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Original Article

Risk factors and prognoses of invasive *Candida* infection in surgical critical ill patients with perforated peptic ulcer

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Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; AUC, area under curve; BMI, body mass index; BUN, blood urea nitrogen; Cr., creatinine; EN, established enteral nutrition; GCS, Glasgow Coma Scale; ICI, Invasive *Candida* infection; ICU, intensive care unit; POSSUM, Physiological and operative severity scores for the enumeration of mortality and morbidity; NAC, *non-albicans Candida species*; OSS, operation severity score; PPU, perforated peptic ulcer; PULP, Peptic Ulcer Perforation score; ROC, receiver operating characteristic; SOFA, Sequential Organ Failure Assessment score.

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KEYWORDS
Perforated peptic ulcer;
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Risk factors;
Prognoses

Abstract *Background:* The risk of invasive *Candida* infection (ICI) is high in patients with perforated peptic ulcer (PPU) who received laparotomy or laparoscopic surgery, but the risk factors and predictors of morbidity outcomes remain uncertain. This study aims to identify the risk factors of ICI in surgical critically ill PPU patients and to evaluate the impact on patient's outcomes.
Methods: This is a single-center, retrospective study, with a total of 170 surgical critically ill PPU patients. Thirty-seven patients were ICI present and 133 were ICI absent subjects. The differences in pulmonary complications according to invasive candidiasis were determined by the Mann—Whitney U test. Evaluation of predictors contributing to ICI and 90-day mortality was conducted by using multivariate logistic regression analysis.
Results: Candida albicans was the primary pathogen of ICI (74.29%). The infected patients had higher incidence of bacteremia ($p < 0.001$), longer intensive care unit ($p < 0.001$) and hospital ($p < 0.001$) stay, longer ventilator duration ($p < 0.001$) and increased hospital mortality ($p = 0.02$). In the multivariate analysis, serum lactate level measured at hospital admission was independently associated with the occurrence of ICI ($p = 0.03$). Liver cirrhosis ($p = 0.03$) and Sequential Organ Failure Assessment (SOFA) score ($p = 0.007$) were independently associated with the 90-day mortality.
Conclusions: Blood lactate level measured at hospital admission could be a predictor of ICI and the surgical critically ill PPU patients with liver cirrhosis and higher SOFA score are associated with poor outcomes.

Introduction

Invasive *Candida* infection (ICI) is the most commonly met severe fungal disease with a high mortality rate (40—60%) and affects more than 250,000 people every year.[1] ICI is usually categorized into three subgroups: candidemia without deep-seated or visceral involvement, candidemia with deep-seated or visceral *Candida* infection and deep-seated (visceral) candidiasis without candidemia.[2,3] Candidemia has been reported as the fourth most common bloodstream infection in the intensive care units (ICUs).[4] Mortality could reach as high as 40% even when the patients received antifungal therapy. The associated risk factors of ICI include older age, underlying diseases, invasive procedures (parenteral nutrition, intravascular catheters and dialysis), multisite *Candida* colonization, medication, upper abdominal surgery, and immunocompromised disorders.[5] Among these risk factors, patients with perforated peptic ulcer (PPU) who received abdominal surgery are considered as high-risk groups.[6] Fungi translocation or perforation through the surgical leakage could cause localized and deep-seated infection (such as peritonitis). Candidemia could occur if the patient's gastro-intestinal tract, skin or upper respiratory tract were colonized by *Candida species*. The fungi could invade and disseminate, causing systemic infection involving multiple organs.[7] This study aims to identify risk factors of ICI in surgical critically ill PPU patients and to evaluate its impact on patient outcomes.

Materials and methods

Study design and definition

This retrospective observational study was conducted from July 2008 to January 2017, in the surgical intensive care units of China Medical University and Hospital (CMUH) in Taichung, Taiwan. We recruited critically ill PPU patients who received surgery and needed ICU care. To reduce the confounding effect of different surgery types for PPU, we only included patients who underwent a simple closure procedure and excluded all other types of surgery such as gastrectomy with B-II anastomosis. ICI is defined by the identification of a new incident of fungemia or fungal peritonitis[8] and these patients would receive antifungal therapy. Meanwhile, a vigorous search of infection sources was performed (e.g. computer tomography scan for intra-abdominal infection or abscess formation). Once the diagnosis was established, a percutaneous drainage procedure or surgery was implemented in addition to antifungal therapy. The use of preemptive antifungal agents was depended on the clinician's judgment.

Data collection

The studied subjects were admitted via the emergency department. Patients' baseline characteristics, namely age, gender, body mass index (BMI), classification of peptic ulcer diseases, comorbidities, laboratory features, including blood urea nitrogen (BUN), creatinine (Cr.), serum lactate, glucose, albumin level were collected. Clinical scores, including Acute Physiology and Chronic Health Evaluation II (APACHE II), Glasgow Coma Scale (GCS), Sequential Organ Failure Assessment (SOFA) score, Physiological and operative severity scores for the enumeration of mortality and morbidity (POSSUM) score, including physiological score and operation severity score and microbiological data were recorded. All the above mentioned measurements of laboratory data, including serum lactate level, were received upon hospital admission and prior to emergent surgery. Outcome assessment was made at

follow-up for 90-day mortality and in-hospital mortality. Other associated outcome parameters include vasopressor use, blood transfusion after surgery, occurrence of pneumonia, reintubation, emergence of bacteremia, days of established enteral nutrition (EN) after the operation, total ventilator use days and the length of stay were also organized for analysis.

Statistical analyses

Data were analyzed using IBM SPSS statistics V20.0.0 software (SPSS, Chicago, IL, USA). Continuous variables were expressed as the mean ± SE and categorical values were expressed as percentages. Comparability of groups was analyzed by the Mann—Whitney U test, the chi-square test, or the Fisher exact test, as suitable. Kaplan—Meier survival curves were employed to assess the time of mortality and were compared using the log-rank test. The comparison of risk factors for fungus-infected and 90-day mortality with PPU patients was performed using univariate analysis and if p-value < 0.05, further using multivariate logistic regression. $p < 0.05$ was considered statistically different.

Results

Patient characteristics

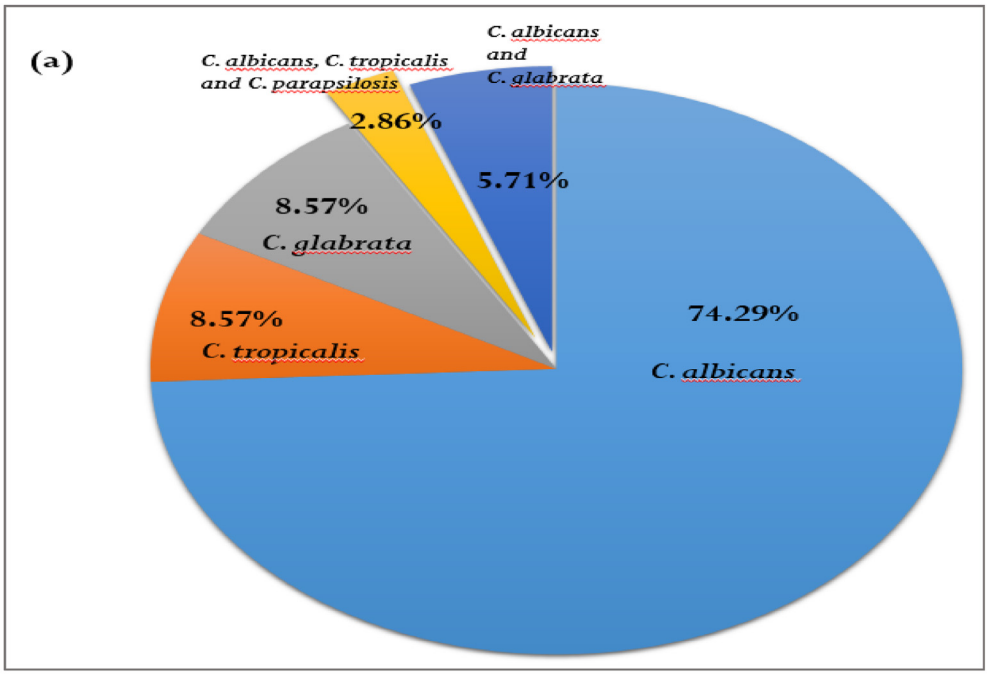
From 2008 July to 2017 January, a total of 193 surgical critically ill PPU patients were recruited and screened. Among these subjects, 23 patients were excluded because of the following reasons. Four patients were excluded because they refused operations, 4 patients were not eligible because they received gastrectomy operations and

Table 1 Clinical and demographic characteristics of PPU patients with and without invasive *Candida* infection (ICI).

Characteristics	ICI (n = 37)	Non-ICI (n = 133)	p value
Age (yrs)	70.19 ± 2.33	70.36 ± 1.36	0.78
Male gender	23 (62.2%)	83 (62.4%)	0.98
BMI	23.29 ± 1.00	22.61 ± 0.41	1.00
Classification of peptic ulcer diseases			
Gastric ulcer	18 (51.4%)	63 (47.4%)	0.67
Duodenal ulcer	17 (48.6%)	70 (52.6%)	0.67
Receipt of preemptive antifungal therapy	11 (29.7%)	10 (7.5%)	0.001[a]
Underlying disease			
Hypertension	16 (43.2%)	56 (42.1%)	0.90
Diabetes mellitus	16 (43.2%)	51 (38.3%)	0.59
Heart-Lung disease	11 (29.7%)	45 (33.8%)	0.64
Liver cirrhosis	5 (13.5%)	18 (13.5%)	1.00
Chronic kidney disease	9 (24.3%)	27 (20.3%)	0.60
Hemodialysis	3 (8.1%)	7 (5.3%)	0.46
Preoperative laboratory features			
BUN (mg/dL)	47.14 ± 5.93	39.54 ± 2.38	0.35
Creatinine (mg/dL)	2.28 ± 0.34	1.90 ± 0.12	0.30
Blood sugar (mg/dL)	189.43 ± 20.53	178.25 ± 8.59	0.77
Lactate (mg/dL)	57.50 ± 8.46	35.17 ± 4.04	0.003[a]
Albumin (g/dL)	2.45 ± 0.09	2.42 ± 0.07	0.60
Enteral nutrition			
Pre-pyloric feeding	12 (32.4%)	55 (41.4%)	0.33
Post-pyloric feeding	25 (67.6%)	78 (58.6%)	0.33
Score			
Apache II (in ICU)	21.51 ± 1.53	19.44 ± 0.74	0.33
Apache II (leave ICU)	17.38 ± 2.17	13.52 ± 0.85	0.28
GCS (in ICU)	9.81 ± 0.69	10.05 ± 0.34	0.91
GCS (leave ICU)	10.24 ± 0.78	12.02 ± 0.35	0.02[a]
SOFA score	6.11 ± 0.79	4.15 ± 0.35	0.02[a]
POSSUM score	42.41 ± 1.96	38.04 ± 0.84	0.08
physiological score	29.43 ± 1.55	27.4 ± 0.65	0.46
operation severity score	12.97 ± 0.77	10.66 ± 0.38	0.002[a]

PPU, perforated peptic ulcer; ICI, invasive *Candida* infection; BMI, body mass index; BUN, blood urea nitrogen; Apache II, Acute Physiology and Chronic Health Evaluation II; GCS, Glasgow Coma Scale; SOFA, Sequential Organ Failure Assessment score; POSSUM, Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity score. Discrete variables are expressed as counts (%) and continuous variables as mean ± SE. [a] p-value < 0.05 was considered significant between groups.

15 patients were precluded because of repeat admission to ICU. As a result, a total of 170 patients were enrolled in this study. In these recruited subjects, 37 patients developed ICI and 133 patients did not develop ICI; their clinical and demographic details are summarized in Table 1. There's a slightly higher proportion of patients who received preemptive antifungal therapy had a prior diagnosis of fungal infection than those without fungal infected subjects (29.7% vs. 7.5%, respectively; $p = 0.001$). The level of serum lactate obtained at admission was also higher in patients with fungal infection (57.50 ± 8.46 vs. 35.17 ± 4.04, respectively; $p = 0.003$). We stratified clinical scores into those that were developed non-specifically for general surgery (APACH II, GCS, and SOFA scores), and those that were used to assess morbidity and mortality for general surgery (POSSUM concept includes physiological and operation severity score). The results show that GCS (leave ICU) was significantly lower when ICI was present compared with when ICI was absent (10.24 ± 0.78 vs. 12.02 ± 0.35, respectively; $p = 0.02$). Moreover, SOFA score (6.11 ± 0.79 vs. 4.15 ± 0.35, respectively; $p = 0.02$) and OSS (12.97 ± 0.77 vs.



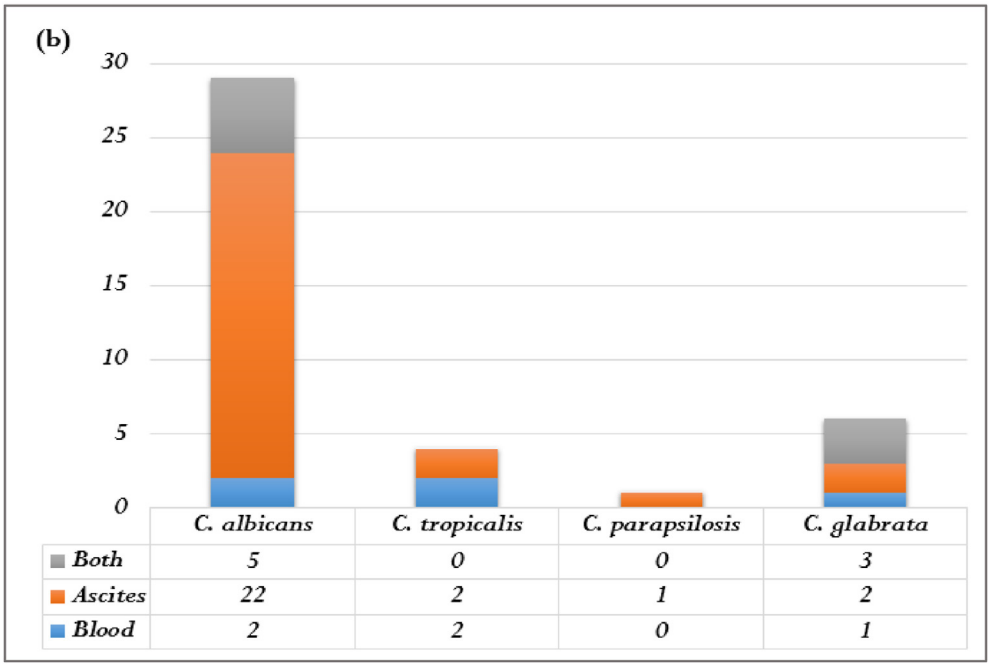


Figure 1. *Candida species* yielded from the ascites and blood cultures. (a) The percentage of *Candidal species* isolated from patients with ICI. (b) The proportion of each *Candidal species* cultured from positive isolates in patients are classified as infected with Candida.

10.66 ± 0.38, respectively; $p = 0.002$) were also remarkably higher in ICI patients.

Microbiological data

The distribution and isolation of *Candida species* in patients with ICI are summarized in Fig. 1. *Candida albicans* was the most prevalent fungal species (74.29%), followed by *Candida glabrata* (8.57%) and *Candida tropicalis* (8.57%). Among these patients, 8.57% had mixed fungal infections including *C. albicans* and *non-albicans Candida species* (NAC) (Fig. 1a). Infection foci are categorized into ascites, blood, and combined both sites. Peritoneal infection was the main source of *C. albicans* infection. (76%); *C. tropicalis* was isolated in both ascites and blood. *Candida parapsilosis* was identified in one patient with fungal infection from ascites; *C. glabrata* infection source was from combined of both sites. (50%; Fig. 1b).

Outcome and survival comparisons between ICI present and absent patients

The prognosis of PPU patients with ICI is summarized in Table 2. In the post-operated infected patient, higher proportion of patients with ICI needed vasopressor (66.7% vs. 34.6%, respectively; $p = 0.001$) and blood transfusion (2.49 ± 0.76 vs. 1.90 ± 0.41, respectively; $p = 0.04$). This implies that these patients had unfavorable hemodynamic condition. We also discovered that bacteremia was more common in ICI subjects with Gram-negative (29.7% vs. 10.5%, respectively; $p = 0.004$) and Gram-positive and negative mixed bacterial infection (32.4% vs. 13.5%, respectively; $p = 0.008$). PPU patients with ICI had longer ICU (14.65 ± 1.60 vs. 9.57 ± 0.98, respectively; $p < 0.001$) and hospital (38.17 ± 4.58 vs. 22.54 ± 1.85, respectively; $p < 0.001$) stays, ventilator use duration (24.54 ± 3.53 vs. 13.12 ± 1.66, respectively; $p < 0.001$) and higher 90-day mortality (37.8% vs. 18.0%, respectively; $p = 0.01$) and in-hospital mortality (37.8% vs. 18.8%, respectively; $p = 0.02$). Kaplan–Meier curve showed that PPU patients had higher 90-day mortality when ICI was present ($p = 0.02$; Fig. 2).

Risk factors analysis for ICI and 90-day mortality among surgical critical ill patients with PPU

In the multivariate analysis, serum lactate level measured at hospital admission was independently associated with the occurrence of ICI (OR 1.012; 95% CI, 1.001–1.022; $p = 0.03$) in the patients of PPU (Table 3a). Moreover, liver cirrhosis (OR 5.078; 95% CI, 1.195–21.569; $p = 0.03$) and SOFA score (OR 1.250; 95% CI, 1.063–1.470; $p = 0.007$) were independently associated with the 90-day mortality in surgical critically ill patients with PPU (Table 3b).

Discussion

In our study, *C. albicans* was the major pathogen for patients with ICI and these infected patients had prolonged stays in ICU and in hospital, a lengthy ventilator use and a higher mortality rate. Serum lactate level measured at the time of hospital admission was identified as a significant risk factor for PPU patients to be infected with ICI, and liver cirrhosis and poor SOFA score were important risk factors for 90-day mortality of surgical PPU patients in critical status.

The days of established enteral nutrition support after the operation were not statistically different between fungal infected and non-fungal infected PPU patients. This implies that the operation success rate was similar in

Table 2 Outcome in PPU patients with and without ICI.

Characteristics	ICI (n = 37)	Non-ICI (n = 133)	*p* value
Vasopressor use (post-OP)	24 (66.7%)	46 (34.6%)	0.001[a]
Blood transfusion (U)	2.49 ± 0.76	1.90 ± 0.41	0.04[a]
Established EN after the operation (days)	3.86 ± 0.50	3.74 ± 0.31	0.56
Pulmonary complication			
Re-intubation	4 (10.8%)	6 (4.5%)	0.23
Pneumonia	13 (35.1%)	27 (20.3%)	0.06
Bacteremia	27 (73.0%)	46 (34.6%)	<0.001[a]
G (+) bacterial	4 (10.8%)	14 (10.5%)	0.96
G (−) bacterial	11 (29.7%)	14 (10.5%)	0.004[a]
Both	12 (32.4%)	18 (13.5%)	0.008[a]
Duration (days)			
ICU duration	14.65 ± 1.60	9.57 ± 0.98	<0.001[a]
Hospital duration	38.17 ± 4.58	22.54 ± 1.85	<0.001[a]
Ventilator duration	24.54 ± 3.53	13.12 ± 1.66	<0.001[a]
In-hospital mortality	14 (37.8%)	25 (18.8%)	0.02[a]
90-day mortality	14 (37.8%)	24 (18.0%)	0.01[a]

ICI, invasive *Candida* infection; EN, enteral nutrition; Discrete variables are expressed as counts (%) and continuous variables as mean ± SE. [a] *p*-value < 0.05 was considered significant between groups.

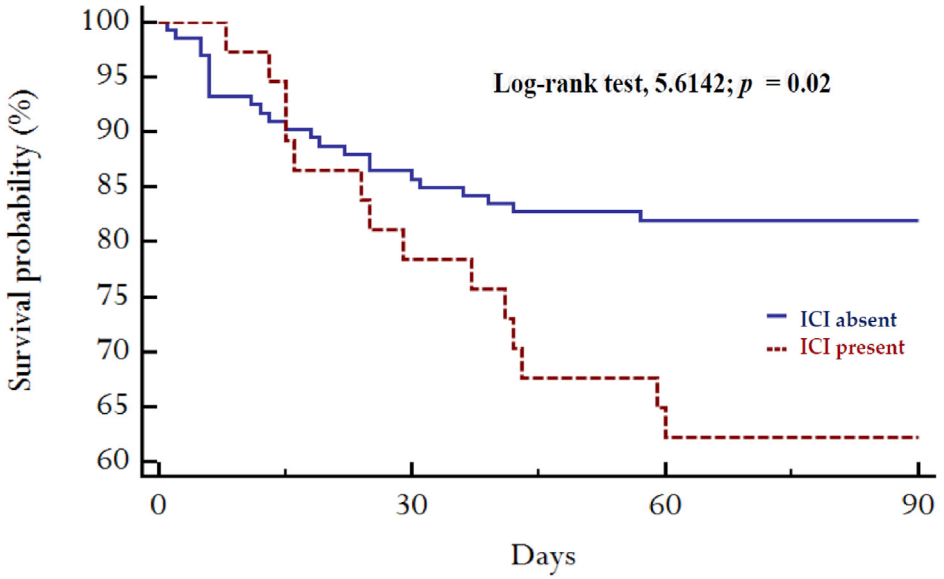


Figure 2. Kaplan–Meier estimates of survival within 90-day of PPU subjects. Patients with ICI had a lower survival probability on 90-day after the operation (p = 0.02).

both groups. Serum lactate level measured at hospital admission was independently associated with the occurrence of ICI in multivariate analysis. Lactate is the final product of pyruvate metabolism by the enzyme lactate dehydrogenase[9–11] and in Surviving Sepsis Campaign, it is an important indicator of the adequacy of resuscitation in the management of sepsis.[12] Moreover, lactate is also a mortality predictor and could be used to determine the presence of organ failure, the severity of sepsis and hospital duration in patients with sepsis.[13–15] V. S. Budipramana et al., reported that the level of lactate checked 1 h prior to surgery could be used as a predictor of

Table 3 Results of multivariate logistic regression analysis of risk factors for (a) ICI; (b) 90-day mortality with critically ill PPU patients.

(a)

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Lactate (mg/dL)	1.01 (1.00–1.02)	0.02	1.01 (1.00–1.02)[a]	0.03
POSSUM score	1.04 (1.01–1.08)	0.03		
operative severity score	1.11 (1.03–1.21)	0.01		
SOFA score	1.11 (1.02–1.22)	0.02		

(b)

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Liver cirrhosis	2.62 (1.03–6.63)	0.04	5.08 (1.20–21.57)	0.03
Lactate (mg/dL)	1.02 (1.01–1.03)	0.002		
APACHE II (in ICU)	1.10 (1.05–1.15)	<0.001		
GCS (in ICU)	0.85 (0.77–0.93)	0.001		
POSSUM score	1.05 (1.01–1.10)	0.02		
SOFA score	1.32 (1.18–1.47)	<0.001	1.25 (1.06–1.47)	0.007
Bacteremia	2.90 (1.38–6.13)	0.005		
Invasive Candida infection	2.76 (1.25–6.14)	0.01		
Shock	4.59 (2.06–10.25)	<0.001		

[a] 1.012 (1.001–1.022).

OR, odds ratio; CI, confidence interval. *p*-value < 0.05 was considered significant.

reperforation after repairing gastric perforation. In their study, lactate level in the reperforation group was higher than non-reperforation subjects (3.74 mmol/L vs. 2.60 mmol/L, respectively; $p < 0.001$), and the area under curve (AUC) for lactate was 0.902 when the cut-off level was set at 3.35 mmol/L[16] The study also demonstrated the importance of serum lactate levels in reperforated patients. In our study, the mean level of serum lactate was higher than 3.35 mmol/L at hospital admission (6.38 mmol/L vs. 3.90 mmol/L, respectively; $p = 0.003$) in PPU patients whether if ICI was present. However, the reperforated rate was not analyzed in our recruited subjects so we could not verify their results. Instead, the constructed receiver operating characteristic (ROC) curves were used to determine the prediction accuracy of lactate levels for ICI and in-hospital mortality. With a cut-off level of 2.93 and 3.04 mmol/L, the AUC for lactate was 0.68 and 0.67 (data not shown). Additional studies are required to determine the clinical application of lactate in PPU patients.

The SOFA score is widely applied in defining the characteristics of sepsis syndrome and predicted ICU mortality.[17–20] POSSUM score was first proposed by Copeland et al., in 1991. The scoring system was applied to evaluate the risk of surgery which involves physiological score and operation severity score, and for the assessment of morbidity and mortality risk.[21] In our study, the ICI group had a higher SOFA score and operation severity score. These results appear to correspond with high in-hospital mortality in these patients. The multivariate logistic regression test also demonstrated that the SOFA score was an imperative predictor for 90-days mortality in our PPU patients. However, the POSSUM score showed no difference between these groups. Possibly, the scoring system is a combination of physiological factors and the operation specificity might be mitigated. Furthermore, in the low risk scenarios, the importance of mortality and morbidity risk assessment may be overestimated by POSSUM.[22,23] Further studies are needed for evaluating the application of POSSUM score focusing on PPU patients with ICI.

Several studies have shown that LC was an important comorbid risk factor and associated with unfavorable surgical outcomes after abdominal surgery.[24–27] Choi et al., found that impaired liver function was the most important factor predicting morbidity, mortality and associated severe complications in PPU patients.[28] Li et al., reported that LC was highly related to a longer hospital stay in univariate analysis for PPU subjects.[29] L. H–B et al., proved that patients with chronic liver disease, particularly LC, had an increased risk of 90-day mortality after hospital admission for peptic ulcer bleeding.[30] This association was probably because patients with liver disease are susceptible to excessive bleeding and accelerated intravascular coagulation.[31] These patients are more likely to develop hypovolemic shock, sepsis, multi-organ failure and are associated with increased mortality risk.[32–34] Besides, LC is the most important risk stratification comorbidity in the Peptic Ulcer Perforation (PULP) score, which was developed to predict mortality following surgical treatment for PPU.[35] In our surgical critically ill subjects with PPU, LC was also an important risk factor for predicting 90-days mortality.

C. albicans infection was commonly occurred in patients indwelled with peritoneal drainage tubes or subclavian vein catheters.[5] Hall, A.M et al., found that the infection source of *C. albicans* was mostly identified from the abdominal fluid samples in patients with severe acute pancreatitis.[36] Bassetti, M et al. studied intra-abdominal candidiasis and found that *C. albicans* was the most frequently isolated pathogen (64%), followed by *C. glabrata* (16%); among these patients, 69% had concomitant bacterial infections, and the ICU mortality rate was 38.9%.[37] We have similar reports in this study; ascites was the main source of *C. albicans* infection and concomitant bacterial and candida infections increased in-hospital mortality.

Previous studies revealed that patient mortality would increase if *C. albican*s and *Escherichia coli* were co-pathogens.[38,39] Sawyer et al. disclosed that in the pathogenesis of mixed fungal and bacterial infections, *C.albicans* might play a major role. They found that a synergistic effect on mortality rates was present when fungal superinfection appeared in patients with *E. coli* and *B. fragilis* infection.[40] Brotfain, E et al., reported that there was a higher frequency of concomitant *coagulase negative Staphylococcus* spp. and *Streptococcus constellatus* infection in the patients with invasive fungal infection.[41] In our results, patients with ICI had a higher incidence of bacteremia; mainly with gram negative bacteria followed by combined gram-positive and -negative bacteria.

There are several limitations in our study. First, the design of this study was retrospective and the use of preemptive antifungal agents was based on the clinician's discretion. Therefore, the effect of preemptive antifungal treatment on the outcome of fungal infection remains to be determined. Second, there was a lack of exact time frame of surgery, ICU admission, and the onset of invasive candida infection, which might prevent drawing a comprehensive deduction. Additionally, the role of the definitive management including adequate antifungal therapy and infection source control (e.g. percutaneous drainage procedure or surgery) was difficult to be evaluated. A large-scale, prospective study is needed for further confirmation.

Conclusions

In conclusion, surgical critically ill PPU patients with ICI are considered as the high-risk group and these infected patients had prolonged stays in ICU and in hospital, a lengthy ventilator use and a higher mortality rate. Serum lactate level measured at hospital admission is a possible predictor of ICI, and comorbidity with liver cirrhosis and higher SOFA score were important mortality risk factors in surgical PPU subjects.

Institutional review board statement

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Research Ethics Committee at China Medical University and Hospital (CMUH106-REC3-085; 24 July 2017).

Declaration of competing interest

The authors declare no conflict of interest.

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