

# Risk factors for candidaemia and their cumulative effect over time in a cohort of critically ill, non-neutropenic patients

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Fungal infections are increasing worldwide.<sup>1</sup> These infections are associated with increasing mortality, morbidity and cost of care, with 30–50% of *Candida* infections occurring in patients in the intensive care unit (ICU).<sup>2,3</sup> *Candida* was the third most common pathogen in ICU patients, associated with 17% of infections, in the 1-day point prevalence (Extended Prevalence of Infection in Intensive Care II) study conducted in 2009 across 75 countries.<sup>4</sup> Emergence of *Candida* infection is further complicated by rising infections with non-albicans *Candida* species, and increasing resistance to antifungal therapies.<sup>4</sup> The common species of *Candida* responsible for bloodstream infection are *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, *C. krusei* and *C. lusitanae*.

Delayed diagnosis of candidaemia may arise as a result of low clinical index of suspicion, and several studies have shown higher mortality associated with delayed initiation of appropriate antifungal therapy.<sup>5,6</sup> Untreated, candidaemia has a mortality rate of over 60%,<sup>7</sup> and even with treatment the overall mortality of candidaemia remains about 30–40%.<sup>8</sup> Conversely, indiscriminate use of antifungal prophylaxis may lead to the development of resistant species. As a consequence, it is crucially important to be able to identify patients at increased risk of invasive fungal infection who may benefit from prophylaxis. Different risk prediction rules have been developed, which fall into three broad categories: microbiological (*Candida* colonisation), clinical (including factors such as total parenteral nutrition [TPN] use, central venous access devices, surgery, immunosuppression, pancreatitis) and a combination of the two.<sup>9</sup>

In view of different health care structures and critically ill patient characteristics in Australia, and some limited evidence of difficulties translating these prediction rules to the local context,<sup>10</sup> it is not well known whether these risk factors remain predictive of candidaemia in Australian ICUs. Additionally, and perhaps more importantly, little is known about the cumulative effect over time of these risk factors with regards to candidaemia. For example, rather than simply regarding variables as binary in nature (such as TPN present or absent), it is not well understood how the number of days a patient is exposed to a risk factor (days receiving TPN) affects the risk of developing candidaemia. Our aim in this study, therefore, was to examine risk factors

## ABSTRACT

**Objectives:** There is an increasing incidence of invasive candidal infections in critically ill patients worldwide, which has prompted development of various risk prediction rules, both clinical and microbiological. To date, however, there is a lack of research into how cumulative risk factors over time affect transition to candidaemia. The aim of this study was to investigate the association of risk factor accumulation over time with candidaemia in a cohort of critically ill, non-neutropenic adult patients.

**Design, setting and participants:** A single centre, retrospective, matched case–control study in a tertiary referral intensive care unit (ICU). Data were retrieved and analysed from 108 patients (54 cases and 54 controls) admitted between 1 January 2008 and 1 August 2016.

**Main outcome measures:** Primary outcome was the association between time-dependent risk factors and candidaemia. Secondary outcomes were ICU and in-hospital mortality.

**Results:** Baseline demographic and clinical factors were similar across both groups. Time dependent univariate factors associated with candidaemia were days of mechanical ventilation, systemic antibiotic use, renal replacement therapy, central venous access, total parenteral nutrition (TPN), systemic inflammatory response syndrome, *Candida* site colonisation and number of surgeries. Factors persisting on multivariate analysis were days of TPN use (odds ratio [OR], 1.8; 95% CI, 1.02–3.22;  $P = 0.041$ ) and total *Candida* site colonisation days (OR, 2.41; 95% CI, 1.30–4.46;  $P = 0.005$ ). Mortality and length of stay (LOS) was greater in patients with candidaemia *v* control patients (ICU mortality, 15 [28%] *v* 10 [19%];  $P = 0.254$ ; hospital mortality, 26 [48%] *v* 16 [30%];  $P = 0.048$ ; ICU LOS median, 13 days [interquartile range (IQR), 5–29 days] *v* 2 days [IQR, 1–5 days];  $P < 0.001$ ; hospital LOS median, 36 days [IQR, 19–63 days] *v* 13 days [IQR, 6–28 days];  $P < 0.001$ ).

**Conclusion:** This study demonstrates an association between TPN use, *Candida* colonisation and cumulative risk over time of developing candidaemia.

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for candidaemia and their cumulative effect over time in a group of critically ill, non-neutropenic patients.

## Methods

### Study design

We conducted a single centre, retrospective, matched case–control study at the Royal Melbourne Hospital (RMH) ICU, a 24-bed tertiary metropolitan ICU that admits over 2000 patients annually. About 20 patients at RMH develop candidaemia every year, of which between 25% and 50% are admitted to the ICU. This low risk project was approved by the Melbourne Health Human Research Ethics Committee as a quality assurance project (QA2016098).

### Study population

All adult non-neutropenic patients admitted to the RMH ICU between 1 January 2008 and 1 August 2016 were eligible for inclusion, as this time period encompassed the era of electronic pathology records and was expected to yield sufficient number of patients with candidaemia for this initial exploratory study. Patients with candidaemia were identified from the RMH pathology database, with cases defined as at least one positive blood culture during ICU admission. Patients were excluded if the first positive blood culture was outside the ICU, or if they had severe neutropenia (neutrophil count < 500 cell/ $\mu$ L). Each case was matched to a control patient on four baseline characteristics: gender, diagnostic code (as defined by the Acute Physiology and Chronic Health Evaluation [APACHE] III-j ICU admission diagnosis), age  $\pm$  10%, and risk of death (derived from the APACHE III score) to within  $\pm$  10%.

### Data collection

Three databases were interrogated: RMH pathology, RMH Health Information Services and the RMH Australian Outcomes Research Tool for Intensive Care (AORTIC) database, which reports ICU data to the Australia and New Zealand Intensive Care Society Adult Patient Database. Additional information was gathered from the paper medical records. The following data were retrieved for each patient:

- ICU and hospital length of stay;
- APACHE III score;
- total *Candida* site colonisation days — a *Candida* site colonisation day is defined as each single positive *Candida* culture from any site per day (sample sites were urine, sputum, tracheal aspirate, wound swabs, surgical drains, central venous catheter tips, and faeces), with each positive culture recorded as a separate “site day”; thus, multiple positive cultures on the same day would be cumulative;
- days positive for systemic inflammatory response syndrome (SIRS), as per the Sepsis 2 definition;<sup>11</sup>
- number of surgeries and type of surgeries (including

whether abdominal bowel, abdominal non-bowel or any other surgery);

- days of TPN use;
- days of systemic antibiotic use;
- days of mechanical ventilation;
- days of renal replacement therapy;
- days and number of central venous access device (central venous line, peripherally inserted central catheter, vascath, permacath);
- days of systemic steroid administration;
- days of antifungal therapy; and
- diagnoses of pancreatitis or diabetes mellitus.

Risk factor data were collected from time of hospital admission until diagnosis of candidaemia for case patients, or until discharge from ICU for controls. Factors before hospital admission potentially modifying the risk of developing candidaemia were also identified for both cases and controls, including steroid administration, recent abdominal surgery, haemodialysis, or antifungal prophylaxis.

### Outcomes

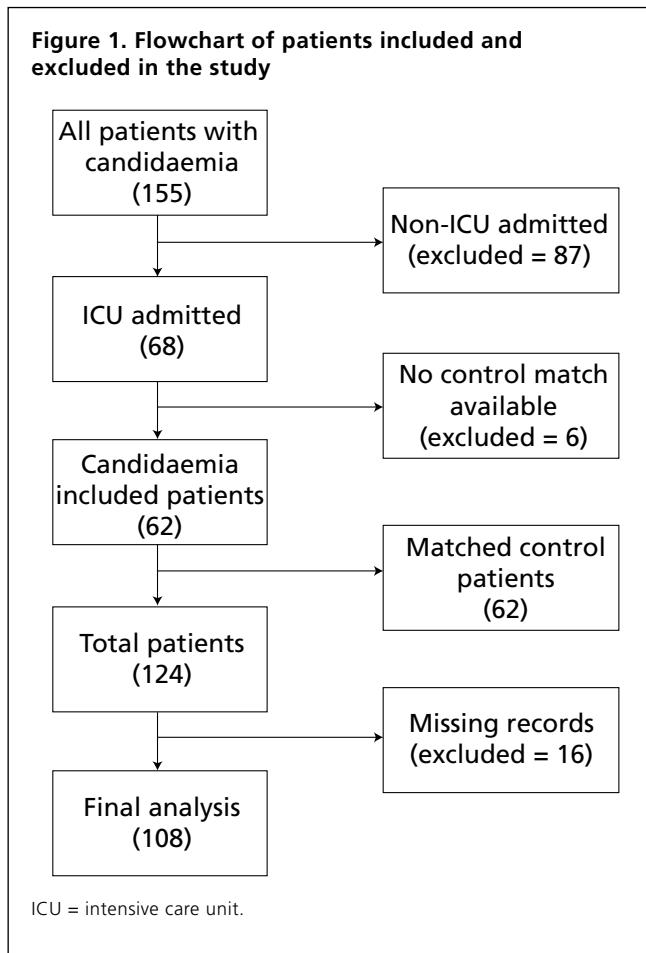
Primary outcome was the association between time-dependent risk factors and candidaemia. Secondary outcomes were in-hospital and in-ICU mortality.

### Sample size

A power calculation was performed based on prior literature informing development of risk prediction models, specifically event to variable ratios.<sup>12,13</sup> We anticipated, based on historical candidaemia rates, that between 50 and 80 case patients would be admitted over the study period. Based on expert guidance recommending event to variable ratios between five and ten for logistic regression risk prediction models, we estimated this would yield sufficient numbers for at least ten candidate predictor variables.<sup>13</sup>

### Statistical analysis

Continuous data were summarised using median (interquartile range [IQR]), and categorical data were summarised using number (percentage). Variables that accumulate over time (eg, days of TPN, mechanical ventilation, renal replacement therapy) were counted for aggregate daily totals before diagnosis of candidaemia for case patients, or until ICU discharge for controls, and summarised as categorical data using number (percentage). Binary variables (eg, diagnosis of pancreatitis, diabetes mellitus) were summarised as proportions. Univariate comparisons between cases and controls were done using either Wilcoxon or  $\chi^2$  or Fisher exact test, where applicable. Variables known from previous literature to be clinically relevant in the development of candidaemia, as well as statistically significant determinants of candidaemia on univariate analysis, were entered into a



multivariate stepwise backward elimination conditional logistic regression model after inspection for collinearity. Statistical analysis was performed using Stata 12.1 (StataCorp, College Station, TX, USA), with a two-sided  $P < 0.05$  considered for all statistical tests.

## Results

Sixty-eight case patients with candidaemia met the inclusion criteria, six cases were unable to be matched to control patients, with the remainder matched 1:1 to controls, thus providing a total of 124 patients for assessment. Four control patients and a further four cases were excluded during data collection due to missing medical records, along with their matched patients (16 in total). Thus, the final number of included patients was 108 (54 cases and 54 control patients) (Figure 1).

Consistent with the matching process, median age, APACHE III scores and gender were similar between cases and controls (Table 1). As expected, duration of ICU stay was significantly longer in candidaemia cases compared with control patients (median, 13 days [IQR, 5–29 days]  $\nu$  2 days [IQR, 1–5 days];  $P < 0.001$ ), with a median time to candidaemia of 9.5 days (IQR, 3–14.5 days). Compared

with included patients with candidaemia, the total 14 non-matched and excluded cases had higher APACHE III scores (median, 101 [IQR, 84–101]  $\nu$  79 [IQR, 60–108];  $P = 0.047$ ), and non-significantly longer ICU length of stay (median, 14 days [IQR, 5–34 days];  $P = 0.773$ ). The following variables were found on univariate analysis to be significantly more common in cases versus controls: days of mechanical ventilation, days of systemic antibiotic use, days of renal replacement therapy, total central venous access days, total number of surgeries, total *Candida* site colonisation days, and days with SIRS. There was no difference in days of systemic steroid use, antifungal therapy, pancreatitis or diabetes mellitus between groups, nor did pre-admission exposure factors differ.

Variables entered into the multivariate model included total days of renal replacement therapy, total days of TPN, total days of SIRS, total *Candida* site colonisation days, total days of central venous access, total days of antibiotic use, total number of surgeries, number of abdominal surgical procedures, diabetes, and pancreatitis. On multivariate analysis, days of TPN use and total *Candida* site colonisation days were found to remain independently associated with candidaemia. Each day of *Candida* site colonisation more than doubled the odds of developing candidaemia (odds ratio [OR], 2.41; 95% CI, 1.30–4.46;  $P = 0.005$ ) while each day of TPN use almost doubled the odds of developing candidaemia (OR, 1.8; 95% CI, 1.02–3.22;  $P = 0.041$ ) (Table 2).

Patients with candidaemia were more likely to die in hospital than control patients, with a 1.6 times higher mortality rate (48%  $\nu$  30%;  $P = 0.048$ ), while there was no difference in ICU mortality rate between the two cohorts (28%  $\nu$  19%;  $P = 0.254$ ) (Table 3).

## Discussion

### Key findings

This novel study has demonstrated a temporal association with cumulative risk factors over time and the development of candidaemia, namely days of TPN use and total *Candida* site colonisation days. This study also confirms previous findings of common risk factors associated with candidaemia: length of ICU stay, mechanical ventilation, antibiotics, renal replacement therapy, central venous access, SIRS, and surgical intervention, although we did not find a cumulative temporal effect for these variables in multivariate modelling. In univariate analysis, days of systemic steroid use, diabetes and pancreatitis were not associated with diagnosis of candidaemia in our study, but this was likely related to the small sample size. Total days of systemic antifungal use did not differ between groups, suggesting that preemptive therapy did not likely modify the risk of developing candidaemia between cases and controls.

**Table 1. Univariate risk factors for development of candidaemia**

	Candidaemia	Control	P
Total number of patients	54	54	
Age (years), median (IQR)	61 (50–72)	65 (48–73)	0.813
Female	18 (33%)	18 (33%)	1.0
Pre-admission exposure	11 (20%)	7 (13%)	0.302
APACHE III, median (IQR)	79 (60–108)	72 (58–100)	0.501
ICU LOS (days), median (IQR)	13 (5–29)	2 (1–5)	< 0.001
Hospital LOS (days), median (IQR)	36 (19–63)	13 (6–28)	< 0.001
Total days of mechanical ventilation, median (IQR)	7.5 (2–12)	2 (0–4)	< 0.001
Total days of renal replacement therapy, median (IQR)	0 (0–3)	0 (0–0)	0.005
Total days of systemic antibiotic use, median (IQR)	18 (8–27)	5.5 (2–10)	< 0.001
Total days of central venous accesses, median (IQR)	12.5 (7–19)	3 (2–6)	< 0.001
Diabetes mellitus	16 (30%)	18 (33%)	0.679
Patients with <i>Candida</i> colonisation	43 (80%)	7 (13%)	< 0.001
Total <i>Candida</i> site colonisation days, median (IQR)	2 (1–4)	0 (0–0)	< 0.001
Total days of systemic steroids, median (IQR)	0.5 (0–4)	0 (0–2)	0.263
Total days of systemic antifungal, median (IQR)	0 (0–0)	0 (0–0)	0.147
Total SIRS days, median (IQR)	10 (5–15)	3 (2–6)	< 0.001
Patients with TPN use	24 (44%)	5 (9%)	< 0.001
Total days TPN use (overall), median (IQR)	0 (0–0)	0 (0–0)	< 0.001
Total days TPN use (if used), median (IQR)	8.5 (6–11.5)	4 (3–7)	0.040
Patients with abdominal bowel surgery	16 (30%)	7 (13%)	0.034
Number of abdominal bowel surgeries, median (IQR)	0 (0–1)	0 (0–0)	0.021
Patients with abdominal non-bowel surgery	19 (35%)	9 (17%)	0.028
Number of abdominal non-bowel surgeries, median (IQR)	0 (0–1)	0 (0–0)	0.021
Patients with other surgeries	40 (74%)	31 (57%)	0.028
Number of other surgeries, median (IQR)	2 (0–4)	1 (0–1)	< 0.01
Pancreatitis	1 (2%)	1 (2%)	1.0

APACHE = Acute Physiology and Chronic Health Evaluation. ICU = intensive care unit. IQR = interquartile range. LOS = length of stay. SIRS = systemic inflammatory response syndrome. TPN = total parenteral nutrition.

### Relationship to previous studies

Various risk prediction tools for candidaemia have previously been investigated, using a combination of microbiological and clinical factors.

Microbiological risk prediction rules rely on markers of *Candida* colonisation, hypothesising a probable link between the burden of colonisation and infection. The Pittet index, also termed the colonisation index or the corrected colonisation index (CCI), was developed based on culture results of samples taken from different distinct body sites, with the colonisation index defined as non-blood distinct body sites colonised by *Candida* divided by total number of sites tested, and CCI defined as colonisation index multiplied by ratio of heavy growth distinct body sites divided by the total number of distinct body sites positive for *Candida*.<sup>14</sup>

Cut-off values of colonisation index > 0.5 and CCI > 0.4 have been found to correctly identify patients with invasive candidiasis.<sup>14</sup> More recently, *Candida* colonisation has been examined within the Australian ICU setting in a prospective cohort of 6015 non-neutropenic, critically ill patients, with throat, perineum and urine samples obtained twice weekly until discharge or death.<sup>15</sup> Sixty-three patients (86%) who developed invasive candidiasis were colonised before infection, with a median time from colonisation to invasive candidiasis of 7 days. Colonisation of two or more sites and heavy colonisation of one or more sites were significant independent risk factors for invasive candidiasis (relative risk, 2.25 and 3.7, respectively). Although multiple site colonisation with *Candida* appears to be an important risk factor for the development of invasive candidiasis, such surveillance is difficult, time consuming and has limited applicability at the bedside.<sup>15</sup>

**Table 2. Results of multivariate analysis: time-dependent risk factors for development of candidaemia in 108 patients**

	Odds ratio (95% CI)	P
Total <i>Candida</i> site colonisation days	2.41 (1.30–4.46)	0.005
Total days of total parenteral nutrition use	1.80 (1.02–3.22)	0.041

**Table 3. Patient outcomes**

	Candidaemia	Control	P
Number of patients	54	54	
ICU mortality	15 (28%)	10 (19%)	0.254
Hospital mortality	26 (48%)	16 (30%)	0.048

ICU = intensive care unit.

Clinical risk prediction tools also exist. The Paphitou and Ostrosky clinical risk prediction rules were developed from separate retrospective studies of 327 and 2890 critically ill patients, respectively, with risk factors identified including an ICU stay  $\geq 4$  days, mechanical ventilation  $\geq 48$  hours, antibiotic use, central venous catheterisation, surgery, immunosuppressive drug or steroid use, pancreatitis, TPN, dialysis or broad spectrum antibiotic use.<sup>16–18</sup> External validation of both of these prediction tools was done by Hermesen and colleagues,<sup>19</sup> demonstrating poor positive predictive values for invasive candidiasis (4.1% and 5.4%, respectively) but high negative predictive values ( $> 98\%$  for both). This suggests that these clinical prediction rules are of more utility in exclusion of patients who are unlikely to benefit from antifungal prophylaxis.

Combining microbiological and clinical factors appears to improve the performance of risk prediction tools. In a 2009 prospective multicentre Australian study of 615 critically ill patients, Playford and colleagues<sup>10</sup> found that addition of the corrected colonisation index to the Ostrosky clinical prediction rules improved the positive predictive value from 5.3% to 23.8%. The Leon (or “*Candida*”) score, perhaps the simplest bedside tool combining both factors, was developed using logistic regression examining candidate risk factors in a cohort of 1699 patients.<sup>20</sup> This score assigns points for multifocal colonisation (1 point), TPN (1 point), surgical intervention (1 point) and severe sepsis (2 points). In the original development study, a score  $> 2.5$  had sensitivity of 81% and specificity of 74% for predicting invasive *Candida* infection. External validation was subsequently performed by the same group in another study of 1107 non-neutropenic ICU

patients, demonstrating a sensitivity of 77.6% for invasive candidiasis, with a *Candida* score  $> 3$ , and specificity of 66.2%.<sup>21</sup>

Importantly, in contrast to the present study, none of the above risk prediction rules have considered the accumulation of risk factors (either clinical or microbiological colonisation) over time. In all previous risk stratification tools, and subsequent validation studies, risk factors considered are binary, either present or absent, with some (such as the colonisation index) continuous variables. The concept of accumulating risk with increased time exposed to a factor has construct validity, and is well proven in similar domains, such as the increased risk of central line-associated bloodstream infections (CLABSIs) with increased intravascular catheter dwell time.<sup>22</sup>

An interesting finding in our study was that certain factors shown to be associated with development of candidaemia in past studies did not demonstrate greater risk over time. Increasing days of central venous access, for example, was not associated with candidaemia on multivariate analysis. This may be attributed to overall very low contemporary rates of CLABSIs in ICUs in Australia and New Zealand compared with historical data, which coincided with the earlier period when these risk prediction studies were conducted. Similarly, increasing numbers of surgeries were not associated with increased risk in our multivariate model; however, this may be due to overall low numbers of surgeries for both cases and controls. Days of antifungal therapy did not modify the risk of developing candidaemia in this cohort, although given the overall median low administration rates (median 0 days in control patients during ICU stay, as well as cases before diagnosis of candidaemia), preemptive therapy was likely suboptimal.

### Clinical implications

This study contributes important insights into the development of candidaemia among critically ill, non-neutropenic patients. Our study findings imply that the longer patients remain persistently *Candida*-colonised (whether unifocal or multifocal) or remain on TPN, the greater odds of development of candidaemia. Over a prolonged ICU stay, significant numbers of critically ill patients will accumulate the various risk factors found to be associated with candidaemia. Many patients, for example, will have undergone surgery, have a central line in situ, have physiology consistent with a diagnosis of SIRS, or a requirement for renal replacement therapy. In deciding to commence empirical antifungal prophylaxis, with attendant concerns including that of development of drug resistance, it may be difficult to weigh up the relative importance of these risk factors over time. Prior literature has identified common risk factors, but the quantification of this risk over

time has not previously been investigated. Our findings imply that accumulated days of TPN and total *Candida* site colonisation days can provide clinically relevant utility for ICU clinicians at the bedside when deciding whether to commence antifungal prophylaxis.

### Strengths and limitations

Strengths of our study include a large dataset representing 8 years of admissions to the ICU, with complete data for included patients. A unique strength of our study is the consideration of accumulation of risk over time, not previously examined in the literature. We were also able to compare many different variables between cases and controls, both clinical and microbiological, including known risk factors for candidaemia and potential modifying factors. We were thus able to control for many factors that may have influenced the development of candidaemia.

There were a number of limitations in this study. First, the retrospective study design means that residual confounding factors, not identified, may persist. Second, data while patients were in the general wards before admission to intensive care may not have been as comprehensive as in the ICU (eg, observations performed episodically only every 4 hours may have missed a diagnosis of SIRS); similarly, comprehensive pre-hospitalisation data were unavailable for patients transferred from other hospitals, where there may have been accumulation of risk factors for candidaemia with subsequent contribution to outcome, although this involved only a minority of patients (eg, only five total patients had abdominal surgery before admission). Third, we did not collect data on concomitant bacterial bloodstream infection either before or after candidaemia diagnosis, which may have influenced exposure variables such as SIRS, longer mechanical ventilation, or requirement for renal replacement therapy. Fourth, some cases were excluded from analysis due to missing medical records and inability to match to control patients; broadening matching criteria to age  $\pm$  20% and risk of death  $\pm$  20% did not result in additional matches being found. Excluded cases had a longer length of stay and higher APACHE III scores; therefore, it is likely that these patients had a greater and longer duration of exposure to the variables considered. We consider it unlikely that exclusion of these patients would have decreased the magnitude of our findings; if anything, it may have biased our results away from the true association over time of these variables with candidaemia. Finally, we considered total *Candida* site colonisation days as a risk factor rather than multifocal colonisation on the same day, as used in prior literature. We believe this has more clinical utility; however, due to logistics and cost, few ICUs perform routine daily site surveillance microbiology (required for diagnosis of multifocal colonisation), but merely perform

samples as clinically indicated. As sampling for *Candida* colonisation was not protocolised, this may have possibly led to introduction of bias (patients with developing sepsis or candidaemia being prone to greater site sampling).

### Conclusion

Our results confirm data obtained in previous studies with respect to risk factors for candidaemia in non-neutropenic critically ill patients. We have also demonstrated a novel association with cumulative risk over time, particularly for TPN and *Candida* colonisation. These interesting associations require further investigation in larger studies, ideally prospective and multicentre, with more comprehensive data collection in a variety of ICU patient populations. The extremely high mortality that candidaemia imparts to the critically ill, with potential modification by timely identification of at-risk patients and provision of preemptive or prophylactic therapy, warrants such future work.

### Competing interests

None declared.

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