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ORIGINAL ARTICLE

Effect of empirical antifungal treatment on mortality in non-neutropenic critically ill patients: a propensity-matched retrospective cohort study

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Abstract

To evaluate the effect of empirical antifungal treatment (EAFT) on mortality in critically ill patients without invasive fungal infections (IFIs). This was a single-center propensity score–matched retrospective cohort study involving non-transplanted, non-neutropenic critically ill patients with risk factors for invasive candidiasis (IC) in the absence of IFIs. We compared all-cause hospital mortality and infection-attributable hospital mortality in patients who was given EAFT for suspected IC as the cohort group and those without any systemic antifungal agents as the control group. Among 640 eligible patients, 177 patients given EAFT and 177 control patients were included in the analyses. As compared with controls, EAFT was not associated with the lower risks of all-cause hospital mortality [odds ratio (OR), 0.911; 95% CI, 0.541–1.531; $P=0.724$] or infection-attributable hospital mortality (OR, 1.149; 95% CI, 0.632–2.092; $P=0.648$). EAFT showed no benefit of improvement of infection at discharge, duration of mechanical ventilation, and antibiotic-free days. However, the later initiation of EAFT was associated with higher risks of all-cause hospital mortality (OR, 1.039; 95% CI, 1.003 to 1.076; $P=0.034$) and infection-attributable hospital mortality (OR, 1.046; 95% CI, 1.009 to 1.085; $P=0.015$) in patients with suspected IC. This effect was also found in infection-attributable hospital mortality (OR, 1.042; 95% CI, 1.005 to 1.081; $P=0.027$) in septic patients with suspected IC. EAFT failed to decrease hospital mortality in non-neutropenic critically ill patients without IFIs. The timing may be critical for EAFT to improve mortality in these patients with suspected IC. ChiCTR2000038811, registered on Oct 3, 2020.

Keywords Empirical antifungal treatment · Hospital mortality · Intensive care · Propensity score matching

Introduction

Invasive candidiasis (IC) is the most common invasive fungal infection (IFI) in hospitals, where the incidence of IC is rising in critically ill patients in recent years with a reported incidence of 7.07 episodes per 1000 ICU admissions in Europe in 2015 and 2016 [1, 2]. Candidemia is the major infective pattern of IC and is associated with high mortality, long hospital stay, and high resource use [3]. Successful IC management depends on timely administration of appropriate antifungal agents and adequate control of the infection source [4]. Delayed antifungal treatment is associated with a significantly higher mortality in patients with candidemia particularly those with concomitant septic shock [4, 5]. However, the diagnosis of IC is very difficult for critically ill patients due to the nonspecific clinical signs, insufficient accuracy of culture method, and invasive

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biopsy [6, 7]. Therefore, antifungal agents have been usually used as an empirical therapy for patients with fever with unknown reasons or unsolved sepsis or septic shock with risk factors for IC as recommended by the current guideline [8].

However, some risk factors of IC have been identified such as major abdominal surgery, necrotizing pancreatitis, immunosuppression, use of broad-spectrum antibiotics, central vascular catheters, and *Candida* colonization [9], which are nonspecific and very common in critically ill patients. It may result in the high consumption and expenditure for costly antifungal agents and the risk of concomitant increase in the prevalence of fungal resistance [10, 11]. Therefore, clarifying the outcome benefits of empirical antifungal treatment (EAFT) would be critical for optimal use of antifungal agents in intensive care unit (ICU) patients with risk factors of IC. The initiation of antifungal treatment would benefit the patients with bone marrow transplantation or neutropenia with suspected IFIs before proven IFIs were identified [12, 13]. For those ICU patients who were diagnosed with IC, the earlier use of empirical antifungal agents before the diagnosis would result in better outcome. However, most ICU patients with clinical infection were non-transplanted and non-neutropenic, and most ICU patients who received systemic antifungal therapy had no proven IFIs as demonstrated by a multicenter cross-sectional study [14]. The previously reported randomized controlled trials have found that the empirical antifungal treatment had no beneficial effect on mortality and other outcomes in non-transplanted, non-neutropenic ICU patients at high risk for IC [15, 16].

However, treatment in the randomized controlled trial would be less tailored to the individual patients than the observational study, and the randomized controlled trial reflects daily clinical practice less closely than the observational study [17], while the EAFT should be individualized for each critically ill patient at risk for IC in the clinical practice. Propensity score matching is a well-established method for estimating causal treatment effects in the observational study [18, 19]. Then, the observational study using propensity score matching could provide important additional evidence of EAFT's effect on outcomes in ICU patients in the daily clinical practice to the previously reported randomized controlled trials. To our knowledge, few observational studies used a propensity score–matched design to assess the effect of EAFT on mortality in ICU patients. Therefore, we conducted a single-center propensity score–matched retrospective cohort study aimed to identify the effect of EAFT on hospital mortality in non-transplanted, non-neutropenic critically ill patients with risk factors for IC in the absence of proven IFIs. This study also aimed to assess the feasibility of larger studies as a pilot study.

Materials and methods

Patient selection

All adult patients admitted to the participating ICU in a teaching hospital with complete medical records between Jan 2017 and Jan 2022 were eligible to be screened for entry into this cohort study. The ICU served a mixed population of medical, surgical, trauma, and neurologic patients. Inclusion criteria were (1) critically ill patients with clinical signs of infection according to the definitions of the International Sepsis Forum [20] such as fever, leukocytosis, and purulent fluid; (2) at least one risk factor of IC; (3) the absence of proven IFIs (the proven IFI was diagnosed according to the criteria from the European Organization for Research and Treatment of Cancer and the Mycoses Study Group [21]); (4) days in ICU for more than 3 days; and (5) age ≥ 18 years.

The risk factors of IC were as follows: (1) malignant tumor of solid organ; (2) administration of immunosuppressive agents, such as prolonged use of corticosteroids at a daily dose of more than 0.3 mg/kg prednisone or equivalent for at least 3 weeks, cancer chemotherapy, cancer radiotherapy, tumor necrosis factor therapy, tacrolimus, and cyclosporine; (3) acute necrotizing pancreatitis; (4) abdominal surgery; (5) gastrointestinal perforation or leak; (6) the use of broad-spectrum antibiotics for more than 4 days within 7 days prior to enrollment; (7) the presence of central vascular catheters; (8) total parenteral nutrition; (9) mechanical ventilation; (10) hemodialysis or hemofiltration; (11) diabetes mellitus; and (12) multiple *Candida* colonization [9].

Exclusion criteria were (1) administration of systemic antifungal treatment for more than 72 h during the week prior to enrollment; (2) prescription of antifungal agents for prophylactics or suspected mold infection (one or more *Aspergillus* species–positive cultures from non-sterile sites or typical radiographic manifestation of mold infection) or suspected pneumocystis infection (typical radiographic manifestation of pneumocystis infection) during inpatient hospitalization; (3) severe multiple organ failure, with an Acute Physiology and Chronic Health Evaluation (APACHE) II score ≥ 35 at enrollment; (4) neutrophil count of less than 500/mm^3 longer than 1 week; (5) previous solid organ or bone marrow transplantation or hematological malignancy; and (6) acquired immune deficiency syndrome and human immunodeficiency virus carriers. The requirement of informed consent was waived for this study by the Ethics Committee of Shandong Provincial Hospital (protocol SWYX:NO 2020–126) due to the retrospective nature of this study.

Study design

This clinical trial was designed as a single-center retrospective observational cohort study. Eligible patients were divided into two cohorts based on their treatment history of EAFT. Patients were included in the EAFT cohort if they were prescribed any intravenous or oral dose of antifungal agents for suspected IC for at least 3 days in the hospital. On the day when the patients in the EAFT cohort were administrated the first intravenous or oral dose of antifungal drugs, the patients would be enrolled in this study. Patients were included in the control cohort if they did not receive any intravenous or oral dose of antifungal agents in the hospital. On the day when the patients in the control cohort were administrated the first dose of antibiotics or antiviral drugs after the onset of signs of clinical infection, the patients would be enrolled in this study. The observational period of this retrospective cohort study continued until discharge from the hospital or death.

Outcomes

The primary outcome variable of this cohort study was all-cause hospital mortality. The secondary outcome variables were infection-attributable hospital mortality, the proportion of patients with improvement of infection at discharge, the proportion of patients with duration of mechanical ventilation more than 7 days during the study period, the proportion of patients with days of antibiotic-free more than 3 days during the study period, the proportion of patients with ICU length of stay more than 10 days, and the proportion of patients with hospital length of stay after ICU more than 7 days.

Potential covariates

The information on the following variables as potential covariates were obtained retrospectively from the patients' medical records: age, gender, admission category (medical, elective surgical, or emergency surgical), diagnosis at ICU admission, Charlson Comorbidity scores, APACHE II scores (range 0–71, with higher scores indicating more severe illness), and Sequential Organ Failure Assessment (SOFA) scores (range 0–24, with higher scores indicating worse outcome) within 24 h after enrollment. The presence or absence of every single risk factor of IC as presented above and *Candida* score at enrollment were also recorded. Colonization of *Candida* was considered as multiple site when *Candida* spp. was simultaneously isolated from at least two different non-sterile sites. *Candida* score (range, 0–5) items are surgery (1 point), sepsis (2 points), multiple sites positive with *Candida* species (1 point), and parenteral nutrition (1 point). The clinical situation assessment (presence or absence of sepsis or septic shock at enrollment, presence or absence of source control, (1,3)-β-D-glucan test positive or negative), and empirical antifungal agents (the timing of initiation and the total duration) were collected too.

Definitions

(1) EAFT was defined as administration of any intravenous or oral dose of antifungal agents in patients with clinical infection suspected with IC in the absence of proven IFIs. The EAFT in this study included antifungal treatment triggered by microbiological evidence of *Candida* spp. without definitive microbiological proof, e.g., positive (1,3)-β-D-glucan test or triggered by signs and symptoms of clinical infection in patients at risk for IC. EAFT was prescribed at the discretion of the ICU physicians, and it was not possible to clarify the physicians' discretion because the data were collected and analyzed retrospectively. (2) The timing of initiation of EAFT was determined from the interval between the first prescription of antibiotics or antiviral drugs for the onset of clinical signs of infection and the first administration of the intravenous or oral dose of antifungal agents. (3) Source control was defined as removal of central vein catheters or documented surgical, radiologic, or endoscopic drainage of abscesses or other fluid collections suspected or proven to be the source of infection. (4) Sepsis and septic shock were defined using current criteria of the Third International Consensus Definitions for Sepsis and Septic Shock [22]. Patients with known or suspected infection with SOFA scores increasing more than 2 points can be diagnosed with sepsis. Patients with septic shock can be identified with a clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain a mean arterial pressure of 65 mmHg or higher and serum lactate level more than 2 mmol/L (> 18 mg/dL) in the absence of hypovolemia. (5) The improvement of infection was defined as elimination or relief of the clinical signs of infection, accompanying radiographic resolution, or improvement and discontinuation of antibiotics, antiviral drugs, and antifungal agents or de-escalation of antibiotics at the same period. (6) The infection-attributable mortality in hospital was defined as death within 3 days after the onset of clinical infection, persistent infection, or infectious complications until mortality in hospital [23].

Statistical analysis

Given the differences in the baseline characteristics of the eligible patients in the two groups (Table 1), propensity score matching was used to identify a cohort of participants with similar baseline characteristics. Matching was conducted using a 1:1 nearest neighbor matching without replacement, with a caliper width equal to 0.2 of the standard deviation of the logit of the propensity score [24]. The baseline variables were listed in Table 1. Standardized difference was calculated for every baseline variable before and after matching to evaluate pre-match imbalance and

Table 1 Baseline patient characteristics before and after propensity score matching

Characteristics	Before matching				After matching			
	EAFT group ($n=236$)	Control group ($n=404$)	*P* value	SD %	EAFT group ($n=177$)	Control group ($n=177$)	*P* value	SD %
Age (years) (median, IQR)	65 (50–76)	63 (50–74)	0.401	1.6	65 (49–75)	63 (50–73)	0.497	1.6
Sex (M/F)	138/98	149/155	0.430	6.4	106/71	106/71	NS	0
APACHE II scores at enrollment (median, IQR)	20 (16–26)	18 (14–24)	< 0.001	35.6	20 (16–25)	21 (15–27)	0.591	3.7
SOFA scores at enrollment (median, IQR)	6 (4–9)	6 (4–8)	0.039	18	6 (4–9)	7 (5–9)	0.418	7.8
Charlson Comorbidity Scores at enrollment (median, IQR)	5 (3–8)	5 (3–7)	0.296	7.2	5 (3–7)	5 (3–7)	0.892	3.2
Admission group (no. (%))			< 0.001	32.6			0.399	3.2
Medical	158 (66.9)	199 (49.3)			108 (66.7)	109 (61.6)		
Elective surgical	47 (19.9)	129(31.9)			34 (19.2)	48 (27.1)		
Emergency surgical	31 (13.1)	76 (18.8)			25 (14.1)	21 (11.3)		
Main reason for ICU admission (no. (%))			0.002	13.0			0.223	9.3
Respiratory disease	80 (33.9)	88 (21.8)			56 (31.6)	49 (27.7)		
Cardiovascular disease	20 (8.5)	55 (13.6)			18 (10.2)	16 (9.0)		
Gastrointestinal disease	67 (28.4)	123 (30.4)			49 (27.7)	46 (26.0)		
Neurologic disease	42 (17.8)	84 (20.8)			33 (18.6)	45 (25.4)		
Urogenital disease	5 (2.1)	16 (4.0)			5 (2.8)	7 (4.0)		
Trauma	3 (1.3)	18 (4.5)			3 (1.7)	4 (2.3)		
Others [a]	19 (8.1)	20 (5.0)			13 (7.3)	10 (5.6)		
Candida score[b] ≥ 3 at enrollment (no. (%))	111 (47.0)	147 (36.4)	0.008	21.3	71 (40.1)	70 (39.5)	NS	1.1
Multiple *Candida* colonization (no. (%))	32 (13.6)	19 (4.7)	< 0.001	25.8	15 (8.5)	14 (7.9)	NS	1.6
Prior broad-spectrum antibiotic treatment (no. (%))	182 (77.1)	153 (37.9)	< 0.001	93.2	124 (70.1)	119 (67.2)	0.630	6.7
Previous abdominal surgery (no. (%))	54 (22.9)	110 (27.2)	0.224	10.3	40 (22.6)	41 (23.2)	NS	1.3
Gastrointestinal perforation or leak (no. (%))	24 (10.2)	19 (4.7)	0.008	18.0	14 (7.9)	16 (9.0)	0.839	3.7
Acute necrotizing pancreatitis (no. (%))	12 (5.1)	15 (3.7)	0.405	6.2	10 (5.6)	7 (4.0)	0.607	7.7
Immunosuppressive therapy (no. (%))	41 (17.4)	30 (7.4)	< 0.001	26.2	22 (12.4)	23 (13.0)	NS	1.5
Malignant tumor of solid organ (no. (%))	52 (22.0)	89 (22.0)	0.999	0	33 (18.6)	33 (18.6)	NS	0
Diabetes mellitus (no. (%))	82 (34.7)	83 (20.5)	< 0.001	29.8	53 (29.9)	52 (29.4)	NS	1.2
Total parenteral nutrition (no. (%))	84 (35.6)	137 (33.9)	0.666	3.5	59 (33.3)	60 (33.9)	NS	1.2
Central venous catheter (no. (%))	230 (97.5)	360 (89.1)	< 0.001	52.9	171 (96.6)	172 (97.2)	NS	3.6
Hemofiltration/hemodialysis (no. (%))	74 (31.4)	80 (19.8)	0.001	24.9	50 (28.2)	49 (27.7)	NS	1.2
Mechanical ventilation (no. (%))	167 (70.8)	192 (47.5)	< 0.001	51.0	113 (63.8)	115 (65.0)	0.917	2.5
Sepsis at enrollment (no. (%))	198 (83.9)	259 (64.1)	< 0.001	53.7	140 (79.1)	138 (78.0)	0.897	3.1
Source control (no. (%))	213 (90.3)	349 (86.9)	0.149	13.0	158 (89.3)	157 (88.7)	NS	1.9

Abbreviations: *EAFT*, empirical antifungal treatment; *IQR*, interquartile range; *APACHE II*, Acute Physiology and Chronic Health Evaluation II; *SOFA*, Sequential Organ Failure Assessment; *SD*, standardized difference; *ICU*, intensive care unit; NS, no significant

[a]Including hyperkalemia, hypokalemia, connective tissue disease such as severe systemic lupus erythematosus, endocrine disease such as thyrotoxic crisis, diabetic ketoacidosis, and acute drug or paraquat poisoning

[b]The *Candida* score is based on the presence of sepsis (2 points), multiple *Candida* colonization (1point), parenteral nutrition (1 point), and surgery (1 point)

post-match balance. Standardized differences of less than 10.0% indicate a relatively small imbalance for a given variable between the two groups [24].

The baseline clinical characteristics were summarized as means with standard deviation for approximately normally distributed continuous variables or medians with interquartile range (IQR) for non-normally distributed continuous variables and as frequencies and percentages for categorical variables. Normality of all data sets was determined using the Kolmogorov–Smirnov test. In the unmatched cohort, categorical variables were analyzed by the chi-square or Fisher exact test, while continuous variables were analyzed by the two-tailed nonpaired Student's *t*-test or Mann–Whitney *U* test. In the matched cohort, paired comparisons were analyzed with the use of McNemar's test for binary categorical variables or Friedman's test for multi-categorical variables and a paired Student's *t*-test or paired Wilcoxon signed-ranked test for continuous variables.

In the unmatched cohort, the comparative risks of primary and secondary outcomes were further analyzed by unadjusted logistic regression analysis using the control cohort as a reference level and presented as odds ratio (OR) along with 95% confidence interval (95% CI). In the matched cohort, primary outcome and secondary outcomes were assessed by unadjusted conditional logistic regression analysis using the control cohort as a reference level and presented as OR along with 95% CI. Kaplan–Meier analyses with log rank tests were performed to measure the probability of survival during the study period in the matched cohort.

Given the bias in subgroups after successful propensity score matching could also be considered as balanced [25], subgroups analyses were performed in the matched cohorts. Clinical subgroups were based on *Candida* score ≥ 3 (yes or no), multiple *Candida* colonization (yes or no), (1,3)-β-D-glucan positive (yes or no), SOFA score ≥ 8 (yes or no), age ≥ 65 years (yes or no), and septic shock (yes or no).

The effect of the timing of initiation and duration of EAFT on the risks of death (all-cause hospital mortality and infection-attributable hospital mortality) was analyzed only in the EAFT group before propensity score matching by unadjusted logistic regression analysis.

A sensitivity analysis was conducted to estimate the effect of EAFT on the risk of death limited to the subgroup of patients with sepsis by repeating the propensity score matching with the same baseline variables as the former propensity score matching except the variable of septic shock instead of sepsis. All the analyses were performed with the use of the SPSS for Windows statistical program (version 22.0; IBM Corp., Armonk, NY). Statistical significance was set at $P < 0.05$, and highly significant values had a significance of $P < 0.01$.

Results

Study population

Between Jan 1, 2017, and Jan 31, 2022, a total of 3052 patients were admitted to the ICU (Fig. 1). Following exclusion of 2412 ineligible ICU admissions, 640 critically ill patients with clinical infection were eligible, of whom 236 (36.9%) patients prescribed with empirical antifungal agents (the EAFT group) and 404 (63.1%) patients without any systemic antifungal treatment (the control group) (Fig. 1). Among the 640 eligible participants, there was a total of 55 (8.6%) patients with only one risk factor of IC, and most of them ($n = 52$) were in the control group. There was a total of 489 (76.4%) patients with more than three risk factors of IC that indicate the most participants enrolled in this study were at high risk of IC. Before propensity score matching, there were differences between the two groups in some of baseline variables (Table 1). With the use of propensity score matching, 177 patients who prescribed with EAFT were matched with 177 control patients.

Cohort before propensity score matching

Baseline patient characteristics

Before propensity score matching, patients in the EAFT group had higher APACHE II scores and higher SOFA scores than controls (Table 1S), indicating the patients in the EAFT group had a higher severity of disease at enrollment than those in the control group. There were more ICU admissions due to medical reasons, respiratory disease, and more septic patients at enrollment in the EAFT group than in the control group (Table 1S). The EAFT group and the control group were comparable in Charlson Comorbidity scores at enrollment, age, sex distribution, and the proportion of patients who underwent source control (Table 1S).

Among those receiving EAFT, there were more patients with *Candida* score over 3 points at enrollment and more patients with the presence of multiple *Candida* colonization than the controls (Table 1S). Moreover, patients with EAFT presented more frequently with prior broad-spectrum antibiotics, gastrointestinal perforation or leak, immunosuppressive agents, diabetes mellitus, the presence of central venous catheter, hemofiltration or hemodialysis, and mechanical ventilation than the controls (Table 1S). However, the proportions of patients with previous abdominal surgery, acute necrotizing pancreatitis, malignant tumor of solid organ, and total parenteral nutrition were similar in the EAFT group and control group (Table 1S).

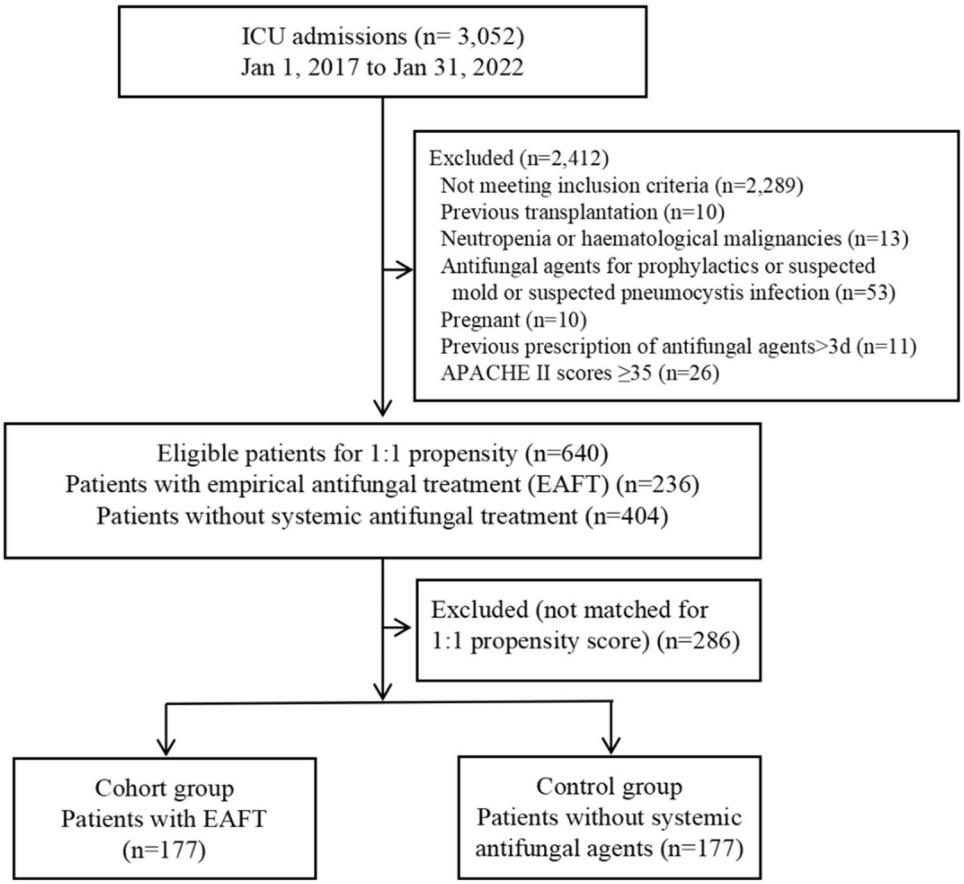

Fig. 1 Flow chart of patient selection

Outcomes

Before propensity score matching, the EAFT was associated with significantly higher risks of death as compared to the control group including all-cause hospital mortality (OR, 1.636; 95% CI, 1.076 to 2.489; $P=0.021$) and infection-attributable hospital mortality (OR, 2.277; 95% CI, 1.415 to 3.665; $P=0.001$) (Fig. 1S). The EAFT was associated with significantly lower risk of improvement of infection at discharge as compared to the control group (OR, 0.378; 95% CI, 0.248 to 0.576; $P<0.001$) (Fig. 1S).

In addition, as compared with controls, the EAFT was significantly related with higher risk of duration of mechanical ventilation over 7 days, higher risk of ICU stay more than 10 days, and with lower risk of hospital stay more than 7 days after ICU (Fig. 1S). However, there was no significant difference between the two groups in the risk of days of antibiotic-free more than 3 days (Fig. 1S).

Cohort after propensity score matching

Baseline patient characteristics

After propensity score matching, the standardized differences were less than 10.0% for all baseline variables, indicating only small differences between the two study groups (Table 1). The two groups were well balanced with respect to age, gender, APACHE II scores at enrollment, SOFA scores at enrollment, Charlson Comorbidity scores at enrollment, admission group, main reason for ICU admission, the proportion of patients with sepsis at enrollment, and the proportions of patients who underwent source control after matching. There was no significant difference between the two groups in the proportion of patients with *Candida* score more than 3 points at enrollment and the proportions of patients with the presence of every single risk factor of IC after matching (Table 1).

Outcomes

The median number of days studied was longer in the EAFT group than in the control group [14 (IQR, 9–26) vs 13 (IQR, 8–20), respectively; $P = 0.021$]. In contrast to the results before propensity score matching, as compared with control patients, the EAFT showed no significant association with the risks of all-cause hospital mortality (OR, 0.911; 95% CI, 0.541 to 1.531; $P = 0.724$) and infection-attributable hospital mortality (OR, 1.149; 95% CI, 0.632 to 2.092; $P = 0.648$) after matching (Fig. 2). The probability of survival during the study period was also comparable for the EAFT group and the control group (Fig. 3).

The EAFT was related with a significantly higher risk of ICU stay longer than 10 days as compared with the controls that was similar to the result before matching (Fig. 2). However, in contrast to the results before matching, the EAFT showed no significant effect on the improvement of infection at discharge, mechanical ventilation over 7 days during the study period, and the hospital stay after ICU more than 7 days (Fig. 2). Also, the EAFT showed no benefit in the risk of days of antibiotic-free over 3 days during the study period, which was similar to the result before matching (Fig. 2).

Comparison of death in predefined subgroups in the propensity score–matched cohort

In the subgroups of patients with *Candida* score over 3 points, the presence of multiple *Candida* colonization, and (1,3)-β-D-glucan positive, neither the all-cause hospital mortality nor the infection-attributable hospital mortality was significantly different between the EAFT group and the control group (Table 2). Similarly, the EAFT did not result in significant improvement of all-cause hospital mortality and infection-attributable hospital mortality not only in the subgroup of patients with age over 65 years but also in the subgroup of patients with SOFA scores more than 8 points as compared with the control group (Table 2). Moreover, the EAFT showed no improvement of all-cause hospital mortality and infection-attributable hospital mortality in the subgroup of patients with septic shock (Table 2).

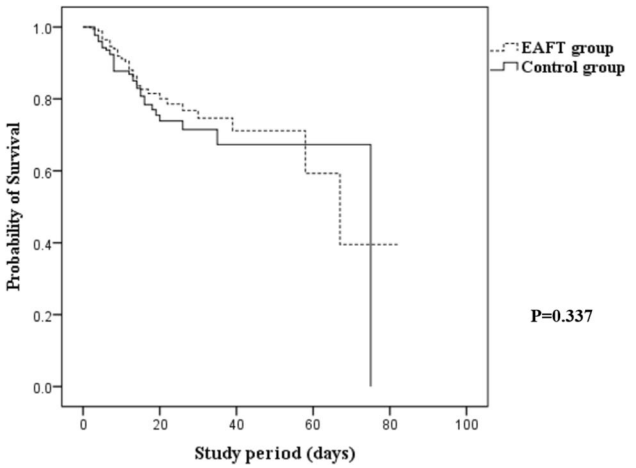

Fig. 3 The probability of survival during the study period in the two groups after propensity score matching. Abbreviations: *EAFT*, empirical antifungal treatment

Effect of the timing and duration of EAFT on the risk of death in patients with suspected IC

Among the 236 patients with suspected IC, EAFT was prescribed for a median duration of 12 days (IQR, 7–18) and a median timing of initiation of 7 days (IQR, 3–13). The most

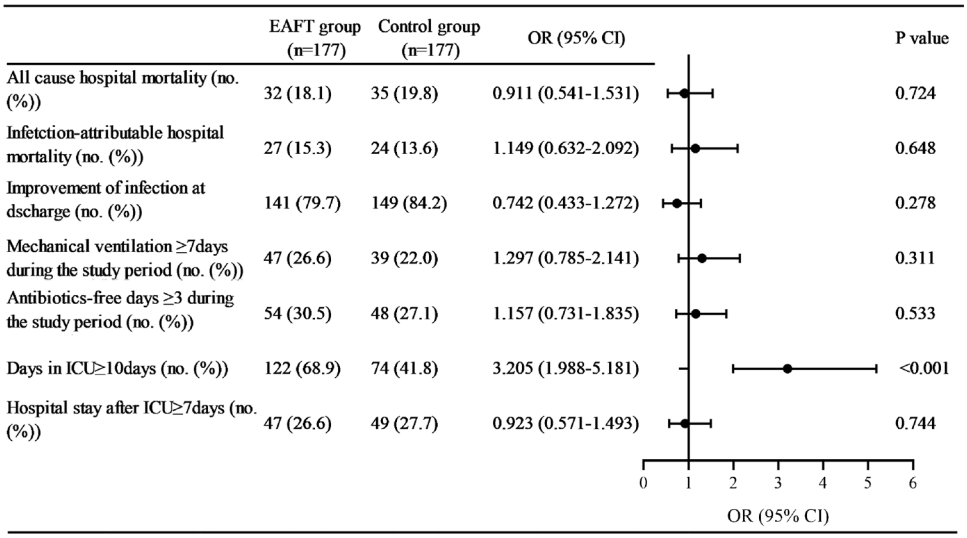

Fig. 2 Primary and secondary outcomes in the propensity score–matched cohort. Abbreviations: *EAFT*, empirical antifungal treatment; *OR*, odds ratio; *CI*, confidence interval; *ICU*, intensive care unit. Data were analyzed by unadjusted conditional logistic regression analysis. The control group was used as reference

Table 2 Comparison of death in predefined subgroups in the propensity score–matched cohort

Subgroups	All-cause hospital mortality			Infection-attributable hospital mortality		
	EAFT group($n=177$)	Control group($n=177$)	*P* value	EAFT group($n=177$)	Control group($n=177$)	*P* value
Candida score ≥ 3 (no. (%))						
Yes	10/71 (14.1)	13/70 (18.6)	0.471	7/71 (9.9)	11/70 (15.7)	0.298
No	22/106 (20.8)	22/107 (20.6)	0.972	20/106 (18.9)	13/107 (12.1)	0.175
Multiple *Candida* colonization (no. (%))						
Yes	7/15 (46.7)	4/14 (28.6)	0.316	4/15 (26.7)	3/14 (21.4)	1.000
No	25/162 (15.4)	31/163 (19.0)	0.392	23/162 (14.2)	21/163 (12.9)	0.729
(1,3)-β-D-glucan positive (no. (%))						
Yes	13/49 (26.5)	6/18 (33.3)	0.584	13/49 (26.5)	4/18 (22.2)	0.719
No	19/128 (14.8)	29/159 (18.2)	0.444	14/128 (10.9)	20/159 (12.6)	0.669
Age ≥ 65 (no. (%))						
Yes	24/92 (26.1)	21/78 (26.9)	0.902	19/92 (20.7)	14/78 (17.9)	0.657
No	8/85 (9.4)	14/99 (14.1)	0.324	8/85 (9.4)	10/99 (10.1)	0.875
SOFA ≥ 8 (no. (%))						
Yes	16/59 (27.1)	22/70 (31.4)	0.593	13/59 (22.0)	15/70 (21.4)	0.934
No	16/118 (13.6)	13/107 (12.1)	0.753	14/118 (11.9)	9/107 (8.4)	0.393
Septic shock (no. (%))						
Yes	14/49 (28.6)	10/33 (30.3)	0.866	14/49 (28.6)	9/33 (27.3)	0.898
No	18/128 (14.1)	25/144 (17.4)	0.457	13/128 (10.2)	15/144 (10.4)	0.944

Abbreviations: *EAFT*, empirical antifungal treatment; *SOFA*, Sequential Organ Failure Assessment. Data were analyzed by McNemar's test

frequent EAFT was monotherapy (89.0%, 210/236 patients) consisting of azoles (45.3%, 107/236 patients) and echinocandins (43.6%, 103/236 patients).

The later initiation of EAFT was significantly associated with higher risks of death including all-cause hospital mortality (OR, 1.039; 95% CI, 1.003 to 1.076; $P=0.034$) and infection-attributable hospital mortality (OR, 1.046; 95% CI, 1.009 to 1.085; $P=0.015$) in ICU patients with suspected IC (Table 3). Moreover, this effect was only found in infection-attributable hospital mortality (OR, 1.042; 95% CI, 1.005 to 1.081; $P=0.027$), but not all-cause hospital mortality (OR, 1.035; 95% CI, 0.999 to 1.072; $P=0.059$) in analysis of the subgroup of septic patients with suspected IC (Table 3). However, there was no significant association of duration of EAFT with the risks of all-cause hospital mortality and infection-attributable hospital mortality not only in all patients with suspected IC but also in the subgroup of septic patients with suspected IC (Table 3). Neither the timing nor the duration of EAFT was associated with risks of all-cause hospital mortality and infection-attributable hospital mortality in the subgroup of patients with septic shock with suspected IC (Table 3).

Sensitivity analysis

The sensitivity analysis in patients with sepsis is presented in Table 2S and Fig. 2S. The standardized differences were less than 10.0% for all the baseline variables after propensity

Table 3 Effect of timing and duration of EAFT on death in patients with suspected IC

	All-cause hospital mortality		Infection-attributable hospital mortality	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
The timing of initiation of EAFT				
All patients ($n=236$)	1.039 (1.003–1.076)	0.034	1.046 (1.009–1.085)	0.015
Sepsis ($n=198$)	1.035 (0.999–1.072)	0.059	1.042 (1.005–1.081)	0.027
Septic shock ($n=64$)	1.045 (0.990–1.103)	0.107	1.045 (0.990–1.103)	0.107
Duration of EAFT				
All patients ($n=236$)	1.014 (0.987–1.041)	0.318	1.014 (0.987–1.042)	0.305
Sepsis ($n=198$)	1.013 (0.986–1.041)	0.343	1.014 (0.986–1.043)	0.321
Septic shock ($n=64$)	1.018 (0.969–1.070)	0.476	1.018 (0.969–1.070)	0.476

Abbreviations: *EAFT*, empirical antifungal treatment; *OR*, odds ratio; *CI*, confidence interval. Data were analyzed by unadjusted logistic regression analysis

score matching as listed in Table 2S. There was no significant mortality improvement between the EAFT group and control group including all-cause hospital mortality (OR, 0.716; 95% CI, 0.389 to 1.316; $P = 0.728$) and infection-attributable hospital mortality (OR, 0.631; 95% CI, 0.322 to 1.236; $P = 0.179$) in the septic patients (Fig. 2S).

The EAFT was significantly associated with a higher risk of ICU stay more than 10 days compared to the control group (Fig. 2S). However, there were nonsignificant differences between the EAFT group and control group in the improvement of infection at discharge, duration of mechanical ventilation over 7 days, days of antibiotic-free more than 3 days during the study period, and days in hospital more than 7 days after ICU (Fig. 2S).

Discussion

Most antifungal agents were used in critically ill patients in the absence of proven IFIs [14]. Here, we report the results of a pilot single-center retrospective cohort study of the effect of EAFT on hospital mortality in critically ill patients without proven IFIs using propensity score matching. The association of EAFT with mortality and other outcomes in these patients was totally different before and after propensity matching in our study, which suggests a matching method is absolutely necessary for observational studies aimed to evaluate the outcomes of EAFT in ICU patients. To our knowledge, this study is the first retrospective cohort study that adopted the propensity score matching to balance the baseline bias between the cohort group and control group.

Before matching, the EAFT was given in patients with more severe illness and was related with significantly higher risks of all-cause hospital mortality and infection-attributable hospital mortality in our study. In contrast to our results, no significant association of EAFT with short-term mortality has been shown in a multicenter cross-sectional study before matching, although in the same study, EAFT was given in patients with more severe diseases and another retrospective cohort study without using any matching method [14, 26]. The different study population among these studies may explain this discrepancy. The enrolled participants in our study were critically ill patients in the absence of documented IFIs during hospitalization. The study population in the retrospective cohort study included those ICU patients diagnosed with proven IFIs after enrollment, and the early initiation of EAFT before diagnosis of IFIs could exert a beneficial effect on the mortality in these patients [26]. The study population included the patients with hematological malignancy, and the proportions of patients with neutropenia, previous solid organ or bone marrow transplantation, and acquired immune deficiency syndrome and human immunodeficiency virus carriers were not mentioned in the cross-sectional study [14]. However, all of these patients were excluded in our study.

After matching, in consistent with the previously reported studies including the two studies mentioned above [14–16, 26–28], we found that EAFT did not improve hospital mortality and other outcomes in non-transplanted, non-neutropenic patients without proven IFIs. It is a paradox to note that until now, lack of survival benefit of EAFT was demonstrated in non-transplanted, non-neutropenic critically ill patients although the administration of antifungal agents as empirical or prophylactic treatment has been shown to decrease the incidence of IC in some well-designed randomized controlled trials and meta-analysis [15, 28–30] or the presence of IFIs in critically ill patients would increase the mortality as demonstrated in numerous studies [31–33]. However, many other evolving factors other than the initiation of EAFT, such as the timing, duration and antifungal sensitivity to the suspected fungal may contribute to the death of critically ill patients with suspected IFIs [31]. In our study, we found later initiation of EAFT, but not the duration of EAFT was associated with significantly higher risk of death in patients with suspected IC. Furthermore, this effect was also found in infection-attributable hospital mortality (OR, 1.042; 95% CI, 1.005–1.081; $P = 0.027$) in the subgroup of septic patients with suspected IC. Knitsch W et al. reported that preemptive antifungal therapy failed to prevent IC in high-risk surgical ICU patients with intra-abdominal infections partially due to the late initiation of preemptive antifungal therapy [34]. Although fungi account for only about ten percent of the primary etiology for sepsis as reported previously [35, 36], the frequency of secondary infection caused by fungi may increase due to the sepsis-induced immunosuppression that occurred even at very early stage of sepsis. Zorio V et al. found that all patients with septic shock had immunosuppression on days 1–2 after the onset of septic shock [37], which was associated with high risk of secondary infection [38]. Therefore, we believe that the timing of initiation is a determining factor for survival benefit of EAFT in sepsis with suspected IC in the absence of proven IFIs. However, the optimal time point for initiating the EAFT especially in the absence of proven IFIs remains unclear until now [39]. Furthermore, prior use of antifungal agents could decrease the sensitivity of blood culture of fungal organisms [40], which may partially explain why the incidence of IC decreased, but the mortality did not decrease after EAFT was given in high-risk patients [40].

In addition, no significant decrease of hospital mortality was observed in analysis of subgroups of patients with sepsis, septic shock, multiple-site *Candida* colonization, (1,3)-β-D-glucan test positive, age above 65 years, and SOFA scores more than 8 points in our study. The critically ill patients were a highly heterogeneous population

with a great variability in the risk of IC. Currently, no precise guidelines are available about indications for antifungal treatment, timing, duration, and selection of antifungal agents for ICU patients without proven IC [14]. Identifying the subsets of ICU patients in the absence of IC who could benefit from EAFT is critical for the balance between the achievement of survival benefit of antifungal treatment and avoidance of overuse of antifungal agents and subsequent fungal resistance. Identifying these subsets of patients depends on the precise prediction rules with good sensitivity and specificity for IC. However, current available prediction scores or biomarkers such as (1,3)-β-D-glucan test have reasonably good negative predictive values but poor positive predictive value for IC in critically ill patients, which may be indicated for antifungal stewardship use [41]. Therefore, finding the potential subsets of ICU patients with benefit from EAFT remains a big challenge for physicians [42].

Several limitations to our study must be addressed. First, the results of this study were derived from a single institution retrospectively, which therefore limited its generalizability to other populations. Moreover, there was a small proportion of the study population having only one risk factor of IC that may indicate these participants were at low risk for IC in this study. Among the 55 participants with only one risk factor of IC, there were 27 participants diagnosed with sepsis, which was reported as a risk factor of IC too. So, it indicates that the proportion of patients with low risk of IC was relatively low in our study. However, the further study still should include an ICU population at higher risk for IC than that in the present study. Secondly, other potential confounders, such as the length of ICU before enrollment, the possible source of infection, and possible microbiology etiology beside *Candida* spp., were not collected in this study, which might lead to different outcomes. However, we tried to balance numerous well-known variables associated with the outcomes of clinical infection using the propensity score matching, such as age, SOFA score, Charlson index, sepsis, and source control at baseline between the two groups, to minimize the bias in this study. Thirdly, the initiation of EAFT including selection, single use or combined use, and sensitivity to the fungal microorganisms of antifungal agents was not evaluated in this study which may influence the beneficial effect of EAFT on outcome. Fourthly, this study was designed as a pilot trial, and the sample size was relatively small. Confirming survival benefit in ICU patient groups, often with multiple comorbidities and high mortality, requires much larger trials to achieve adequate power. Actually, the enrolled participants at low risk for IC and the small sample size made it difficult to detect the mortality difference between the two groups, which may partially account for no mortality benefit of EAFT in this study. However, our results provide evidence to support further well-designed studies with larger sample size evaluating the effect of EAFT on mortality in patients at higher risk of IC in the absence of the proven IFIs.

Conclusions

The EAFT failed to decrease hospital mortality in non-transplanted, non-neutropenic critically ill patients at risk for IC in the absence of proven IFIs. However, later initiation of EAFT was associated with higher risks of death in these patients with suspected IC, which indicates the timing of initiation may be critical for EAFT to decrease mortality. The data from this study justifies further larger studies to demonstrate outcome benefits of EAFT, including the optimal timing, duration, and antifungal drug selection in patients at higher risk of IC without proven IFIs.

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Author contribution Yue Tang, Wenjing Hu, Shuangyan Jiang, and Maoyu Xie contributed to collecting the clinical data and drafting the manuscript. Wenying Zhu, Lin Zhang, Jing Sha, and Tengfei Wang contributed to the study design and the statistical analysis. Min Ding, Juan Zeng, Jinjiao Jiang, and Yue Tang participated in the interpretation of data and drafting and reviewing the manuscript. All authors read and approved the final manuscript. All authors had full access to all the data and accept responsibility for the decision to submit for publication.

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Data availability The data analyzed during the current study may be made available upon written request to the corresponding author.

Declarations

Ethics approval Ethical approval was waived by the Ethics Committee of Shandong Provincial Hospital in view of the retrospective nature of the study, and all the procedures being performed were part of the routine care.

Consent to participate The requirement of informed consent was waived for this study by the Ethics Committee of Shandong Provincial Hospital due to the retrospective nature of this study.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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