Department of Pharmacy[1], Huashan Hospital, Fudan University; Department of Clinical Pharmacy[2], Shanghai Tenth People's Hospital, Tongji University School of Medicine, Shanghai, China

Development and validation of a risk score for predicting invasive fungal infectious in an intensive care unit

YUN LIAO[1,2,*], MING-KANG ZHONG[1], HONG-BIN XU[2,*], LING LI[2]

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Ming-Kang Zhong, Department of Pharmacy, Huashan Hospital, Fudan University, Shanghai 200072, China
mkzhong@medmail.com.cn
Hong-Bin Xu, Department of Clinical Pharmacy, Shanghai Tenth People's Hospital, Tongji University School of Medicine, Shanghai 200072, China
xuhongbin@tongji.edu.cn
**These authors equally contributed to this work.*

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Delay in the initiation of appropriate antifungal therapy is associated with substantial morbidity and mortality. The aim of this study was to derive a risk score system for the development of invasive fungal infections in an intensive care unit (ICU). We retrospectively evaluated 1812 patients who stayed in the ICU for ≥ 4 days, used univariate and multivariable logistic regression to identify potential risk factors associated with invasive fungal infections (IFI), and created a risk score system. Seven variables were identified as important predictors of ICU-IFI (diabetes mellitus, gastrointestinal surgery, hematological malignancies, mechanical ventilation ≥ 2 days, central venous catheter, total parenteral nutrition, broad-spectrum antibiotic use ≥ 4 days). The area under the receiver operating characteristic curve was 0.807 and was similar in the validation set. The percentages of patients with ICU-IFI in the low, intermediate, and high risk groups were 5.2%, 31.6%, and 63.2% in the derivation cohort and 4.2%, 30.1%, and 66.7% in the validation cohort, respectively. A new risk score was developed to predict ICU-IFI and was validated in an independent cohort. The new risk score may help clinicians identify patients who are at high risk of developing ICU-IFI and increase their odds of survival.

1. Introduction

The number of cases of fungal sepsis in China has tripled over the past few decades (Yin et al. 2008). The vast majority of nosocomial fungal infections are due to *Candida* species infections, and a substantial percentage of such infections occurs within the intensive care unit (ICU) (Hajjeh et al. 2004). These infections are associated with increased length of ICU stay and are reported as an independent predictor of death (Leleu et al. 2002). Furthermore, patients with invasive fungal infections (IFI) are more likely to die than those with a bacterial pathogen-induced bloodstream infection (Jarvis et al. 1995).

Delayed initiation of appropriate antifungal therapy is associated with increased morbidity and mortality in the ICU. Blood cultures are notoriously insensitive to disseminated fungal infections. In an autopsy series, fungemia was detected in only 58% of patients with widely disseminated candidiasis (Berenguer et al. 1993). Once IFI is detected by blood culture, the associated mortality may be as high as 49% (Gudlaugsson et al. 2003). Under such circumstances, widespread antifungal prophylaxis is used in response to this issue. However, its use is not strongly advised due to uncertainty about which patients would be most likely to benefit and problems including drug toxicity and antibiotic resistance. Taken together, early antifungal intervention strategies have been developed to identify those patients who are at high risk of invasive fungal infections and may benefit from the use of prophylactic or pre-emptive/empirical antifungal therapy. In the present study, we sought to develop a simple scoring system for the early prediction of IFI that could potentially be applied in clinical trials that investigate prophylaxis, preemptive, or empirical therapy. Based on the observation by Pelz et al. (2001) that early initiation of antifungal prophylaxis would maximize its value, we limited our risk factors to routinely available data on or before the third ICU day.

2.. Investigations and results

2.1. Baseline characteristics

A total of 1937 patients were admitted to the ICU between January 2008 and January 2011. Of these, 1832 stayed in the ICU ≥ 4 days and met our inclusion criteria. Eight patients had a diagnosis of invasive candidiasis on or before the third ICU day and were excluded from further analysis. An additional 12 patients who had received a systemic antifungal agent were excluded as well. Of the total sample, 128 cases of IFI occurred from day 4 of ICU admission to day 7 after ICU discharge, including 110 proven cases and 18 probable cases of IFI. Among them, 89 patients (69.5%) were in the derivation cohort and 39 patients (30.5%) were in the validation cohort. The infections were caused by *Candida albicans* (83 patients); *Candida parapsilosis* (17 patients); *Candida glabrata* (12 patients); *Candida krusei* (11 patients); and *Aspergillus fumigatus* (3 patients). Two patients were infected by 2 species: *C. albicans and C. parapsilosis* (1 patient), *C. albicans and C. krusei* (1 patient). The infection presentations included 71 bloodstream infections, 25 urinary tract infections, 31 catheter-related infections, and one

Table 1: Demographic and clinical characteristics of patients in the two study cohorts*

	Derivation Set (n = 1253)	Validation Set (n = 559)
Demographic		
Age, yrs	61.5 ± 18.7	61.9 ± 17.2
Male sex	609 (48.6)	260 (46.5)
APACHE II score on admission	13 ± 6.1	15 ± 8.8
Length of ICU stay	19.4 ± 20.1	18.3 ± 19.9
Diagnosis on ICU admission		
Medical	317 (25.27)	175 (31.28)
Surgical	706 (56.31)	282 (50.47)
Trauma	230 (18.41)	101 (18.09)
Underlying disease		
Diabetes mellitus	190 (15.16)	91 (16.24)
History of COPD	271 (21.66)	127 (22.67)
Gastrointestinal surgery	81 (6.49)	39 (6.91)
Solid malignancies	160 (12.76)	67 (11.98)
Hematologic malignancies	57 (4.57)	29 (5.11)
Special treatments total		
Central venous catheter	421 (33.57)	184 (32.98)
Peripheral catheter	231 (18.41)	100 (17.87)
Foley catheter	457 (36.46)	208 (37.18)
Nasogastric tube	474 (37.79)	207 (36.97)
Mechanical ventilation ≥ 2 days	549 (43.80)	251 (44.89)
Broad-spectrum antibiotic ≥ 4 days	724 (57.76)	330 (59.01)
Gastric acidity-lowering agents	956 (76.31)	419 (74.93)
Total parenteral nutrition	547 (43.68)	212 (37.91)
Immunosuppressive therapy	202 (16.13)	95 (17.02)

*Values are number (%) or mean(SD). APACHE II, Acute Physiology and Chronic Health Evaluation II; ICU, intensive care unit; COPD, chronic obstructive pulmonary disease

meningitis infection. The male-to-female ratio in the sample of eligible patients was almost 1:1 (599 male patients, 654 female patients), while the median age was 61 years. Table 1 shows the demographic and clinical characteristics of these two cohorts.

2.2. Construction of a new scoring system

All of the potential risk factors are shown in Table 1, while the association between potential risk factors and IFI by univariate analysis is shown in Table 2a . All of the significant factors were entered into multivariate analysis. The final logistic regression model, termed the Invasive Fungal Infections Risk Score (IFIRS), consisted of seven significant risk factors: diabetes mellitus, gastrointestinal surgery, hematological malignancies, use of mechanical ventilation ≥ 2 days, central venous catheter, TPN, and the use of broad-spectrum antibiotics ≥ 4 days (Table 2b). Table 3 shows the points of these risk factors in the final logistic model based on the 831 patients in the derivation cohort. Each patient's risk score was the sum of 7 points according to the patient's special characteristics. The theoretical range of the risk score is 0–26. A higher score implies a higher infection risk.

CART modeling of the derivation cohort was used to identify four risk level cutoffs: < 5, 68, 9–13, and > 14 points. In the validation cohort, the four cutoff values identified by CART were < 5, 6–10, 11–13, and > 14. Based on these results, we developed three discrete risk level categories: low (score ≤ 8), intermediate (score 9–13), and high (score ≥ 14) (Table 3). In the derivation cohort, the proportions of participants at low, intermediate, and high risk of developing IFI were 5.2%, 31.6%, and 63.2%, respectively. These proportions were similar in the validation cohort (Fig. 1).

2.3. Score system validation

The derivation model was then examined in the study population, and the score distribution was similar between the cohorts

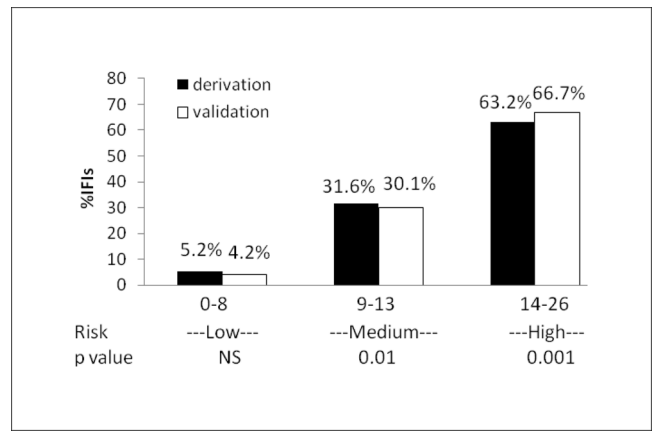

Fig. 1: Percentage of patients with invasive fungal infections by risk stratum

(Figs. 2 a and b). The areas under the receiver operating curve were 0.802 and 0.830 for the derivation and validation sets, respectively (Figs. 3a and b). Other measures of model performance were also comparable (Table 4). The Hosmer and Lemeshow goodness of fit test results for the derivation and validation sets were $\chi^2 = 11.81$ (d.f. = 7; $P = 0.107$) and $\chi^2 = 4.66$ (d.f. = 7; $P = 0.463$), respectively, indicating good performance by both sets.

3. Discussion

IFI have emerged as major causes of morbidity and mortality in the ICU. The objective of this study was to develop a risk model that could function as a simple tool for identifying risk-targeted antifungal prophylaxis in the ICU. The risk score model showed good predictive accuracy in both the derivation and validation sets and was able to discriminate among cohorts at low, intermediate, and high risk of developing ICU-IFI. The perfor-

Table 2: Analysis of potential risk factors for deep fungal infection *(a) Univariate analysis**

	IFI case (n = 89) n (%)	Control (n = 1164) n (%)	p
Demographic			
Age, yrs	62.5 ± 16.6	60.9 ± 19.6	0.591
Male sex	45 (50.9)	569 (48.9)	0.682
APACHE II score on admission	14.3 ± 6.1	12.6 ± 8.9	0.131
Length of ICU stay	21.4 ± 13.6	17.3 ± 19.6	0.068
Underlying disease			
Diabetes mellitus	35 (39.1)	278 (23.9)	0.002
Hypertension	28 (31.1)	414 (35.6)	0.442
History of COPD	19 (21.1)	294 (25.3)	0.397
Gastrointestinal surgery	26 (29.3)	173 (14.9)	0.001
Solid malignancies	15 (16.7)	114 (9.8)	0.048
Hematologic malignancies	8 (9.1)	37 (3.2)	0.011
Special treatments total			
Central venous catheter	86 (96.2)	737 (63.3)	< 0.001
Peripheral catheter	44 (49)	537 (46.1)	0.686
Foley catheter	79 (89.3)	915 (78.6)	0.263
Nasogastric tube	38 (42.2)	385 (33.1)	0.077
Mechanical ventilation ≥ 2 days	53 (59.1)	526 (45.2)	< 0.001
Broad-spectrum antibiotic ≥ 4days	67 (75.2)	684 (58.8	< 0.001
Gastric acidity-lowering agents	77 (86.3)	929 (79.8)	0.137
Immunosuppressive therapy	24 (27.3)	211 (18.1)	0.051
Total parenteral nutrition	68 (76.5)	398 (34.2)	< 0.001

(b) Multiple logistic regression analysis. APACHE II, Acute Physiology and Chronic Health Evaluation II; ICU, intensive care unit; COPD, chronic obstructive pulmonary disease

Variable	β	SE	OR	95% CI	*p*
Diabetes mellitus	1.54	.27	5.30	3.14−8.97	.000
Gastrointestinal surgery	1.46	.38	4.30	2.03−9.12	.000
Hematologic malignancies	1.21	.41	3.34	1.38−8.06	.007
Mechanical ventilation ≥ 2 days	.59	.25	1.82	1.11−2.98	.017
Broad–spectrum antibiotic ≥ 4 days	1.24	.29	3.52	2.01−6.17	.000
Central venous catheter	.86	.25	2.29	1.39−3.74	.001
Total parenteral nutrition	.93	.35	2.71	1.29−6.22	.009

*Values are number (%) or mean ± SD β, coefficient in the multivariate model; SE, standard error; OR, odds ratio; CI, confidence interval

mance characteristics of our model maximized specificity but had relatively low sensitivity. This trade-off serves to enhance the model's positive predictive value, which is important to clinicians identifying high-risk patients who might more easily develop IFI.

The accuracy of these findings is based on the strength of the IFI diagnosis. The definitions we developed in this regard were based on a wide range of clinical and microbiological data and also followed by the principles outlined in the IDSA guidelines for the treatment of candidiasis and central venous catheter-

Table 3: Point allocation for Invasive Fungal Infections Risk Score (IFIRS) predictors based on regression coefficients from the derivation model

Risk factor	Points
Diabetes mellitus	5
Gastrointestinal surgery	5
Hematologic malignancies	4
Broad-spectrum antibiotic therapy ≥ 4 days	4
Central venous catheter	3
Total parenteral nutrition	3
Mechanical ventilation ≥ 2 days	2
Total points	26

Regression coefficients were scaled to the nearest integer using the lowest regression coefficient as a scale.

Risk stratum	IFIRS points
low	≤ 8
medium	9–13
high	≥ 14

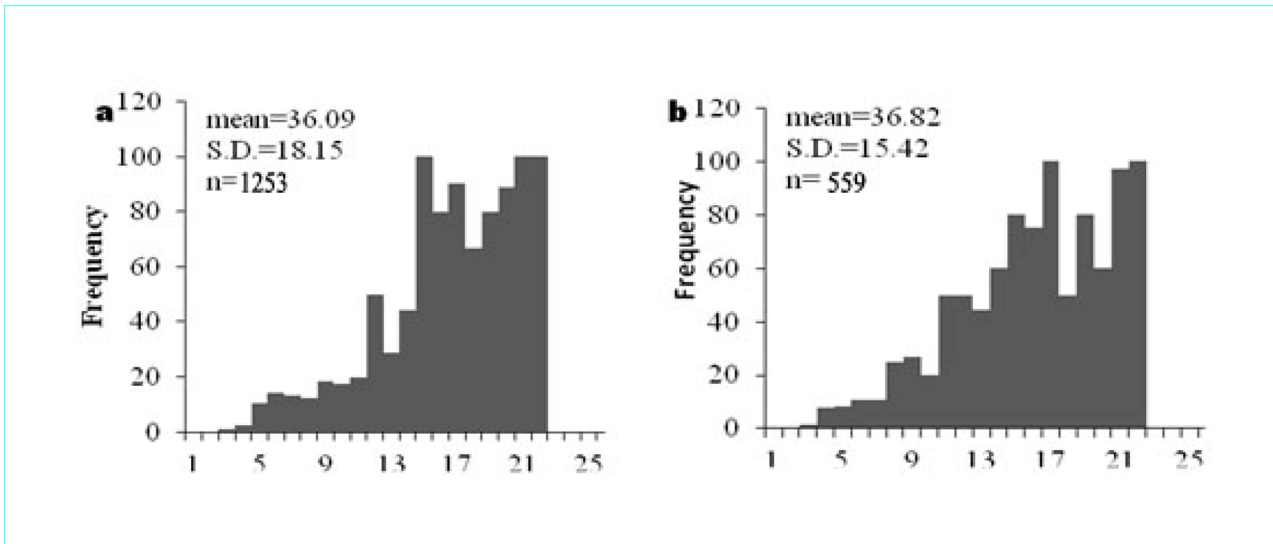

Fig. 2: Distribution of scores for the (a) validation and (b) derivation cohorts

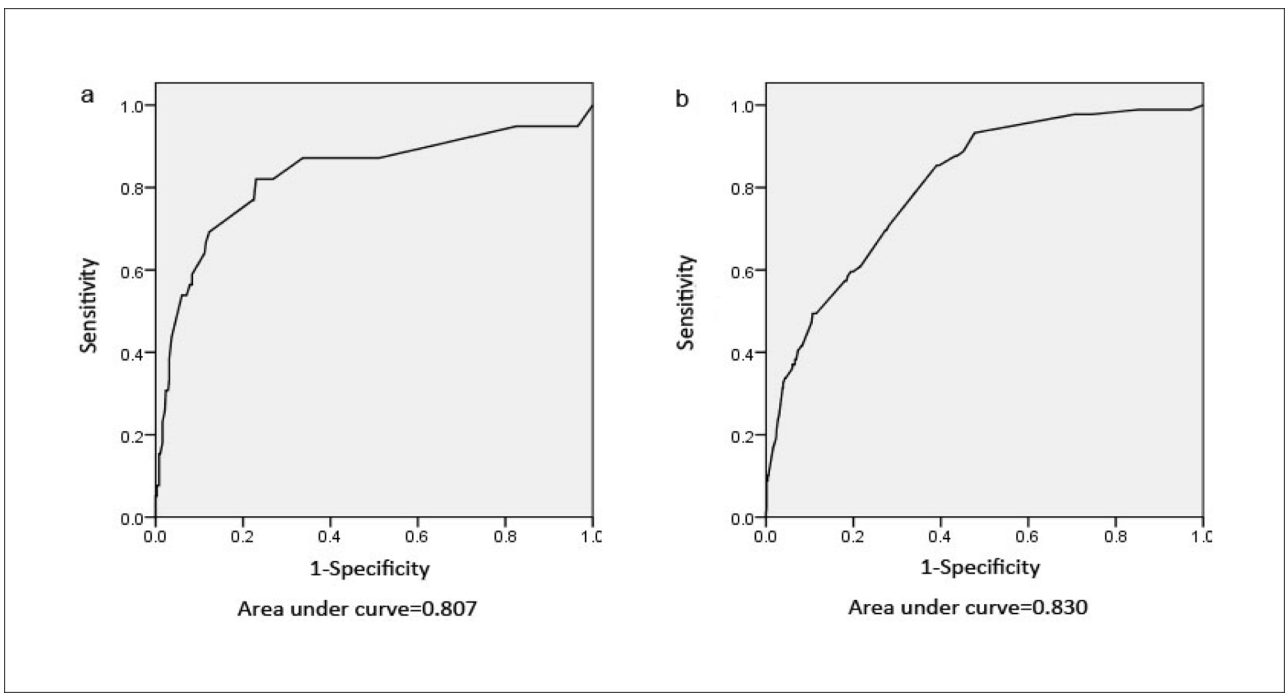

Fig. 3: Area under the receiver operating curve of the (a) derivation and (b) validation cohorts

related infections, the published consensus on the management of severe candidal infections (Bone et al. 1992). Based on the above diagnosis standard, we found an approximate 6% incidence of IFI within the ICU, a finding that was similar to those in other studies (Edmond et al. 2004; Paphitou et al. 2005). In this study, seven potential risk factors emerged as being independently associated with higher IFI risk. Diabetes mellitus was the first factor independently associated with ICU-IFI. Consistent with a previous study (Leroy et al. 2009), our data substantiated the impact of diabetes: many of our patients had diabetes mellitus or hyperglycemia. Elevated serum glucose may lead to impaired neutrophil and monocyte adherence, chemotaxis, phagocytosis, pathogen killing, and respiratory burst and has been associated with the development of fungal infections (Shoham et al. 2009). As such, cooperative efforts between the ICU and endocrinology department to adopt a protocol to control blood glucose can dramatically affect patients' adverse outcomes.

Table 4: Performance measures for the derivation and validation models

Performance measure	Derivation model (%)	Validation model (%)
Sensitivity	10.1	17.9
Specificity	87.6	94.4
Positive predictive value	69.2	62.5
Negative predictive value	90.2	92.4

We also identified gastrointestinal surgery, TPN, and the use of central venous catheters or mechanical ventilation as four independent predictors of ICU-IFI. Transition of *C. albicans* from a fungus that lives harmlessly in the gastrointestinal tract and skin to an opportunistic pathogen requires disruption of the anatomical barriers (Spellberg et al. 2008). Intestinal injury or ischemia, surgical manipulation, and the use of TPN may alter the gut barrier and lead to subsequent fungal infections. Disruption of the cutaneous barriers by indwelling devices, particularly vascular catheters and mechanical ventilation devices, facilitates the translocation of cutaneous fungi into the bloodstream.

Hematological malignancy was the sixth independent predictive factor of IFI in our model. Under normal circumstances, neutrophils, macrophages, and monocytes damage and kill *Candida* yeast cells, hyphae, and pseudohyphae as well as *Aspergillus* conidia (Koh et al. 2008). Patients with hematological malignancies, who have impaired neutrophil and monocyte counts, are at an increased risk of developing fungal infections. In addition, some co-morbid conditions in this population such as diabetes mellitus, cancer chemotherapy, underlying renal dysfunction, and corticosteroid use all resulted in phagocyte dysfunction and a high rate of fungi infections. Broad-spectrum antibiotic therapy was the last factor that was independently associated with IFI, an association that has been widely reported, particularly in critically ill patients (Castaldo et al. 1991; Wenzel et al. 1995).

In this retrospective study, our goal was not simply to identify risk factors of the development of IFI, as numerous data exist on this issue (Savino et al. 1994; Pelz et al. 2001). We sought to integrate many of the well-established risk factors into a risk predictive model. Some clinical prediction rules for invasive candidiasis have been developed and published in the past 10 years (Paphitou et al. 2005; Ostrosky-Zeichner et al. 2007). Although derived from a different patient population, their results are similar to ours. From a clinical perspective, the major advantages of our system are that it uses only easily ascertainable clinical factors, allows for immediate risk stratification, and does not require sophisticated computations. Other prediction rules either derived data from a relatively small ICU cohort or lacked validation of a prospective patient cohort.

This study was performed in a single hospital, and its major limitation is the power of the model that requires the inclusion of more patients. Another potential limitation of this data set is the exclusion of patients who were receiving antifungal agents or those whose antifungal drug status was unknown upon the day of ICU admission to day 3. Since this approach required excluding patients who may have had baseline fungal infections, a substantial number of high-risk patients may have been excluded.

Some researchers might question the absence of fungal colonization as an important risk factor in our model. Fungal colonization has been found to be associated with the development of invasive candidiasis (Pittet et al. 1994), yet only a small proportion (3–25%) of previously colonized patients subsequently develop the disease (Blumberg et al. 2001; Krcmery et al. 2002). However, we deliberately did not chose it as a potential risk factor for several reasons: First and foremost, use of such data as part of any study would require the availability of routine fungal cultures. Such testing is costly, is not widely used, may take several days to yield results, and (in our experience) is difficult to be implemented systematically. Second, obtaining culture results takes time, and we believe that the prompt initiation of prophylactic treatment is likely important to its success. Thus, we sought to base our scoring system on other routinely collected information that is available soon after ICU admission.

In conclusion, this study developed and validated the IFIRS, a risk score system that can objectively identify patients at high risk of developing IFI and hence help clinicians determine whether targeted antifungal prophylaxis and/or empirical therapy should be used for critically ill patients.

4. Experimental

4.1. Study setting and population

We collected data of 1812 consecutive adult ICU patients from January 2008 to January 2011 at Shanghai Tenth People's Hospital (affiliated with Tongji University). Data collected during the first 24 months (n = 1253) were included in the derivation cohort, and data collected during the next 12 months (n = 559) were included in the validation cohort. This study was approved by the ethics committee of the hospital.

4.2. Collection of risk factors data

Based on earlier studies of invasive fungal infections (Petri et al. 1997; Borzotta et al. 1999), data regarding the presence or absence of a wide range of potential risk factors were collected for the time period extending from 7 days prior to ICU admission through the third ICU day (D_{-7} to $_3$). For patients with more than one episode of infection, only those data relevant to the first episode were collected. Neutropenia was an exclusion criterion. The following variables were collected from the database: age, gender, underlying disease, reason for ICU admission, and presence and duration of IFI risk factors. The possible IFI risk factors included: diabetes mellitus; hypertension; chronic obstructive pulmonary disease; the use of mechanical ventilation ≥ 2 days; gastrointestinal surgery; solid or hematological malignancies; trauma; the use of broad-spectrum antibiotics ≥ 4 days (including antibiotic agents with activity against both Gram-positive and -negative organisms), central venous catheter, peripheral catheter, Foley catheter, nasogastric tube, or gastric acidity-lowering agents; foreign material within the body; total parenteral nutrition (TPN); and immunosuppressive therapy. Illness severity upon ICU admission was calculated using the Acute Physiology and Chronic Health Evaluation II system (Knaus et al. 1985).

At the time of ICU admission, patients were classified as being surgical, trauma, or medical cases according to diagnosis. Surgical patients were those for whom the indication for ICU admission was the postoperative control of an elective or urgent procedure, trauma patients were those admitted for acute trauma-related lesions, and medical patients were those admitted for any other reason. Outcome assessment eligibility and database consistency were verified by two reviewers.

4.3. IFI definitions

The period beginning from 4th ICU day to the 7th day after ICU discharge was defined as the outcome period, and the IFI data during this period were collected. Patients with evidence of IFI during the period $D_{-7\ to\ 3}$ were excluded from the analysis, as they would have already received a systemic antifungal agent during this period. IFI was defined as being proven or probable using the European Organization for Research and Treatment of Cancer criteria (Ascioglu et al. 2002). The definition also followed the principles outlined in the Infectious Diseases Society of America (IDSA) guidelines for the management of intravascular catheter-related infections (Mermel et al. 2001).

4.4. Statistical methodology

The study sample was divided into two sets: a derivation set, which was used to construct a prediction model; and a validation set, which was used to validate the performance of the clinical prediction model. For both samples, patient baseline characteristics were summarized using descriptive statistics.

4.4.1. Model derivation

Within the derivation cohort, risk factors were evaluated using univariate and multivariable logistic regression. Variables associated with an increased IFI risk ($P < 0.05$) in univariate analysis were included in the multivariate logistic model. Beta (regression) coefficients, odds ratios, and their corresponding 95% confidence interval for the final model were reported with the criterion for statistical significance. Each coefficient estimate was multiplied by the same factor and rounded to the nearest integer. The global score was the sum of these individual points. A higher global score indicated a greater likelihood of IFI. Classification and regression tree (CART) modeling was used to define risk levels (high, intermediate, and low) according to total score. CART methodology produces a simple decision tree that is relatively easy to apply in clinical practice, and it was previously used to develop prediction models in other medical fields (Fonarow et al. 2005; Takahashi et al. 2006). The sensitivity, specificity, and positive and negative predictive values of this model were then evaluated.

4.4.2. Validation cohort

The validation cohort was analyzed to test the derived prediction score performance. Receiver operating characteristic curves were calculated to compare model performance in the derivation and validation cohorts. All statistical analyses were performed using SPSS 10.1 software (SPSS, Chicago, IL, USA).

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