Risk prediction for invasive candidiasis

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Abstract

Over past few years, treatment of invasive candidiasis (IC) has evolved from targeted therapy to prophylaxis, pre-emptive and empirical therapy. Numerous predisposing factors for IC have been grouped together in various combinations to design risk prediction models. These models in general have shown good negative predictive value, but poor positive predictive value. They are useful in selecting the population which is less likely to benefit from empirical antifungal therapy and thus prevent overuse of antifungal agents. Current article deals with various risk prediction models for IC and their external validation studies.

Keywords: Critically ill, invasive candidiasis, risk factors, risk prediction models

Introduction

One of the most important skills of intensive care physicians is their ability to preempt critical events while caring for severely sick individuals. In order to give a universally acceptable and scientifically sound shape to the prediction skill, various risk prediction models have been developed for a number of medical illnesses (e.g. deep venous thrombosis, community-acquired pneumonia).

Fungal infections are increasing worldwide.[1,2] These infections are associated with high mortality, morbidity and increased cost of care.[3,4] *Candida* is the most common fungal pathogen in human beings. According to the 1-day point prevalence (Extended Prevalence of Infection in Intensive Care II) study conducted over 75 countries in 2007, *Candida* was third most common pathogen with an infection rate of 17% after *Staphylococcus aureus* and *Pseudomonas* spp.[5] Half to one-third of *Candida* infections occur in Intensive Care Unit (ICU) patients. Emergence of *Candida* is further complicated by increased rate of infections due to non-*albicans* species and growing

resistance to antifungal agents.[6,7] Five common species of *Candida* responsible for blood stream infection are *Candida albicans, Candida glabrata, Candida parapsilosis, Candida tropicalis,* and *Candida krusei*. Other species causing *Candida* infections are *Candida lusitaniae, Candida guilliermondii, Candida rugosa*.

Candida infection is associated with excess attributable mortality of 10-49% and increase in length of hospital stay of 3-30 days.[8] Delayed diagnosis of fungal infections is a common occurrence, and several studies have shown higher mortality associated with delayed initiation of appropriate antifungal therapy.[9-11] At least five meta-analyses studied the role of prophylactic antifungal among surgical and critically ill patients.[12-16] All showed successful reduction in the rate of fungal infections with the use of antifungal prophylaxis while two showed a significant reduction in total mortality. Indiscriminate use of antifungal prophylaxis can lead to the development of resistant species. Playford *et al*. recommended that prophylaxis should be given to a subgroup of the population where incidence of invasive candidiasis (IC) is > 10%. In such a situation, the number needed to treat to prevent one infection is twenty. Therefore, it is necessary to identify those patients who are at increased risk of IC.

Colonization almost invariably precedes *Candida* infection and frequency of infection increases with an

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increased number of sites colonized. Besides colonization and immunosuppression, factors known to be associated with increased risk of invasive fungal infections (IFIs) are broad spectrum antibiotic use, total parenteral nutrition (TPN), central venous catheter (CVC), surgery, renal replacement therapy, diabetes, prolonged mechanical ventilation, severe sepsis, and high Acute Physiology and Chronic Health Evaluation (APACHE) II score.[17] These risk factors have been used in various combinations to design risk prediction models [Table 1]. Current article is a review of risk prediction models developed to predict IC and external validation of these models.

Review

Literature search was done on PubMed and Medline databases from January 1990 to June 2013. Terms like "risk factors for IC," "prediction models/scores for IC," "validation of *Candida* score," "validation of clinical prediction rules (CPRs) for IC" were used for the search. References from the relevant articles were also searched manually by two researchers separately. Studies dealing with the development of risk prediction models for IC, as well as studies on external validation of any of the

already developed model, were included for evaluation. Studies in which risk factors for IC were studied, but no model was developed or validated were excluded from our study.

A total of 14 studies met the inclusion criteria. There were total 9 derivation studies (studies in which a risk prediction model was developed) and 5 external validation studies (studies in which risk prediction models were validated). The studies were further classified as risk prediction models based on microbiological parameters only, models based on clinical parameters only, and models based on clinical as well as microbiological parameters [Tables 2, 3 and 4].

Models based on microbiological parameters only
Derivation study

Pittet *et al.* attempted to quantify the severity of *Candida* colonization and hypothesized a probable link between the severity of colonization and infection.[18] Based on culture reports of samples taken from different distinct body sites (dbs), colonization index (CI) and corrected colonization index (CCI) were developed. The study was conducted over a period of 6 months on patients

Table 1: Risk factors used in various studies for risk prediction models

Risk factors	Pittet et al.	Dupont et al.	Michalopoulos et al.	Paphitou et al.	Ostrosky-Zeichner et al.	Ostrosky Zeichner et al. (revised)	León et al.	Hermsen et al.	Shorr et al.
Colonization	Yes						Yes		
Broad-spectrum antibiotic use	Yes	Yes		Yes	Yes	Yes		Yes	
Surgery					Yes	Yes	Yes		
Diabetes milletus			Yes	Yes					
Immuno suppressive agents					Yes	Yes		Yes	
Total parenteral nutrition					Yes	Yes	Yes		
Central venous catheter					Yes	Yes		Yes	
New hemodialysis				Yes					
Any dialysis					Yes	Yes			
Steroids					Yes	Yes			
Pancreatitis					Yes	Yes			
Severe sepsis							Yes		
High APACHE II	Yes								
Mechanical ventilation for more than 48 h						Yes			
Mechanical ventilation for >10 days			Yes						
ICU stay for more than 72 h				Yes	Yes	Yes			
Female gender		Yes							
Upper GI peritonitis		Yes							
Cardiovascular failure during surgery		Yes							
Abdominal surgery							Yes		
Pre-ICU stay							Yes		
Age <65 years									Yes
Temperature <98°F or altered mental status									Yes
Cachexia									Yes
Admission from other healthcare									Yes
Hospitalization within 30 days									Yes
Mechanical ventilation at admission									Yes
Nosocomial bacterial infection			Yes						
Cardiopulmonary bypass >120 min			Yes						

Y: Yes (risk factor used in the making of risk prediction model). FIRE study model has not been included as there was very large number of variables (at admission, 24 h and 3rd day) in the model. ICU: Intensive care unit; APACHE: Acute physiology and chronic health evaluation; GI: Gastrointestinal

Table 2: Various developmental studies of risk prediction models

Name of the study	Year	Study characteristics							Study results				
		Design	Centers	Cohort	Total number of patients	Cases (n)	Incidence of invasive candidiasis (%)	Basis of risk prediction	Name of best performing risk prediction model/rule (see text for explanation)	PPV %	NPV %	Sensitivity	Specificity
Pittet et al.	1994	Prospective	Single	Surgical/neonates	29	11	38	Microbiological	Colonization index	66	100	100	100
									Corrected colonization index	100	100	100	100
Dupont et al.	2003	Retrospective	Single	Surgical with peritonitis	221	71	32	Clinical	Grade C	67	72	84	50
Michalopoulos et al.	2003	Prospective case control study	Single	Cardiothoracic surgery patients	30 cases 120 control	30	-	Clinical	Model had 4 risk factors	100	89	53.3	100
Paphitou et al.	2005	Retrospective	Single	Surgical	327	23	7	Clinical	Paphitou rule 2	NA	NA	NA	NA
Leon et al.	2006	Prospective	Multicentre	Surgical/medical	1699	97	5.8	Microbiological+Clinical	Candida score	NA	NA	81	74
Ostrosky et al.	2007	Retrospective	Multicentre	Surgical/medical	2890	88	3	Clinical	Original	9	97	34	94
Ostrosky et al.	2009	Retrospective	Multicentre	Surgical/medical	597	22	3.7	Clinical	Revised	10	97	50	83
Shorr et al.	2009	Retrospective	Multicentre	All patients at admission	64,019	738	1.2	Clinical	Model had 6 risk factors. Score≥1	NA	99.6	90.7	28.9

PPV: Positive predictive value; NPV: Negative predictive value; NA: Not available

Table 3: Validation studies of various risk prediction models

Name of the study	Year	Study characteristics							Study results				
		Design	Center	Cohort	Total patients	Cases	Incidence of invasive candidiasis %	Basis of risk prediction	Name of risk prediction model/rule	PPV	NPV	Sensitivity	Specificity
León et al.	2009	Prospective	Multicenter	Surgical/medical	1107	58	5.2	Microbiological+clinical	Candida score≥3	13.8	97.7	77.6	66.2
Leroy et al.	2011	Prospective	Multicenter	Surgical/medical	94	5	5.3	Microbiological+clinical	Candida score>3	23.8	100	NA	NA
Playford et al.	2009	Prospective	Multicenter	Surgical/medical	615	15	2.4	Clinical+microbiological	Ostrosky original without CCI*	5.3	98	47	79
									Ostrosky original with CCI*	23.8	98	33	97
									Ostrosky revised without CCI*	4	99	80	51
									Ostrosky revised with CCI*	17	99	53	94
Hermsen et al. (NMC study)	2011	Prospective	Multicenter	Surgical/medical	352	88	2.3	Clinical	Paphitou 1	4.8	98	40	81
									Paphitou 2	5.4	98	45	81
									Ostrosky original	4.1	98	65	64
									Ostrosky revised	4.2	99	73	60
									NMC	4.7	99	84	60
Hall et al.	2013	Retrospective	Single	Severe acute pancreatitis patients	101	18	17.8	Microbiological+clinical	Candia score≥3	39	72	23	85
									Ostrosky original (modified)	21	85	61	49
									CI>0.5	43	91	67	79

*CI: Colonization index; CCI: Corrected colonization index; PPV: Positive predictive value; NPV: Negative predictive value

Table 4: Calculation of commonly used risk prediction scores/models for invasive candidiasis

Risk model	Components	Cut off
Candida score	Parenteral nutrition-1, Surgery- 1 point, Multifocal colonization (colonization at more than1 site) -1 point and severe sepsis- 2 points	Score ≥3 is considered positive
Colonization index	Number of nonblood dbs (distinct body sites) colonized by *Candida* spp divided by the total number of body sites cultured	Score ≥0.5 is considered positive
Corrected colonization index	CI multiplied by the ratio of heavily colonized sites to total number of sites colonized	Score ≥0.4 is considered positive
Ostrosky clinical prediction rule	ICU stay X 72 hours and Mechanically ventilated X 48 hours and Antibacterial antibiotic use X day 1-3 and CVC X day 1-3 AND at least one of the following Any surgery, day −7-0 Immunosuppressive use, day −7-0 Pancreatitis, day −7-0 TPN, day 1-3 Any dialysis, day 1-3 Steroid use, day −7-0	

ICU: Intensive care unit; CVC: Central venous catheter; TPN: Total parenteral nutrition; CI: Colonization index

admitted in surgical and neonatal ICU. All patients found to have significant colonization in surveillance cultures were included in the study. Colonization was defined as isolation of *Candida* from three or more samples from same or different sites for two or more consecutive screening days. Infection was defined as patient having candidemia or severe *Candida* species infection requiring use of antifungal therapy. Patients were divided into two groups, infected (n = 11) and colonized (n = 18). The infected group had three characters significantly different from the colonized group, namely higher APACHE II score at the time of admission, longer duration of antibiotic exposure and increased intensity of *Candida* colonization. Out of three variables, APACHE II and intensity of colonization proved to be an independent predictor of *Candida* infection in logistic regression analysis. They defined CI as nonblood dbs sites colonized by *Candida* divided by total number of sites tested and CCI as CI multiplied by ratio of heavy growth dbs upon the total number of dbs positive for *Candida* and proposed these indices as method of assessing severity of colonization. CI in the infected group was 0.70 as compared to 0.47 in the colonized group (P < 0.01). Mean CCI of the colonized group was 0.16 while that of the infected group was 0.56 (P < 0.01). A cut off value of CI >0.5 and CCI >0.4 identified all infected patients.

These indices (CI and CCI) have never been validated in robustly designed studies particularly in nonsurgical patients. Though clinicians do tend to consider multiple site colonization with *Candida*, an important risk factor for the development of IC, such type of surveillance is

difficult and therefore various researchers attempted to design prediction rules only on the basis of clinical risk factors.

External validation

Colonization index and CCI have never been validated in large randomized control trials. There are at least 10 studies dealing with CI and CCI, but none qualified the inclusion criteria for our study and are not discussed here.

Models based on clinical parameters (clinical prediction rules)

Derivation studies

Dupont *et al*. conducted a study to identify risk factors for isolation of fungus (yeast) from peritoneal fluid in surgical patients.[19] The risk score was generated by retrospective study of a cohort of 221 patients and prospectively validated on 57 patients in the same ICU. They identified four risk factors (cardiovascular failure, upper gastrointestinal tract origin for peritonitis, female gender, and previous antimicrobial therapy) independently associated with isolation of *Candida* from peritoneal fluid. Four grades of the score were formed (grade A, B, C, D). Grade A = no risk factor/one risk factor, grade B = 2 risk factors, grade C = 3 risk factors, grade D = 4 risk factors. Grade C (presence of at least three risk factors) was considered to have the best overall accuracy with sensitivity 84% and specificity 50%. The prediction rule was made only for secondary peritonitis patients and hence cannot be generalized in other population group.

Michalopoulos *et al*. studied risk factors for candidemia on cardiothoracic ICU patients in case–control study (30 candidemia patients and 120 control patients).[20] They proposed a model based on four risk factors found to be independently associated with candidemia in stepwise logistic regression (mechanical ventilation for >10 days, nosocomial bacterial infection and/or bacteremia, cardiopulmonary bypass duration >120 min and diabetes mellitus). The model had a sensitivity of 53.3%, specificity of 100%, (positive predictive value [PPV]) PPV of 100% and (negative predictive value [NPV]) NPV of 89%.

The model was validated by the same group at two centers. There were 19 candidemia patients in the validation study. The model performed well in the validation study (sensitivity 57.9%, specificity 100%, PPV 100%, NPV 99.6%).

Paphitou *et al*. developed prediction rule for surgical patients.[21] It was a single center retrospective study conducted on 327 nonneutropenic patients staying for >4 days in ICU. Total percentage of IC was 11% (36 cases) which included 2.8% proven, 4.3% probable and possible 3.9% cases. Various risk factors identified by multivariate analysis were starting of new hemodialysis, diabetes mellitus and use of broad spectrum antibiotics. On the basis of these findings, three CPRs were developed and compared. The best-performing rule (referred as Paphitou rule 2 in this manuscript) was described as ICU stay equal to or more than 4 days and no antifungal use from day 7 to 3 and any of the following: Diabetes or TPN prior to ICU entry or new onset hemodialysis, or broad spectrum antibiotic use. Paphitou rule 1 was same as rule 2 except for the exclusion of broad spectrum antibiotic use.

Ostrosky-Zeichner *et al*. conducted a retrospective multicenter study on 2,890 patients from 12 medical and surgical ICUs in USA and Brazil.[22] There were 88 cases of IC out of which 84 were proven, and 4 were probable. The incidence of IC the study population was 3.0%. Two groups namely; training group and validation group were formed with 75% and 25% samples respectively. Various risk factors for IC identified in were grouped together in different combinations to form a number of CPRs. The performance of these CPRs was tested using sensitivity, specificity, PPV, NPV. The best performing rule (referred as Ostrosky original CPR in this manuscript) had a capture rate of 45.5% cases. It included following criteria; antibiotic use or CVC use and at least two of additional risk factor (surgery, immunosuppressive use, pancreatitis, TPN, dialysis and steroid use).

In 2009, they published another study after comparing modifications of the above-described rule.[23] This was also a large multicenter retrospective study conducted on 597 patients. The incidence of IC in the study population was 3.7%. In this study the best performing CPR (referred as Ostrosky revised CPR in this manuscript) was described as mechanical ventilation for least 48 h and antibiotic use and CVC and at least one of the following additional risk factors: Any surgery, immunosuppressive use, pancreatitis, TPN, any dialysis, steroid use. This rule had PPV of 10% NPV 97%, specificity of 83% and sensitivity of 50%.

Shorr *et al*. developed a model to identify patients with bloodstream infection likely to be caused by *Candida* spp. at hospital admission.[24] They used a very large cohort (64,019 patients) from 176 acute care hospitals of United States. Rate of candidemia was 1.2% (738 patients). Six risk factors were identified as best discriminator of candidemia at admission (age < 65 years, temperature < 98°F or altered mental status, previous hospitalization within 30 days, mechanical ventilation at admission, cachexia and admission from other healthcare facility). The rates of candidemia increased from 0.4% to 27.3% as the number of risk factors increased from 0 to 6. A score > 1 had a sensitivity of 90.7% and specificity of 28.9%. In the same study, this model was validated on a cohort of 24,685 patients with similar findings. Area under receiver operator curves (AUROCs) of derivation cohort and validation cohort was 0.70 and 0.71 respectively.

Harrison *et al*. developed and internally validated risk prediction model for IC in a multicenter study conducted in England, Wales and Northern Ireland.[25] Out of 60,778 patients studied 383 (0.6%) were admitted with or developed invasive fungal disease. The model was calculated at admission, at 24 h and at 3 days. Different variables were used for admission, 24 h and day 3 calculations. They used C-index (equivalent to the area under receiver operating characteristic curve) to assess the discriminatory power of the model. C-index at admission was 0.705 which improved to 0.823 at 24 h and 0.835 at the end of 3 days. The performance of these models dropped in validation samples (C-index 0.655, 0.732 and 0.709 for the three models). It was worst when applied to different geographical setting.

External validation studies

External validation of Paphitou and Ostrosky CPRs was done by Hermsen *et al*. (NMC Nebraska study).[26] Playford *et al*. did external validation of Ostrosky original and Ostrosky revised CPRs in 2009.[27]

Playford *et al*. conducted a prospective multicenter study for external validation of Ostrosky original and Ostrosky revised CPRs with and without the addition of CI and CCI. The study demonstrated an improvement in PPV after addition of CCI to Ostrosky CPRs (from 5.3% to 23.8% for Ostrosky original and from 4% to 17% for Ostrosky revised). They recommended addition of colonization to the clinical risk factors for better performance of the CPRs.

Hermsen *et al*. conducted external validation study to compare Paphitou and Ostrosky's CPR. The success of CPR was assessed in the cohort which was divided into case and control group in 1:3 ratios. They also developed their own prediction rule named on the institute (NMC rule). The risk factors showing statistical significance

in the study were different from the ones described in original two studies. New factors like abdominal surgery and pre-ICU length of stay were found to be significantly related to IC while pancreatitis, surgery, diabetes and hemodialysis were not shown to be statistically significant. This difference could be because of the difference in study population. The study showed poor PPV for both Paphitou and Ostrosky rule which was between 4.1% and 5.4%. On the contrary, NPV was high for all the rules (>98%). This shows that CPRs can be helpful in excluding the patient who are not likely to benefit from antifungal therapy rather than selecting the group who will benefit from such therapy.

The CPRs performed less well in validation studies as compared to derivation studies. The difference in results could be due to the difference in the study population and clinical practices. The PPV was <5% in all studies while NPV was >97%. Therefore, present literature supports the use of CPR to identify patients who are not likely to benefit from antifungal therapy.

Models based on the basis of both microbiological and clinical parameters

Derivation study

León *et al*. 2006 conducted a prospective multicenter study on 1,699 critically ill ICU patients and developed *Candida* score.[28] Patients were divided into three groups, noncolonized noninfected (*n* = 719), colonized with *Candida* species (*n* = 883) and proven *Candida* infection (*n* = 97). Mortality rates were higher in patients with multifocal colonization (50.9%) and proven candidiasis (57.7%) as compared to 33.2% in noncolonized noninfected group. Risk factors independently associated with proven *Candida* infection as found by multivariate analysis were surgery on ICU admission, TPN, severe sepsis and multifocal colonization. For calculating *Candida* score, each risk factor was given one point except for sepsis which was given two points. A score above 2.5 had a sensitivity of 81% and specificity of 74% in predicting *Candida* infection.

External validation studies

León *et al*. conducted external validations study on 1,107 nonneutropenic ICU patients.[29] The sensitivity of *Candida* score > 3 was 77.6%, and specificity was 66.2%. They also studied utility of beta-D-glucan as a diagnostic tool for IC. A cut off value of 75 pg/ml had a sensitivity of 77.8%, however, the specificity was low (52.7%). A summary of above described studies is given in Tables 2 and 3.

Leroy *et al*. conducted external validation of *Candida* score in a prospective, observational multicenter study conducted in five ICUs of France.[30] Total 94 patients were enrolled. Rate of IC was 5.3%. They found a significant association between rising *Candida* score and IC (*P* < 0.0001). They reported a PPV of 23.8% and NPV of 100% for a *Candida* score > 3. Note that the cutoff used in this study was > 3 rather than > 3 as used in external validation study done by León *et al*.

Hall *et al*. conducted a single center retrospective study on 101 patients of severe acute pancreatitis.[31] Rate of candidal infection was 17.8%. Out of three (CI, Ostrosky CPR and *Candida* score) risk prediction models compared CI showed the best discrimination power (area under receiver operating curve of 0.79).

Conclusion

Many diverse clinical conditions have been found to be associated with risk of IC. Based on these risk factors risk prediction models have been designed. Models which include clinical as well as microbiological parameters for identifying high-risk group perform better as compared to models using clinical parameters alone. These models should be judiciously used for identifying the high-risk group and early initiation of antifungal therapy. Waiting for a positive culture report can result in a delay in initiation of therapy and increased morbidity and mortality. Issues regarding the present literature on IC are following; First many diverse clinical conditions have been found to be significantly associated with risk of IFI. These conditions have not been uniformly studied.

Second, a particular risk prediction model will be applicable only if the cohort is similar to that on which derivation study was conducted. Model developed in a particular cohort cannot be applied to all patients. Geographical variation, temporal variation, difference in antibiotic prescription policies, virulence of the most commonly colonizing *Candida* species etc., are some of the factors that can affect the model performance.

Third, broad spectrum antibiotic use and sepsis are important risk factors for IC. These factors are commonly present in many ICU patients making it difficult to design models solely based on clinical parameters. Further research should be done on models based on clinical as well as microbiological parameters (biomarkers and colonization). Fourth, most of the risk prediction models have high NPV and poor PPV. They are useful in identifying the patients less likely to benefit from antifungal therapy and thus restrict irrational use of antifungal agents.

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