chronic bronchitis, and coronary heart disease (CAD) were 7.85%, 13.13%, 26.12%, 16.37%, and 16.24%, respectively. Interestingly, the number of HAIs patients with CAD (P=0.011) was lower than in the non-HAIs group, showing statistically significant difference. However, there was no statistically significant difference in the number of patients with other chronic diseases.

Comparison of fungal detection between the two groups revealed that 28.42% of all COVID-19 patients had fungi detected. The percentage of fungi detected in HAIs patients was 79.25%, significantly higher than the 24.49% in non-HAIs patients (P<0.001). Similarly, MDRO was found in 12.45% of all COVID-19 patients, with 60.38% detected in HAIs patients and 8.75% in non-HAIs patients, showing a statistically significant difference (P<0.001). Interestingly, non-HAIs patients had higher proportion of hormone drug usage compared to HAIs patients (P=0.006). Moreover, there is no statistical difference in the distribution of other variables between the two groups.

Univariate and Multivariate Logistic Regression Analysis of Risk Factors

Univariate and multivariate logistic regression analyses were conducted to screen the influenced variables related to HAIs in COVID-19 patients (Table 2). Univariate analysis showed that patients who admitted to ICU at the first admission

Table 2 Univariate and Multivariate Analysis of Demographic and Clinical Factors for Patients with COVID-19 with Healthcare-Associated Infections

Variables	Univariable Model (n =53)		Multivariable Model (n = 686)	
	OR (95% CI)	P value	OR (95% CI)	P value
Basic Information				
Age, n (%)				
20~40	1			
41~60	3.22 (0.61, 59.67)	0.2681	0.02 (0.00, 45.01)	0.2490
61~80	2.75 (0.55, 50.10)	0.3298	0.15(0.00, 311.26)	0.5321
>80	1.83 (0.35, 33.60)	0.5641	0.06 (0.00, 122.17)	0.3741
Gender, n (%)				
Female	1		1	
Male	0.98 (0.53, 1.80)	0.9448	3.15 (0.26, 67.08)	0.3943
Inpatient department, n (%)				
Internal medicine department	1		1	
Surgical department	0.23 (0.03, 1.79)	0.1590	12.63 (0.21, 623.64)	0.3971
ICU	8.91 (4.30, 18.47)	<0.0001	18.18 (0.61, 1940.24)	0.1501
Geriatrics	2.39 (0.79, 7.23)	0.1227	3.59 (0.05, 170.56)	0.5021
Emergency Department	0.00 (0.00, Inf)	0.9864	0.00 (0.00, Inf)	0.9940
Treatment Strategies				
Antiviral treatment, n (%)				
No	1		1	
Yes	0.71 (0.41, 1.25)	0.2340	4.14 (0.12, 193.87)	0.4348
Azvudine, n (%)				
No	1		1	
Yes	0.73 (0.41, 1.31)	0.2927	0.12 (0.00, 2.83)	0.2166

(*Continued*)

Table 2 (Continued).

Variables	Univariable Model (n =53)		Multivariable Model (n = 686)	
	OR (95% CI)	P value	OR (95% CI)	P value
Paxlovid, n (%)				
No	1		1	
Yes	1.30 (0.62, 2.76)	0.4874	4.14 (0.16, 129.39)	0.3989
Non-steroidal anti-inflammatory drugs, n (%)				
No	1		1	
Yes	0.46 (0.26, 0.80)	0.0066	9.40 (1.56, 99.11)	0.0294
Hormone Drugs, n (%)				
No	1		1	
Yes	0.00 (0.00, Inf)	0.9851	0.02 (0.00, 0.16)	0.0024
Immunosuppressive drugs, n (%)				
No	1		1	
Yes	1.06 (0.60, 1.88)	0.8323	0.00 (0.00, Inf)	0.9931
Biological agents, n (%)				
No	1		1	
Yes	1.59 (0.65, 3.90)	0.3109	13.13 (0.53, 405.99)	0.1154
Anticoagulant therapy, n (%)				
No	1		1	
Yes	1.06 (0.60, 1.88)	0.8323	0.20 (0.02, 1.55)	0.1351
Antibiotics, n (%)				
No	1		1	
Yes	9652576.25 (0.00, Inf)	0.9860	0.18 (0.01, 2.30)	0.2300
Blood transfusion, n (%)				
No	1		1	
Yes	3.77 (2.11, 6.72)	<0.0001	0.55 (0.03, 7.14)	0.6488
Underlying Disease Prior to Hospitalization				
Hypertension, n (%)				
No	1		1	
Yes	1.18 (0.67, 2.07)	0.5623	0.69 (0.08, 5.03)	0.7243
Tumor, n (%)				
No	1		1	
Yes	1.60 (0.78, 3.30)	0.2025	1.78 (0.08, 39.43)	0.7133
Diabetes, n (%)				
No	1		1	
Yes	0.91 (0.48, 1.75)	0.7848	0.18 (0.02, 1.35)	0.1204
COPD or Chronic bronchitis, n (%)				
No	1		1	
Yes	0.90 (0.41, 1.96)	0.7940	0.38 (0.02, 5.53)	0.5043
CAD, n (%)				
No	1		1	
Yes	0.19 (0.05, 0.79)	0.0220	0.00 (0.00, Inf)	0.9890
Microbial Detection Capability				
Fungi Detected or Not, n (%)				
No	1		1	
Yes	11.77 (5.93, 23.38)	<0.0001	24.87 (3.34, 354.97)	0.0058
MDRO Detected or Not, n (%)				
No	1		1	
Yes	15.90 (8.63, 29.29)	<0.0001	543.81 (37.47, 27,074.52)	0.0001

(*Continued*)

Table 2 (Continued).

Variables	Univariable Model (n =53)		Multivariable Model (n = 686)	
	OR (95% CI)	P value	OR (95% CI)	P value
Laboratory Results at Admission				
Complete Blood Count				
WBC ($\times 10^9$/L)	1.01 (0.98, 1.04)	0.5247	0.91 (0.68, 1.14)	0.4553
NEUTR (%)	1.01 (0.99, 1.03)	0.2245	0.93 (0.85, 1.03)	0.0942
LYMR (%)	0.97 (0.93, 1.00)	0.0456	0.77 (0.57, 0.96)	0.0376
Platelet ($\times 10^9$/L)	1.00 (1.00, 1.00)	0.5684	1.00 (0.99, 1.02)	0.7127
Hb (g/L)	0.98 (0.97, 0.99)	0.0005	1.00 (0.94, 1.04)	0.8622
Coagulation Function				
D-dimer (mg/L)	0.99 (0.98, 1.01)	0.4390	0.98 (0.85, 1.01)	0.8145
Blood Biochemistry				
BNP (pg/mL)	1.00 (1.00, 1.00)	0.8045	1.00 (1.00, 1.00)	0.9156
BUN (mmol/L)	1.01 (1.00, 1.01)	0.0483	1.03 (1.00, 1.07)	0.0649
Cr (μmol/L)	1.00 (1.00, 1.00)	0.1569	1.00 (0.99, 1.01)	0.7173
ALT (U/L)	1.00 (0.99, 1.01)	0.7183	1.01 (0.97, 1.04)	0.5993
AST (U/L)	1.00 (1.00, 1.00)	0.5741	0.99 (0.96, 1.00)	0.3314
UA (μmol/L)	1.00 (1.00, 1.00)	0.0621	0.99 (0.98, 1.00)	0.0957
eGFR (mL/min/1.73m^2)	1.00 (0.99, 1.01)	0.6776	0.96 (0.91, 1.00)	0.0885
LDH (U/L)	1.00 (1.00, 1.00)	0.1059	1.00 (0.99, 1.00)	0.3008
TBIL (μmol/L)	1.01 (1.00, 1.01)	0.0457	0.33 (0.08, 0.44)	0.8333
DBIL (μmol/L)	1.02 (1.01, 1.04)	0.0045	2.52 (1.91, 10.31)	0.8590
IBIL (μmol/L)	1.04 (1.01, 1.07)	0.0088	4.20 (3.19, 17.24)	0.7831
TP (g/L)	1.00 (0.96, 1.04)	0.9184	8.20 (0.07, 204.49)	0.1990
Albumin (g/L)	1.01 (0.95, 1.08)	0.6383	0.13 (0.01, 15.24)	0.2093
Globulin (g/L)	0.99 (0.95, 1.04)	0.7674	0.11 (0.00, 13.14)	0.1847
"Three Catheters" Monitoring				
Ventilator supporting days				
0	1		1	
1~7	0.42 (0.02, 2.05)	0.4047	1.97 (0.00, 25,434.86)	0.9475
8~30	1.85 (0.84, 3.72)	0.1002	1.13 (0.03, 55.60)	0.9483
>30	3.94 (0.86, 13.24)	0.0414	842.41 (0.01, inf.)	0.2890
CVC days				
0	1		1	
1~7	1.73 (0.57, 4.33)	0.2789	0.07 (0.00, 2.47)	0.1820
8~30	1.93 (0.95, 3.77)	0.0591	4.11 (0.29, 78.20)	0.3030
>30	3.28 (1.16, 8.04)	0.0143	134.88 (1.80, 51,117.76)	0.0513
Urinary catheter intubation days				
0	1		1	
1~7	0.61(0.14, 1.77)	0.426	0.11 (0.00, 7.70)	0.3644
8~30	1.29 (0.64, 2.46)	0.460	0.06 (0.00, 1.10)	0.0773
>30	1.82 (0.52, 4.97)	0.286	0.00 (0.00, 0.90)	0.1303
Surgery, n (%)				
No	1		1	
Yes	7.34 (3.62, 14.87)	<0.0001	34.82 (1.67, 1166.92)	0.0277
Be referral to ICU, n (%)				
No	1		1	
Yes	8.47 (4.54, 15.79)	<0.0001	0.22 (0.01, 4.95)	0.3722

Abbreviations: CI, Confidence Interval; ICU, Intensive Care Unit; COPD, Chronic obstructive pulmonary disease; CAD, Coronary artery disease; MDRO, Multiple Drug Resistant Organism; WBC, White Blood cell; NEUTR, Neutrophil ratio; LYMR, Lymphocyte ratio; Hb, Hemoglobin; BNP, Brain natriuretic peptide; BUN, Blood urea nitrogen; Cr, Creatinine; ALT, Alanine transaminase; AST, Glutamate aminotransferase; UA, Uric acid; eGFR, Estimated glomerular filtration rate; LDH, Lactate dehydrogenase; TBIL, Total bilirubin; DBIL, Direct bilirubin; IBIL, Indirect bilirubin; TP, Total protein; CVC, Central venous catheter.

(OR=8.91, 95% CI=4.30–18.47, P<0.0001), the increase of BUN (OR=1.01, 95% CI=1.00–1.01, P=0.0483), TBIL (OR=1.01, 95% CI=1.00–1.01, P=0.0457), DBIL (OR=1.02, 95% CI=1.01–1.04, P=0.0045) and IBIL (OR=1.04, 95% CI=1.01–1.07, P=0.0088), the fungi (OR=11.77, 95% CI=5.93–23.38, P<0.0001) or MDRO (OR=15.90, 95% CI=8.63–29.29, P<0.0001) was detected, the longer the ventilator (OR=1.10, 95% CI=1.07–1.13, P<0.0001), CVC (OR=1.07, 95% CI=1.05–1.09, P<0.0001) and Urinary catheter intubation (OR=1.07, 95% CI=1.05–1.10, P<0.0001) was used, blood transfusion (OR=3.77, 95% CI=2.11–6.72, P<0.0001), be referral to ICU (OR=8.47, 95% CI=4.54–15.79, P<0.0001) and surgery (OR=7.34, 95% CI=3.62–14.87, P<0.0001), which in turn leads to increased incidence of HAIs in COVID-19 patients. However, the use of NSAIDs (OR=0.46, 95% CI=0.26–0.80, P=0.0066), the increase of Lymphocyte ratio (OR=0.97, 95% CI=0.93–1.00, P=0.0456) and Hb (OR=0.98, 95% CI=0.97–0.99, P=0.0005) on the patient's admission and coronary artery disease (CAD) (OR=0.19, 95% CI=0.05–0.79, P<0.0001) are protective factors against HAIs.

All clinical factors were added to the multivariate logistic regression analysis. Results suggested that use of NSAIDs (OR=9.40, 95% CI=1.56–99.11, P=0.0294) became risk factor of COVID-19 patients to develop HAIs. The rising rate of HAIs in COVID-19 patients was significantly associated with fungi (OR=4.77, 95% CI=1.08–21.17, P=0.0398) or MDRO (OR=23.43, 95% CI=3.94–139.28, P=0.0005) detected or not and patients who had undergone surgery (OR=34.82, 95% CI=1.67–1166.92, P=0.0277). However, use of hormone drugs (OR=0.02, 95% CI=0.00–0.16, P=0.0024) and increased LYMR (OR=0.77, 95% CI=0.57–0.96, P=0.0376) are protective factors of HAIs in COVID-19 patients.

Variables Selection for HAIs in COVID-19 Patients

Lasso regression analysis was applied to identify the most valuable parameters and predictive signature building and the variation characteristics of the coefficient of these variables are shown in Figure 2A and the lasso model has a good discrimination (Figure 2B). Vertical dashed lines are drawn at the best values using minimum conditions and 1-standard error (SE) conditions (Figure 2C). When optimal value of λ was 0.034 (Log λ= −3.502) according to 632-fold cross-validation, the model was with the excellent performance. At this value, 62 parameters were reduced to 7 screened variables, including hormone drugs, be admitted to ICU, surgery, CAD, DBIL, Fungi or MDRO detected or not.

Construction and Evaluation of the Nomogram

According to the above results, NSAIDs, hormone drugs, surgery, LYMR, and MDRO or fungi detected are independent influence factors. What's more, we also screened 7 variables in lasso model. To get a more accurate prediction model, we incorporate the variables screened by logistic model, lasso model, the union or the intersection of logistic and lasso model into the nomogram, respectively. The AUC for each of the four models at HAIs incidence was: logistic model 0.925 (95% CI=0.890–0.959), lasso model 0.948 (95% CI=0.923–0.974), union model 0.953 (95% CI=0.928–0.978) and intersection model 0.915 (95% CI=0.877–0.954) (Figure 3A). Among the four models, the lasso model and the union model had superior clinical diagnostic capabilities, but the difference between them was not statistically significant (Z = −1.073, P = 0.283).

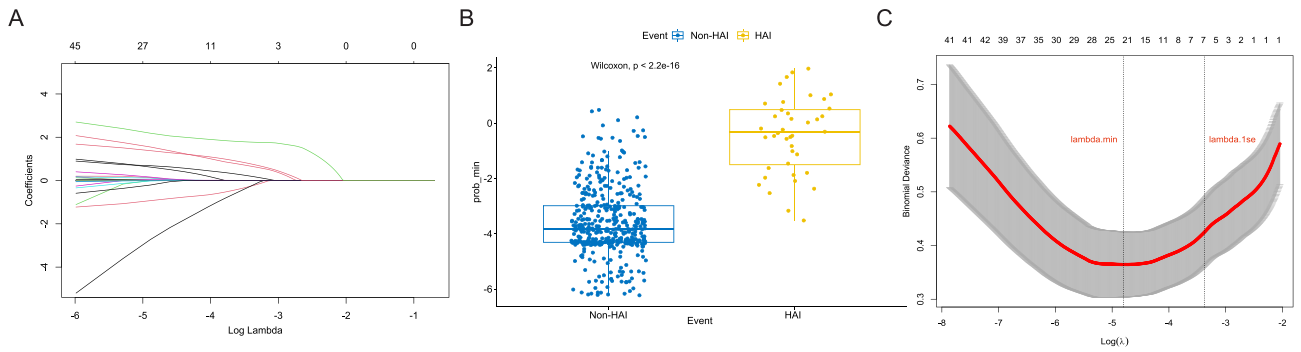

Figure 2 Selection of significant features using lasso regression. (**A**) LASSO coefficient profiles. (**B**) Box plot to compare the discrimination of lasso models (Wilcoxon P<2.2×1016). (**C**) Cross-validation for parameter screening in the lasso model, 21 screened variables when under minimum criteria and 7 variables under 1-standard error (SE) criteria.

Abbreviation: Lasso, least absolute shrinkage and selection operator.

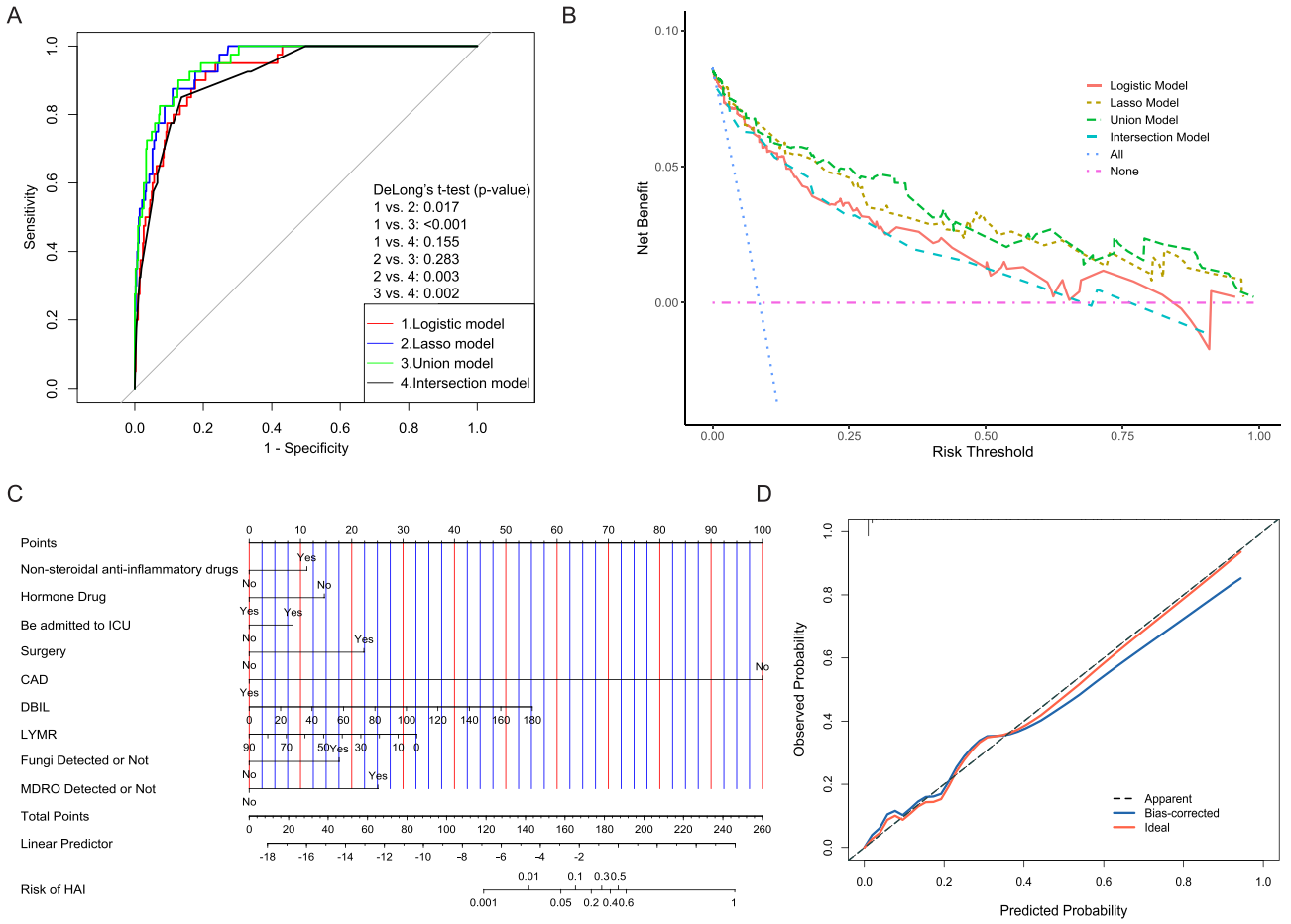

Figure 3 Selection of predictive signatures and accuracy capability evaluation of nomogram. (**A**) ROC of four models and comparison of their clinical diagnostic capabilities. (**B**) Clinical net benefits analysis of four models by using DCA. (**C**) Nomogram used to predict occurrence of HAI in patients with COVID-19. (**D**) Concordance and discrimination ability analysis of Nomogram by using calibration curve.

Abbreviations: ROC, receiver operating characteristic curve; DCA, decision curve analysis; HAI, Healthcare-associated Infections.

However, the DCA suggested that the nomogram of union model had the best clinical net benefits at different HAIs outcomes in four models (Figure 3B). Therefore, we chose to incorporate 9 variables screened by the lasso and logistic models into the final predictive signature, including NSAIDs, hormone drugs, be admitted to ICU, surgery, CAD, DBIL, LYMR, and MDRO or fungi detected or not. When the maximum of the Youden's index is 0.703, the sensitivity is 95.6%, the specificity is 74.7%, the LR is 3.778, and when the sensitivity reaches the maximum of 97.8%, the specificity is 68.8%, LR is 3.134, and the Youden's index is 0.666, indicating that the prediction ability of our model is also excellent (Supplementary Table 1). In addition, the specificity, sensitivity and accuracy were 87.3%, 90.0% and 87.5% (Figure 3C). Moreover, the calibration curve of union model was demonstrated quality favorable concordance and showed good discrimination ability. (Hosmer–Lemeshow $\chi 2$=0.843, P=0.656) (Figure 3D).

Discussion

The COVID-19 pandemic has had a huge impact on the global healthcare system. Given the high mortality rate of the disease and the lack of effective antiviral treatment, treatment for COVID-19 has focused mainly on symptoms and respiratory support and strict implementation of public health measures. While guidelines for dealing with HAIs exist, the effectiveness of these practices during a pandemic has not been effectively investigated. Careful and detailed patient care during the COVID-19 pandemic may reduce the risk of HAIs. Increased isolation measures and improved levels of personal protective equipment (PPE) have increased the burden on medical personnel during the diagnosis and treatment process, leading to the neglect of routine measures to prevent HAI. Previous studies have suggested that changes in

diagnostic activity and protective measures may be associated with an increase in the incidence of HAIs.[18,19] However, current study findings on the pandemic's impact on HAIs are inconclusive.[20–22] The objective of this study was to investigate the impact of this pandemic on HAI in a general hospital in China.

As discovered on the basis of real-world data, NSAIDs, hormone drugs, surgery, LYMR, detection of fungi and MDRO were independent factors affecting HAIs. Unlike other studies, the risk of HAIs was not primarily affected by age and gender.[20] Due to the special symptoms of the COVID-19, most young people have mild symptoms and do not need to be hospitalized, resulting in most of the hospitalized patients are elderly, the average age was 72.55 years, the age range is unevenly distributed might demolish the effect of age on HAIs. Result shows that LYMR is an independent risk factor, which suggest that COVID-19 may cause damage to multiple organ systems when developing into HAIs. The increase in lymphocytes may be due to activation of the body's immune response, and lymphocytopenia is the primary feature of clinical exacerbation, which can be caused by inflammatory storm, is similar in Middle East respiratory syndrome (MERS).[23] Results also suggested impaired liver functions in COVID-19 patients with HAIs. However, there is no clear pathological evidence that SARS-CoV-2 can directly cause multiple organ function lesion.[24]

Meanwhile, we found that patients who were undergoing surgery were more vulnerable to develop HAIs, which also had been reported before.[20,25] Except for surgery, no other clinical symptom and chronic diseases were significantly related to the occurrence of HAIs, which made the discrimination more difficult. Patients who have undergone surgery have poorer basic health and more complications, which lead to aggravated symptoms of the COVID-19 and are more likely to cause HAIs. Current reports have shown that hormone drug is a powerful tool in clinical treatment if the patient's condition worsens (such as inflammation storm).[26] On this basis, some adjuvant treatment will be given, including anti-inflammatory drugs such as hormones and NSAIDs in clinical practice.[27] In our study, results demonstrated that NSAIDs is an independent risk factor. However, the use of hormone drugs could decrease the risk of HAIs and is an independent risk factor, which is related to the anti-inflammatory and immunosuppressive effects of hormone therapy. Both mild and severe patients should be given anti-COVID-19 drugs. Nevertheless, there was no statistical difference in the effect of the use of antiviral drugs such as Azvudine or Paxlovid on reducing the rate of HAIs. In addition, the increased ability to detect MDRO and Fungi is more helpful for the diagnosis of HAIs, and the accuracy and positive rate of HAIs diagnosis are also improved. Interestingly, elevated LYMR level was also a risk factor and correlated to the severity of inflammation storm and usually occurred in severe viral infection and systemic inflammatory response syndrome.[28]

In this study, representative predictive variables are used to construct nomograms to predict risk of HAIs in COVID-19 patients. Lasso regression analysis is not only more effective than the traditional method of selecting predictors based on the strength of their multivariate association with the outcome, but it also allows researchers to combine selected features into a single model. The study extracted 62 candidate clinical features were extracted from cohort and 7 potential predictors were screened by using lasso regression model to develop the predictive signatures. In order to obtain a model with more accurate predictive ability, we evaluated the AUC of the predictive models obtained from the logistic model, the lasso model, the intersection of the two models, and the union of the two models, respectively. We found that the predictive model obtained from the ensemble of variables of the logistic and lasso model had the best discrimination of the severity of COVID-19, with an AUC of 0.953 (95% CI=0.928–0.978), and had the optimal clinical benefit. The results of DCA and calibration curve stated that the predicted veracity of our nomograms was well differentiated. In this study, the incidence of HAI was 7.2% in patients with COVID-19, when the maximum of the Youden's index is 0.703, the sensitivity is 95.6%, the specificity is 74.7%, the LR is 3.778, the sensitivity of this model was higher than the negative rate (92.7%) of the HAI in patients with COVID-19, proving that our predictive model has significant clinical appliance for screening the HAI in COVID-19 patients and is effective for the early diagnosis. What's more, the crude HAI prevalence of COVID-19 patients in this study (7.2%) was consistent with other studies, ranging from 5.5% to 10%.[29,30] However, there are few studies on models that predict the occurrence of HAIs in COVID-19 patients, and our predictive model outperforms existing study. Chen Wang et al[31] demonstrated that their nomogram showed AUC 0.863 (95% CI: 0.834–0.892) in the development cohort with a sensitivity of 80.41% and specificity of 77.38% and 0.813 (95% CI: 0.760–0.866) in validation cohort with a sensitivity of 82.98% and specificity of 70.43%. Therefore, through the application of the predictive model, the effect of prevention and control measures can be continuously monitored and evaluated, so as to timely identify problems and make improvements, and optimize the infection prevention and control strategy of the hospital.

This predictive model has certain innovation, pertinence and practicability. Firstly, this prediction model was constructed utilizing lasso regression analysis to filter risk factors and combined them with the independent risk factors obtained from logistic regression analysis, the AUC of the nomogram was 0.953 which had a higher ideal predictive ability, and the predictive performance of this model outperforms other existing studies on the acquisition of HAIs in COVID-19 patients. Secondly, the prediction model can be visualized in the form of nomogram to make it more maneuverable. Thirdly, compared with previous studies,[32–34] this model for HAI prediction of COVID-19 patients incorporated common indicators based on current clinical diagnosis and treatment, which was easier to obtain and more conducive to the practical application. Most importantly, the model covered all adult COVID-19 patients and has wider applicability, which is helpful for physicians to diagnose the risk of HAIs in COVID-19 patients. However, some limitations of this study need to be acknowledged. Firstly, symptoms may not be comprehensively collected due to the questionnaire's design, such as the severity of symptoms or the number of days. Secondly, the impact of vaccines on the risk of HAIs was unable to accurately assess due to the deficiency of clinical record. Thirdly, due to the limitations of the detection conditions, the participants who tested positive for SARS-CoV-2 were not further identified by lineage with RT-PCR. Based on the contemporaneous data released by China Centers for Disease Control, the Omicron variant may be assumed to be dominant at the time of this study. Thirdly, due to the limited sample size, it was challenging to construct the validation cohort to evaluate the predictive consistency of our nomogram. Fourthly, this is a single-center retrospective study and systematic error is unavoidable, potentially leading to selection bias. In future research, multicenter studies should be carried out to validate this model.

Conclusion

The nomogram model is built on real-world data and integrates multi-dimensional clinical characteristic variables to enrich a reliable visual prediction tool for assessing COVID-19 patients' risk of HAI development. In addition, this study focuses on predicting the risk of HAIs in COVID-19 patients for the first time, and creates a prediction model with strong practicality and high prediction accuracy. It may become a practical clinical tool for predicting the occurrence of HAIs in COVID-19 patients and could help save health-care resources, improve patients' survival and develop strategies for early intervention.

Abbreviations

COVID-19, Coronavirus Disease-2019; HAIs, Healthcare-associated Infections; WHO, World Health Organization; NSAIDs, non-steroidal anti-inflammatory drugs; PPE, personal protective equipment; CI, Confidence Interval; ICU, Intensive Care Unit; COPD, Chronic obstructive pulmonary disease; CAD, Coronary artery disease; MDRO, Multiple Drug Resistant Organism; WBC, White Blood cell; NEUTR, Neutrophil ratio; LYMR, Lymphocyte ratio; Hb, Hemoglobin; BNP, Brain natriuretic peptide; BUN, Blood urea nitrogen; Cr, Creatinine; ALT, Alanine transaminase; AST, Glutamate aminotransferase; UA, Uric acid; eGFR, Estimated glomerular filtration rate; LDH, Lactate dehydrogenase; TBIL, Total bilirubin; DBIL, Direct bilirubin; IBIL, Indirect bilirubin; TP, Total protein; CVC, Central venous catheter; MERS, Middle East respiratory syndrome.

Data Sharing Statement

The data supporting the findings of this study are available from the corresponding author upon request.

Ethics Approval and Consent to Participate

We carried out this study according to the revised Declaration of Helsinki, and the ethics committee of the First Affiliated Hospital of Nanjing Medical University approved the study with informed consent. Informed consent was obtained from all participants in this study.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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