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Development and validation of COVID-19 associated candidemia score (CAC-Score) in ICU patients

Bircan Kayaaslan[1] | Fatma Eser[1] | Dilek Asilturk[2] | Zeynep Oktay[2] | Imran Hasanoglu[1] | Ayşe Kaya Kalem[1] | Gülen Dönertaş[2] | Betul Kaplan[2] | Isıl Ozkocak Turan[3] | Deniz Erdem[3] | Hesna Bektas[4] | Rahmet Guner[1]

[1]Department of Infectious Disease and Clinical Microbiology, Ankara City Hospital, Ankara Yildirim Beyazit University, Ankara, Turkey

[2]Department of Infectious Disease and Clinical Microbiology, Ankara City Hospital, Ankara, Turkey

[3]Department of Intensive Care Unit, University of Health Sciences Ankara City Hospital, Ankara, Turkey

[4]Department of Neurology, Ankara City Hospital, Ankara Yildirim Beyazit University, Ankara, Turkey

Correspondence
Bircan Kayaaslan, Infectious Disease and Clinical Microbiology, Ankara Yildirim Beyazit University, Ankara City Hospital, Bilkent Street no:1, Ankara, 06800, Turkey.
Email: drbican@gmail.com

Abstract

Background: The development of candidemia is a highly fatal condition in severe COVID-19 infection.

Objectives: This study aimed to develop a candidemia prediction score in COVID-19 patient based on the patient's clinical characteristics, and healthcare-related factors during intensive care units (ICU) follow-up.

Patients/Methods: Severe COVID-19 patients hospitalised in ICU in Ankara City Hospital during the one-year period (August 15, 2020, and August 15, 2021) were included. After univariate analysis, multivariate analysis was applied using variable selection approach to investigate the effects of variables together and to create a score model for candidemia. Statistically significant factors were included in the development process of candida prediction score.

Results: Of 1305 COVID-19 ICU patients, 139 had a candidemia episode. According to the final model, four variables, presence of central venous catheter (CVC) (OR 19.07, CI 8.12–44.8, $p < .0001$), multifocal colonisation (OR 2.28, CI 1.39–3.72, p 0.001), length of ICU stays ≥14 days (OR 3.62, CI 2.42–5.44, $p < .0001$) and corticosteroids (OR 0.51, CI 0.34–0.76, p 0.0011) were the only statistically significant independent risk factors for candidemia. Score model was demonstrated by a nomogram, and the risk for candidemia was calculated to be high in patients who scored ≥56 points by using the criteria [CVC = 51, multifocal colonisation = 14, prolonged hospitalisation = 23, no steroid use = 12 points]. The AUC of the score is 0.84 (CI 0.81–0.87).

Conclusion: We developed and validated an easy-to-use clinical prediction score for candidemia in severe COVID-19 infection. In COVID-19 ICU patients, the risk of candidemia is high if one of the other risk factors is present together with CVC.

KEYWORDS
candida, candidemia, COVID-19, COVID-19 associated candidemia, risk factors, score

1 | INTRODUCTION

Candidemia is one of the most common nosocomial bloodstream infections in critically ill patients, accounting for 7%–15% of the episodes, and is associated with increased mortality, prolonged hospital stays and cost.[1,2] Non-neutropenic intensive care unit (ICU) patients undergoing multiple invasive procedures, and immunocompromised patients are at high risk for the development of

candidemia.[3,4] The COVID-19 pandemic causes an increase in the number of patients who need to be followed up in ICU, creating a great burden on the capacity of the intensive care bed and health care services.[4] Critically ill COVID-19 patients have a higher incidence of candidemia compared to non-COVID-19 patients, resulting in higher mortality rates.[5] The early recognition of candidemia or the prediction of high-risk situations for the development of candidemia has become more important because of its higher incidence than in patients without COVID-19 and its 2 weeks earlier appearance in patients with COVID-19.[5–7] The growth of the microorganism in blood culture is the gold standard for the diagnosis of candidemia but it takes time and blood cultures were positive in only half of the patients.[8] Detection and therefore treatment of candidemia are frequently delayed until the patient's clinical worsening and death. In some patients, *Candida* spp. is isolated from blood cultures after the patient dies.[3] Considering that microorganism growth in blood culture takes time, blood cultures are positive in only half of patients, and delayed antifungal therapy is associated with adverse outcomes, the need to develop a predictive tool for early detection of candidemia using infection-related risk factors becomes evident. The increase in risk for the development of candidemia associated with each factor alone may not be decisive, but the combination of these risk factors may become a definite risk for the development of candidemia. In certain studies performed in pre-COVID-19 period, some clinical predictive rules for the development of candidemia in ICU patients have been developed using well-described risk factors for candidemia, however, the use of these rules may not provide a strong estimation in COVID-19 patients due to the differences in patients' characteristics and administered treatments.[1,9,10] In this study, we aimed to develop a prediction score using a combination of defined risk factors to early predict COVID-19 patients at high risk of developing candidemia in the intensive care unit.

2 | PATIENTS AND METHODS

2.1 | Study design and participant

This retrospective study was conducted in Ankara City Hospital, which is Turkey's largest hospital and pandemic center with 3810 hospital beds and 696 intensive care beds. Ethical approval was obtained from Ankara City Hospital Ethics Committee 1. The study period was determined as 1 year, August 15, 2020, and August 15, 2021. The patients older than 18 years who were followed-up with a definite diagnosis of COVID-19 in the ICUs during the study period were included in the study. In our previous study, we had investigated risk factors for the development of candidemia in COVID-19 ICUs.[11] In this study, we planned to develop an easy-to-use prediction score for candidemia. Because we had recognised that the patients with candidemia could not be predicted in the early time of ICU follow-up and almost 40% of these patients were died before antifungal treatment could be started. The previously developed candidemia prediction scores such as candida colonisation index, candidemia score and clinical prediction rule for candidemia were also not adequately useful in COVID-19 patients. Therefore, we aimed to develop a candidemia prediction score special for COVID-19 patients. We had included all the patients followed-up in determined three ICUs. We also used the same patient's population in this study with the previous study. However, we increased the number patients with candidemia in order to develop a strong prediction score for the candidemia. We included the COVID-19 patients with candidemia who were followed-up in another three ICUs between the same study period. All six ICUs are anesthesiology and reanimation clinics and have the same properties and opportunities. The patients who need intensive care are hospitalised in these ICUs according to bed occupancy without any discrimination. In routine practice, these ICUs are daily visited by infectious disease specialists, and patients are followed prospectively with special patient forms.

In the forms, pre-existing comorbidities (hypertension, diabetes mellitus, coronary artery disease, cardiac failure, chronic renal disease, chronic liver disease, haemodialysis, and immunosuppression), surgical history, previous infection episodes and antibiotic uses of the patients are recorded. The patients' daily progress including all the clinical and laboratory properties, the administered treatments, and applied non-invasive (nasal cannula, or high flow nasal cannula oxygen support) and invasive procedures (central venous catheter [CVC], mechanical ventilation, urinary catheter), and their implementation duration are recorded. We used the included data in the forms and hospital automation system. Other previously described risk factors for candidemia were also recorded. The used antibiotics were categorised as broad-spectrum and narrow-spectrum antibiotics. Cephalosporins, piperacillin-tazobactam, anti-pseudomonal carbapenems, colistin, fosfomycin, and tigecycline were classified as broad-spectrum antibiotics, and other than these mentioned ones were accepted as narrow-spectrum. Antibiotics (vancomycin, teicoplanin, linezolid and daptomycin) used against methicillin-resistant *S. aureus* (MRSA) infection were combined under the title of anti-MRSA therapy for ease of analysis. We also collected data on low (40 or 80 mg methylprednisolone) and high dose (250–500-1000 mg methylprednisolone) corticosteroid use. Patients were followed until discharge, transfer to other clinics or death.

2.2 | Potential risk factors

We described potential risk factors for candidemia based on previous literature data before data recording.[3,4] These risk factors were chronic renal disease, haemodialysis, concomitant bacteremia, sepsis, total parenteral nutrition (TPN), gastrointestinal instrumentation/surgery, the use of prior antibiotics, invasive mechanical ventilation, presence of CVC, immunosuppression. We also investigated the impact of COVID-19 specific treatment such as low-doses and high doses of corticosteroids, and anti-cytokine treatment (tocilizumab and anakinra) on the development of candidemia. Corticosteroid use was described as a risk factor for candidemia in ICU patients in the pre-pandemic period and during the early time of the COVID-19 pandemic. However,

we found corticosteroid use as a protective factor for the development of candidemia in COVID-19 ICU patients in our previous study. In this study, we included a higher number of COVID-19 patients with candidemia and analysed them. Prolonged ICU stay was considered a potential risk factor for the development of candidemia as it resulted in increased exposure to invasive procedures and pathogens, and we defined hospital stays longer than 14 days as prolonged ICU stays. The COVID-19 patients with and without candidemia were compared in terms of demographical characteristics, comorbidities and exposure to invasive procedures, and other possible risk factors for candidemia.

2.3 | Definitions

The isolation of at least one *Candida species* from at least one blood culture bottle was accepted as candidemia in patients with pre-existing compatible symptoms and signs of infection.[9] In our hospital, VitekMS (bioMerieux) device and MALDI-TOF methods are used for the identification of Candida species and the determination of antifungal susceptibilities. The presence of *Candida species* on the two or more culture of different sites including urine, oropharyngeal mucosa, respiratory secretions (sputum, deep tracheal aspirate, or endotracheal aspirate), or inguinal or axillary skin sites were considered as multifocal candida colonisation. Candida colonisation index (CCI) was calculated as the ratio of the candida-detected body sites to the number of culture-tested sites.[10] A rate of 0.5 was used as the threshold. Patients with and without candidemia were compared in terms of having a Candida colonisation index of 0.5. Candida score was calculated as the total points of the following variables: TPN (1 point), multifocal candida colonisation (1 point), surgery (1 point), and sepsis (2 points).[9] If the variable is present, the valid point was coded, if the variable is absent, the point was coded as zero. The risk of developing candidemia is high in patients with a candidemia score equal and higher than 2.5. Patients with and without candidemia were also compared in terms of having a Candidemia score of 2.5 and above. In our patient population, the clinical prediction rule, which is the other candida prediction score, was also investigated.[1] The patients were classified according to whether they met the rule or not. The rule is met by the presence of any systemic antibiotic use (days 1–3) or CVC (days 1–3) in addition to at least two of the followings: TPN (days 1–3), any dialysis (days 1–3), any major surgery (days −7-0), pancreatitis (days −7-0), any use of steroids (days −7-3), or use of other immunosuppressive agents (days −7-0). For the definition of sepsis, the definition criteria of 2016 surviving sepsis company guideline was used.[12]

2.4 | Statistical analysis

Statistical analyses were carried out by using IBM SPSS Statistics for Windows version 23.0 and R Studio 1.4.1106 and R software 4.0.4. Comparisons of candidemia groups (absent, exist) and patient groups (died during the study period, discharged/transferred to clinic) in terms of numerical variables were made by using Mann–Whitney *U* test due to the violation of the parametric test assumptions. Relationship between candidemia and categorical variables were investigated by using Pearson Chi-square test when the test assumptions were satisfied. Otherwise, Fisher's Exact test for 2×2 tables and Fisher–Freeman–Halton Exact test for RxC tables was used. Univariate and multiple logistic regression analysis were applied to estimate the association between demographical and clinical variables and candidemia. Several independent risk factors such as the presence of CVC and usage of the broad-spectrum antibiotics caused quasi-complete separation problem due to relatively imbalanced sample size (rare event). Therefore, univariable penalised logistic regression analysis was applied for those variables. Linearity in logit assumption was evaluated using Box-Tidwell test for numeric independent variables such as age (in years) and length of stay (days) which indicates the estimated risk of candidemia does not increase linearly when the length of stay increases. Therefore, we consider discretizing the length of stay according to literature (below 14 days, equal and above 14 days of stay). After univariate logistic regression analysis, all variables considered in the univariable logistic regression analysis were considered as candidates for multiple logistic regression analysis. We apply Fast backward elimination method for variable selection with bootstrap sampling (1000 successful bootstrap samples) using Akaike Information Criteria (AIC) to develop a score model for estimating the risk of candidemia and provided a quantitative tool to evaluate the COVID-19 patient's probability of developing candidemia. Before the variable selection process, multivariable model was evaluated for multicollinearity by using Variance Inflation Factor (VIF) values. Estimations obtained from final multivariable model was based on penalised maximum likelihood estimations with best penalty parameter obtained using pentrace function in R rms package. Selected variables were represented as odds ratio (OR) with 95% confidence interval (CI) and two-tailed p-values. Both univariate and multivariable logistic regression analysis were carried out using R rms package. Discrimination was evaluated using bias-corrected Harrell's Concordance index (C-index). Bias-corrected Harrel's C-index was calculated from rms package validate function with 1000 successful bootstrap samples. Validated final model is also checked for multicollinearity. Hence, VIF values of all the predictor variables in the multivariable model were below 5 (ranged between 1.01–1.07). In addition, linearity in logit assumption was satisfied. In addition, model's discriminative power was evaluated with ROC analysis using R pROC package. Calibration plots were developed to assess the predictive accuracy and agreement between predicted and observed candidemia with 1000 bootstrap samples and calibration curve analyses were performed in addition to Hosmer–Lemeshow goodness of fit evaluation.

3 | RESULTS

3.1 | Characteristics of study cohort

The study included 1305 COVID-19 patients followed in ICUs, of whom 139 had an episode of candidemia. Of all patients, 62.1% were male gender, and median age was 73 (IQR 62–81) years, and there

was no difference between the patients with and without candidemia in terms of age and gender (p 0.950 and 0.178, respectively). Of the patients, 87.1% had at least one comorbid disease, and the most commons were hypertension (53%) and diabetes (32.3%). The groups were similar in terms of underlying comorbid diseases (for all, $p > .05$). The characteristics of the patients are shown in Table 1 in detail.

Mechanical ventilation and the presence of CVC were statistically higher in the group with candidemia than in those without candidemia. The need for mechanical ventilation was 87.8% in the group with candidemia and 48.8% in those without candidemia (p 0.001). Similarly, the use of CVC was 96% in the candidemia group, while it was 48.6% in the non-candidemia group (p 0.001). Only five of the candidemia cases (4%) developed in patients without CVC. The presence of TPN, sepsis and multifocal colonisation were also statistically higher in patients with candidemia (for all, $p < .001$). Candida colonisation index, Candida score and the clinic prediction rule were positive at higher rates in patients with candidemia compared to in those without candidemia (for all, $p < .001$) (Table 1). The sensitivities of CCI, candida score, and clinical prediction rule were detected as 51.8%, 25.9%, and 36.7%, respectively, and the specificities of CCI, candida score, and clinical prediction rule were 91.5%, 89.2%, and 76.5%, respectively.

There was a statistically significant difference in terms of the presence of concurrent infection and bacteriemia, the rate of broad-spectrum antibiotic use, and the rate of anti-MRSA treatment use between the groups. All of these parameters were higher in candidemia group (p 0.001 for all). Corticosteroid use was higher in the patients without candidemia ($p < .001$), there was no difference between groups in terms of anti-cytokine treatment (p 0.407) (Table 1). The rate of the patient who was given antifungal treatment was significantly higher in the group with candidemia than in those without candidemia ($p < .001$). However, only 58.7% of the patients with candidemia received antifungal treatment with a median of 2 days (IQR 0–7). The median duration of antifungal therapy was a median 1 day (IQR 0–6) in patients with candidemia who died and was statistically shorter than in alive patients (16.5 days, IQR 0–19.25). The mortality rate was statistically higher in patients with candidemia group than in those without candidemia (87.1% vs 44.7%, $p < .001$). Duration of ICU stay was longer in candidemia group ($p < .001$).

3.2 | Construction of score model for predicting development of candidemia

In order to reveal the variables affecting the development of candidemia and estimate the risk of candidemia caused by possible covariates/factors, firstly, univariate analysis was performed. Univariate analysis showed that CVC, sepsis, TPN, mechanical ventilation, use of corticosteroids, bacteremia, use of broad-spectrum antibiotics, anti-MRSA therapy, and length of stay in ICU had potential effects on the development of candidemia (for all, $p < .001$). The presence of CVC was found to be the most predictive factor resulting a 26-fold increased risk for the development of candidemia (OR 26.73, CI 11.2–63.80, $p < .001$). Broad-spectrum antibiotic use (OR 18.49, CI 5.12–66.79, $p < .0001$), and length of ICU stay equal and above 14 days (OR 6.46, CI 4.41–9.46, <0.0001) were other the most predictive risk factors in univariate analysis.

After the univariate analysis, multivariate analysis was applied using the variable selection approach to investigate the effects of the variables together and to create a score model. We developed a score model for predicting the risk of developing candidemia. All variables were included for the variable selection process. Four variables including CVC, multifocal colonisation, corticosteroid use, and the length of ICU stay equal and above 14 days were selected by variable selection process in multivariate analysis. According to the final model, presence of CVC (OR 19.07, CI 8.12–44.8, $p < .0001$), multifocal colonisation (OR 2.28, CI 1.39–3.72, p 0.001), length of ICU stays equal and above 14 days (OR 3.62, CI 2.42–5.44, $p < .0001$) and corticosteroid use (OR 0.51, CI 0.34–0.76, p 0.0011) were the only statistically significant independent risk factors for the development of candidemia (Table 2). Score model was demonstrated by a nomogram (Figure 1). Among all factors affecting the development of candidemia in COVID-19 ICU patients, the most determinant one was the presence of CVC. The presence of CVC was 100 points, the others were as follows; multifocal colonisation (28 points), the length of ICU stays equal and above 14 days (26 points), and absence of corticosteroid use (24 points). In case of obtaining a total point of 110 from these four factors, the possibility of candidemia is high. The patients with CVC were at increased risk for candidemia if they also had any of the other three risk factors. On the other hand, in the absence of CVC, a total of 110 points cannot be obtained from the other three factors.

3.3 | The validity of score model

Final score model had high predictive performance for estimating the possibility of developing candidemia. The model had an AUC of 0.8431 with 95% CI 0.8153–0.8708 (Figure 2). In addition, we evaluate the validation of the final model using bootstrap resampling method and obtained corrected C-index of the score model as 0.831 which implies good discriminative value for classifying patients who develop and did not develop candidemia during hospitalisation. We used prevalence as a model's threshold since candidemia may considered as a rare event. Model's negative predictive performance was significantly higher (97.0%). Sensitivity, and specificity were 78.4%, and 73.4%, respectively.

3.4 | Calibration of the final score model

To evaluate how well our score model fits the data, Hosmer–Lemeshow goodness of fit test was used (X-squared = 3.124, df = 8, p-value = 0.9263). In addition, calibration curve analysis was

TABLE 1 Clinical characteristics, treatments, and outcomes of patients with and without candidemia in COVID-19 ICU patients

	All patient $n = 1305$	Patients without candidemia $n = 1166$	Patients with candidemia $n = 139$	p value
Clinical features				
Age, years, median (IQR[†])	73 (62–81)	72 (62–81)	74 (59–81)	.950
Age, 65 years and above	876 (67.1)	780 (66.9)	96 (69.1)	.607
Sex, male	810 (62.1)	731 (62.7)	79 (56.8)	.178
Comorbidities, at least one	1137 (87.1)	1016 (87.1)	121 (87.1)	.977
Diabetes	422 (32.3)	379 (32.5)	43 (30.9)	.709
Hypertension	692 (53)	627 (53.8)	65 (46.8)	.117
Cardiac failure	191 (14.6)	175 (15)	16 (11.5)	.270
Coronary arterial disease	354 (27.1)	316 (27.1)	38 (27.3)	.953
Chronic renal failure	134 (10.3)	120 (10.3)	14 (10.1)	.936
Haemodialysis	73 (5.6)	65 (5.6)	8 (5.8)	.930
Chronic lung disease	225 (17.2)	205 (17.6)	20 (14.4)	.346
Malignancy	143 (11)	126 (10.8)	17 (12.2)	.611
Immunodeficiency	75 (5.7)	66 (5.7)	9 (6.5)	.697
Prior cerebrovascular event	106 (8.1)	98 (8.4)	8 (5.8)	.280
Pancreatitis	0 (0)	0 (0)	0 (0)	–
Gastrointestinal instrumentation	0 (0)	0 (0)	0 (0)	–
Mechanical ventilation (MV)	691 (53)	569 (48.8)	122 (87.8)	<.001
Duration of MV	5 (3–10)	5 (3–9)	5 (2–11)	.562
Central venous catheter	701 (53.7)	567 (48.6)	134 (96.4)	<.001
Sepsis	583 (44.7)	498 (42.7)	85 (61.2)	<.001
Total parenteral nutrition	81 (6.2)	51 (4.4)	30 (21.6)	<.001
Multifocal candida colonisation	132 (10.1)	97 (8.3)	35 (25.2)	<.001
Days of candidemia after admission	11 (5–24)	–	11 (19)	–
Candida in urine	213 (16.3)	153 (13.1)	60 (43.2)	<.001
Candida in DTA[‡]	161 (12.3)	119 (10.2)	42 (30.2)	<.001
Candida in other cultures[§]	33 (2.7)	30 (2.6)	3 (4.8)	.237
Candida colonisation index[¶]	0 (0–0.3)	0 (0–0)	0.67 (0.3–0.7)	<.001
<0.5	1134 (86.9)	1067 (91.5)	67 (48.2)	<.001
≥0.5	171 (13.1)	99 (8.5)	72 (51.8)	
Candida score	0 (0–2)	0 (0–2)	2 (1–3)	<.001
≤2 points	1143 (87.6)	1040 (89.2)	103 (74.1)	<.001
≥3 points	162 (12.4)	126 (10.8)	36 (25.9)	
Candida predictive rule[‡‡]	325 (24.9)	274 (23.5)	51 (36.7)	.001
Concurrent infection	743 (56.9)	637 (54.6)	106 (76.3)	<.001
Bacteriemia	1102 (84.4)	246 (21.1)	66 (47.5)	<.001
Medications				
Prior antibiotics	1027 (78.7)	965 (82.8)	137 (98.6)	<.001
Extended spectrum antibiotics[§§]	249 (19.1)	890 (76.3)	137 (98.6)	<.001
Narrow-spectrum antibiotics	325 (24.9)	220 (18.9)	29 (20.9)	.571
Anti-methicillin resistant *S. aureus*[*]	462 (35.4)	363 (31.1)	99 (71.2)	<.001
Antifungal treatment, at least one agent	97 (7.9)	60 (5.1)	37 (58.7)	<.001
Type of antifungal				<.001

(Continues)

TABLE 1 (Continued)

	All patient $n = 1305$	Patients without candidemia $n = 1166$	Patients with candidemia $n = 139$	p value
Fluconazole	33 (2.5)	20 (1.7)	13 (9.5)	
Anidulafungin	35 (2.7)	14 (1.2)	21 (15.3)	
Micafungin	8 (0.6)	3 (0.3)	5 (3.6)	
Caspofungin	6 (0.5)	4 (0.3)	2 (1.5)	
Liposomal amphotericin B	17 (1.3)	16 (1.4)	1 (0.7)	
Voriconazole	3 (0.2)	3 (0.3)	0 (0)	
Duration of antifungal treatment	0 (0–0)	0 (0–0)	2 (0–7)	<.001
Corticosteroid at any dose	855 (65.5)	778 (66.7)	77 (55.4)	.008
High-doses corticosteroid¶¶	307 (23.5)	277 (23.8)	30 (21.6)	.025
Anti-cytokine therapy**	122 (9.4)	112 (9.6)	10 (7.4)	.407
Anakinra	72 (5.5)	67 (5.7)	5 (3.7)	.326
Tocilizumab	55 (4.2)	48 (4.1)	7 (5.2)	.341
Outcomes of patients				
Discharged/transferred to service	663 (508)	645 (55.3)	18 (12.9)	<.001
Died	642 (49.2)	521 (44.7)	121 (87.1)	
Length of stay	9 (5–15)	9 (5–14)	21 (11–39)	<.001a
Length of stay, 14 days and above	387 (29.7)	292 (25)	95 (68.3)	

Note: Data are presented as *n* (%) unless noted otherwise.

†IQR: Interquartile range (25% and 75%).

‡DTA: Deep tracheal aspirate.

§Other samples: Cerebrospinal fluid. Sputum. and pleural fluid.

¶Candida colonisation index: the ratio of the candida-detected body sites to the number of culture-tested sites. Threshold 0.5.

††Candida score: the total points of the following variables: Multifocal colonisation with *Candida species* (1 point). surgery (1 point). total parenteral nutrition (1 point). sepsis (2 points). Threshold 2.5.

‡‡A positive clinical prediction rule for candidemia: The presence of any systemic antibiotic use (days 1–3) or CVC (days 1–3) in addition to at least two of the followings: TPN (days 1–3), any dialysis (days 1–3), any major surgery (days −7-0), pancreatitis (days −7-0), any use of steroids (days −7-3), or use of other immunosuppressive agents (days −7-0).

§§Extended spectrum antibiotic includes anti-pseudomonal cephalosporins, piperacillin-tazobactam, carbapenems, fosfomycin, colistin, and tigecycline.

¶¶ High dose corticosteroid: Methylprednisolone doses of 250–500-1000 mg.

*Anti-methicillin resistant S. aureus treatment contains vancomycin, teicoplanin, daptomycin, linezolid and tigecycline.

**Anti-cytokine therapy includes anakinra and tocilizumab.

conducted to see how concordant the predictive calibration curve and the ideal curve for estimating the candidemia status (Figure 3). Both the Hosmer–Lemeshow test results and the calibration curve indicate that the score model is calibrated.

4 | DISCUSSION

Candidemia is one of the common causes of bloodstream infections, mostly developed in intensive care setting. Previous studies demonstrated that COVID-19 patients have an increased risk for the development of candidemia and higher mortality rates compared to patients without COVID-19.[5–7,13] Early prediction of candidemia by using potential risk factors and initiation of empirical antifungal therapy, as recommended by current guidelines, is crucial to prevent the devastating effects of the disease in ICU patients with multiple risk factors.[1,14] However, it is not always easy to predict which patients will develop candidemia, as ICU patients often have comorbidities and undergo invasive procedures. In studies conducted before the COVID-19 pandemic, some predictive rules were defined to identify patients at high risk for candidemia, however, COVID-19 patients followed in the ICU differ from patients in the pre-pandemic period in terms of risk factors such as the rarity of pancreatitis and surgical history and the frequent use of corticosteroids. Therefore, the contribution of the use of the previous rules may be limited in COVID-19 patient population. In this study, we described risk factors for candidemia in COIVD-19 ICU patients and developed an easy-to-use clinical prediction score for the prediction of candidemia.

This study showed that the presence of CVC is the main determinant for candidemia in patients with COVID-19, and the risk of candidemia is very high in the presence of any one of the risk factors defined together with CVC. The risk of development of candidemia in patients without CVC was very low. Similar to our study, Ostrosky-Zeichner et al. defined the presence of CVC as

TABLE 2 Univariate and multivariate analysis of predictive parameters for the development of candidemia in COVID-19 ICU patients

	Univariate				Multivariate			
Variable	OR	95% CI L	95% CI U	*p*	OR	95% CI L	95% CI U	*p*
Age	1.00	0.99	1.01	.7406				
Age, 65 years and above	1.10	0.76	1.62	.6069				
Sex, female	1.28	0.89	1.82	.1792				
Comorbidities, at least one	0.99	0.59	1.68	.9774				
Diabetes	0.93	0.64	1.36	.7086				
Hypertension	0.76	0.53	1.07	.1183				
Cardiac failure	0.74	0.43	1.27	.2718				
Coronary arterial disease	1.01	0.68	1.50	.9526				
Chronic renal failure	0.98	0.54	1.75	.9357				
Haemodialysis	1.03	0.49	2.20	.9301				
Chronic lung disease	0.79	0.48	1.30	.3472				
Malignancy	1.15	0.67	1.97	.6117				
Immunodeficiency	1.15	0.56	2.37	.6968				
Prior cerebrovascular event	0.67	0.32	1.40	.2829				
Central venous catheter	26.73	11.20	63.80	<.0001	19.07	8.12	44.8	<.0001
Sepsis	2.11	1.47	3.03	<.0001				
Total parenteral nutrition	6.02	3.68	9.84	<.0001				
Mechanical ventilation	7.53	4.48	12.67	<.0001				
Multifocal candida colonisation	3.71	2.40	5.73	<.0001	2.28	1.39	3.72	.0010
Concurrent infection	2.67	1.77	4.01	<0.0001				
Bacteriemia	3.38	2.36	4.85	<.0001				
Corticosteroid	0.62	0.43	0.88	.0083	0.51	0.34	0.76	.0011
Extended spectrum antibiotics	18.49	5.12	66.79	<.0001				
Narrow-spectrum antibiotics	1.13	0.73	1.75	.5717				
Anti-cytokine therapy	0.75	0.38	1.48	.4083				
Anti-methicillin resistant *S. aureus*	5.48	3.72	8.07	<.0001				
Length of ICU stay	1.08	1.06	1.09	<.0001				
Length of stay, 14 days and above	6.46	4.41	9.46	<.0001	3.62	2.42	5.44	<.0001

Note: Anti-methicillin resistant *S. aureus* treatment contains vancomycin, teicoplanin, daptomycin, linezolid and tigecycline.Anti-cytokine therapy includes anakinra and tocilizumab.

Final multivariate score model was constructed using variable selection. Score parameters: C-index = 0.831 (obtained from 1000 bootstrap samples); Area under the curve: 0.8431 with 95% CI: 0.8153–0.8708 (DeLong).

the main component of the clinical prediction rule for nosocomial invasive candidiasis.[1] CVC has been identified many times as a risk factor for the development of candidemia and has been included as part of the score in almost all candidemia score or prediction rule development studies.[1,9,10,15,16] In the study of 'Candida score' conducted by Leon et al., CVC was not found as a significant risk factor for proven candida infection.[9] However, the designs of the score studies differ from each other, and the 'candida score', which gained acceptance by clinicians, is a scoring system with a different design aiming to predict the development of candidemia in patients with *Candida* colonisation. While evaluating the impact of risk factors, it did not compare the patients with and without candidemia but aimed to compare the patients who developed candidemia with the patients who were colonised but did not develop candidemia. In our study, CVC had a stronger effect with an OR 19 on the development of candidemia in ICU patients with COVID-19 compared to previous score studies conducted in ICU patients. This may be due to differences in risk profiles of patients with and without COVID-19, such as comorbidities and healthcare-related factors.

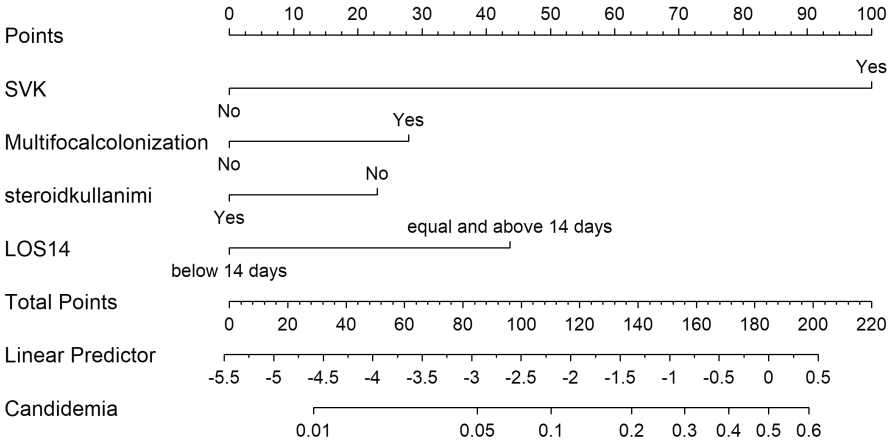

FIGURE 1 Demonstration of score model by a nomogram

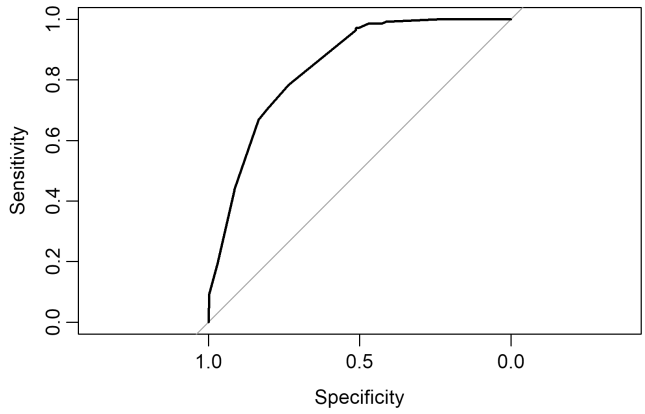

FIGURE 2 Performance of score for estimating the possibility of developing candidemia

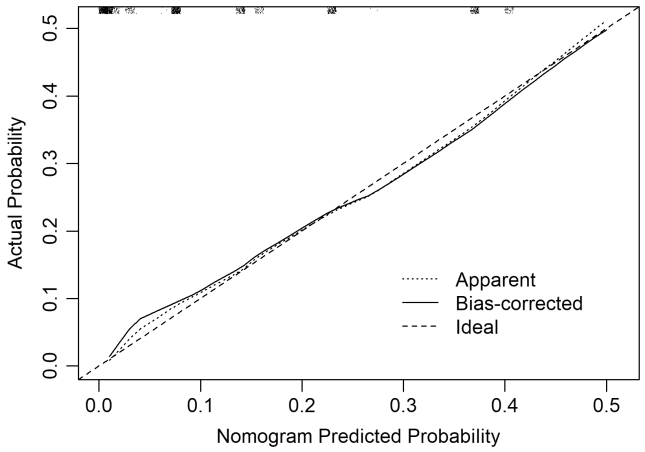

FIGURE 3 Predictive calibration curve and ideal curve for estimating the candidemia

Multifocal candida colonisation has been defined before as an independent risk factor for candidemia in the large cohorts of both medical-surgical ICU, and COVID-19 ICU.[9–11,17,18] The follow-up of candida colonisation is not a routine work in many of ICUs. However, prospective studies clearly demonstrated that multifocal candida colonisation can be a useful predictor for candidemia. Candida score study performed multiple-site cultures weekly to screen for multifocal candida colonisation.[9] Similarly, Kazancioglu et al. obtained multiple cultures on the day of admission to ICU and once a week thereafter until discharge or death.[17] In the present study, all patients were screened on the day of admission and in case of clinical necessity. Similar to previous studies, multifocal candida colonisation was an independent risk factor for the development of candidemia. In our previous study on candidemia in COVID-19 ICU patients, the rate of multifocal candida colonisation was reported higher in patients with candidemia than in those without candidemia.[11] However, in all previous studies, multifocal candida colonisation rates in patients with candidemia were reported to be around 40–55%.[9–11,17] Therefore, there is a need to increase the predictive value on candidemia by evaluating risk factors together. Detection of multifocal colonisation is a useful predictor for candidemia, especially in patients with CVC. While its sensitivity alone is 51.8%, the sensitivity of the score rises to 78.4%.

In the present study, it was determined that the length of ICU stays equal to and above 14 days increased the risk of candidemia in COVID-19 patients and it was included as a parameter in the candidemia score. Prolonged hospitalisation may result in candidemia due to prolonged exposure to invasive procedures or increased candida colonisation. In our previous study, a prolonged ICU stay (≥14 days) had been also detected to be significantly associated with candidemia (OR 1.9, 95% CI 1.08–3–37, $p < .05$).[11] The duration of ICU/ward hospitalisation had not usually been included in candidemia score studies. In the clinical prediction rule study of Guillamet et al., investigating the presence of candidemia in 2597 sepsis and septic shock patients with positive blood culture, although the duration of hospitalisation prior to blood culture positivity was found to be longer in the candidemia group than in non-candidemia group (those with bacteremia) in univariate analysis, it was not significantly associated with an increased risk of sepsis or septic shock with *Candida* spp. in multivariate analysis and was not included in the score.[15]

One of the parameters in the present candidemia score was corticosteroid use. Corticosteroids were found to have a protective effect against candidemia in COVID-19 ICU patients. This was a result we expected based on our previous study.[11] In Leon's Candida score study, the rate of corticosteroid use was similar in patients with

unifocal/multifocal *Candida* spp. colonisation and those with proven candida infection (24.2% vs 22.7%), and corticosteroid use was not an independent risk factor for proven candida infection.[9] In the literature, steroid use has generally been associated with an increased risk of infection.[19] However, there are also infections for which corticosteroid therapy is effective and indicated. Corticosteroids have found a place in the treatment of some infectious diseases such as septic shock that do not respond to intravenous fluid and vasopressor therapy or bacterial meningitis.[12,20] At the onset of the pandemic, there was uncertainty about the use of corticosteroids in the treatment of COVID-19, accumulating data have shown that corticosteroid use is associated with reduced mortality in critically ill patients.[21–24] Earlier recovery from severe COVID-19 disease with corticosteroid treatment may result in a reduction in candidemia in ICU patients. However, there are also studies reporting that steroid treatment predisposes the development of candidemia in COVID-19 patients.[25,26] Therefore, the clear effect of corticosteroid use on the development of candidemia in critically ill patients is still a controversial issue that needs to be investigated.

Risk factors included in the candidemia scores are closely related to the characteristics of the study populations. Their frequencies can determine whether the factors are included in the score. In the Leon's Candida score study, conducted in the medical-surgical ICU, surgery was detected as a component of the score. Ostrosky-Zeinchner et al. found pancreatitis as a component of the best performing rule in intensive care setting.[1,9] However, our patient population was entirely different from those in these score-development studies. None had undergone surgery or had pancreatitis. On the other hand, corticosteroid use was very frequent. To be realistic, these scores were unsuitable for the application in the COVID-19 patient population. Therefore, we believe that our study provides an important contribution to the literature.

This study has some limitations. First of all, the study has a retrospective character with some disadvantages such as data collection problem, but we tried to overcome this problem by keeping a well-filled special patient form. Second, we were unable to collect data on baseline clinical status with a clinical severity score such as the Acute Physiology and Chronic Health Assessment II (APACHE II) score.

In conclusion, candidemia results in high mortality and *Candida* spp. cannot be isolated from the blood of all patients with candidemia. Candidemia should be kept in mind in the differential diagnosis of infection in all patients whose clinical condition deteriorates, especially in the presence of CVC and other risk parameters. This candidemia score with a high negative predictive value can be used as a predictive tool to distinguish between patients at high risk for candidemia and those without.

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The authors declare that no funding was required for this study.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

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

ORCID

Bircan Kayaaslan https://orcid.org/0000-0001-5225-8319

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