Characteristics and outcomes of culture-negative versus culture-positive with fungus in sepsis patients: a retrospective analysis of the MIMIC-III database

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Research

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Abstract

BACKGROUND: We compared the characteristics of culture-positive and culture-negative with fungi in septic patients to determine whether fungi culture status is associated with mortality and the relationship between antifungal therapy and sepsis patient mortality.

METHODS: The study was based on the Medical Information Mart for Intensive Care (MIMIC) III database, we included all intensive care unit (ICU) admissions between 2001 and 2012 with sepsis, which met the Martin's criteria. The primary outcome was hospital mortality. Secondary outcomes included the usage of antifungal drugs, duration of mechanical ventilation and hospital stay. Multivariable logistic regression and propensity score matching were used to investigate any association.

RESULTS: The study population included 836 fungi-positive patients (16.6%) and 4191 fungi-negative patients (83.4%). Fungi-positive patients had more congestive heart failure and chronic pulmonary, higher sequential organ failure assessment (SOFA), and more need for renal replacement therapy on day one than fungi-negative patients. There was no correlation between antifungal therapy and hospital mortality (adjusted odds ratio = 1.03, 95% CI [0.89, 1.20]; P=0.676). Hospital mortality was lower in the fungi-negative group (25.5%) than in the fungi-positive group (37.3%, P<0.001). After propensity score matching, 613 cases from each group were matched. The hospital mortality remained significantly higher in the fungi-positive group (167/613 vs. 216/613, p=0.003).

CONCLUSIONS: Although residual confounding cannot be excluded, significant differences between fungi-positive and fungi-negative sepsis are identified, with the former group having more comorbidities, worse severity of illness, longer hospitalizations, and higher mortality. Antifungal therapy does not affect the outcome.

Introduction/background

Sepsis is a leading cause of death, morbidity, and expense, contributing to one-third to half of the deaths of hospitalized patients, depending on definitions(1). Bacteria are the most common cause of sepsis in patients, but bacterial culture is positive in only about 50% of patients(2, 3). Fungal sepsis is also on the rise, and fungal bloodstream infections have risen to number four(4). Among immunocompromised patients admitted to the ICU with influenza pneumonia, the probability of finding invasive aspergillus at approximately three days was 32%(5).

There's been a lot of research on fungal positive patients(6). Many fungi were identified at autopsy and were not found clinically, Patients with negative fungal culture are not absolutely free of fungal infection(7). Less is known though about the other half of the equation: sepsis for which fungi are not found. In addition, failure to administer antifungal to which the pathogens are susceptible is associated with increased mortality(8). However, many studies have shown that antifungal strategies did not influence outcomes(9, 10).

Hence, our study aimed to compare the characteristics and outcomes of fungi culture-positive versus fungi culture-negative sepsis and analyzed the effect of antifungal therapy on mortality.

Methods

Database introduction

We extracted the data from an online international database— Medical Information Mart for Intensive Care III (MIMIC III), with approval from the review boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center. We did not need informed consent because all the patients in the database were de-identified for privacy protection. One author (Zhiye Zou) obtained access to this database (certification number 35951237) and was responsible for data extraction.

Study design

Inclusion and exclusion criteria

We included all patients who met the criteria for Martin sepsis, consisting of codes that imply a disseminated bloodstream infection (septicemia, bacteremia, and fungemia)(11, 12). Patients who were younger than 18 years in the ICU were excluded. For patients admitted to the ICU more than once, only the first ICU stay was considered.

Data collection

Data collected were baseline variables on entry to the ICU including patient demographics, source of admission, comorbidities, vital signs and blood investigations (white blood cell count, and Neutrophils where available), and variables on the first day of ICU admission including the Sequential Organ Failure Assessment (SOFA) score. We defined organ failures as a SOFA score of >2 for the organs concerned(13).

To ensure that any fungi and bacteria isolated were associated with sepsis that resulted in ICU admission, we recorded results of all fungi and bacteria cultures collected within the two days before and the two days after ICU admission. The use of antifungal drugs, including azole, echinocandins, nystatin, and amphotericin, was also extracted.

The primary outcome variable was hospital mortality, while the secondary outcome variables were duration of mechanical ventilation, hospital stays, and the effect of antifungal agents on mortality.

Statistical analyses

Continuous variables were expressed as the mean± standard deviation or median (interquartile range) as appropriate. The Student's t-test and Wilcoxon rank-sum test were used as appropriate. Categorical data were expressed as proportions and compared using the chi-square test. The included patients were divided into two subgroups according to whether the fungi were positive or negative. Hierarchical chi-square analysis was used to test for homogeneity between the two subgroups. Multivariable logistic

regression was used for covariate adjustment. The logistic models were built using the stepwise backward method.

PSM(Propensity score matching)(14) was used to minimize confounding factors such as Comorbid conditions and disease severity, which may lead to outcome bias. A one-to-one nearest neighbor matching algorithm was applied using a caliper width of 0.05. The following variables were selected to generate the propensity score: age, male, hypertension, congestive heart failure, chronic pulmonary, liver disease, chronic kidney disease, and SOFA score on ICU admission. Kernel density plots of the p score were used to examine the PSM degree. Finally, 613 matched pairs were generated and applied to further analyses.

Results

baseline characteristics

The study population included 836 fungi-positive patients (16.6%) and 4191 fungi-negative patients (83.4%). Table 1 describes their characteristics at baseline and on day one of the ICU stay. Fungi-positive patients had more congestive heart failure and chronic pulmonary, less hypertension and chronic kidney disease, higher white blood cell and neutrophils, higher sequential organ failure assessment, more respiratory, Cardiovascular, renal and hepatic failure, and more need for renal replacement therapy on day one than fungi-negative patients. In addition, antifungal therapy was used more frequently in patients with positive fungal culture (48.0% vs. 25.2%, P<0.001).

As shown in Table 2, More than half of the fungi 487 (58.3%) were cultured in sputum, and the mortality rate was 38.2%. Bronchoalveolar lavage fluid, urine, and blood also had many fungi, while other sources of the fungi are less.

Table 3 details the variables associated with Positive Fungi. Multivariable analysis revealed the following independent predictors of positive fungi: age, sex, chronic pulmonary, congestive heart failure, neutrophils, SOFA score, respiratory failure.

Table 4 details the variables associated with hospital mortality. Fungi positivity was associated with higher mortality both in univariate and multivariate analyses. Fungi in sputum (including other yeast fungi, aspergillus spp. and candida spp.), bronchoalveolar lavage, and urine were also associated with higher mortality. Multivariable analysis revealed the following independent predictors of mortality: age, maximum respiratory rate, liver disease, SOFA score, organ failure. In addition, there was no correlation between antifungal therapy and hospital mortality (adjusted odds ratio = 1.03, 95% CI [0.89, 1.20]; P=0.676). Fungus positive in the lungs, with or without antifungal therapy, is a risk factor for death. Fungus negative in the lungs, the use of antifungal therapy had no effect on hospital mortality, while the absence of antifungal therapy was a protective factor for death (adjusted odds ratio = 0.79, 95% CI [0.68, 0.90]; P=0.001). The same results appear in the urine. Fungus negative in the blood is a protective factor for death.

Patient outcomes are presented in Table 5. Fungi-positive patients had a longer duration of mechanical ventilation, longer duration of hospital stay (14.20days (7.80 to 24.56) versus 10.42 (5.70 to 20.25), P<0.001) and higher 28-day mortality. Hospital mortality was lower in the fungi-negative group (25.5%) than in the fungi-positive group (37.3%, P<0.001).

After PSM, 613 cases from each group were well matched by a 1:1 matching algorithm (Table 6). There was no significant difference between the two matched groups with regards to all nine covariates, including SOFA score (6 (4, 9) vs. 7 (4, 10), p = 0.69). Among the 613 propensity-matched pairs, we found that the hospital mortality was significantly lower in the fungi-negative patients (167/613 vs. 216/613, P=0.003).

Figure1 In both bacteria-negative and bacteria-positive subgroups, the mortality rate of fungi-positive patients was significantly higher than that of fungi-negative patients.

Discussion

To the best of our knowledge, no previous study has focused on the differences between fungi-positive and fungi-negative sepsis. This study's main findings are that patients with fungi-positive sepsis had more comorbidities, more organ failure, a longer duration of mechanical ventilation, a longer length of hospital stay, and higher hospital mortality. Antifungal therapy did not affect the outcome. After multivariate analysis and PSM, the results remained unchanged.

Fungal culture-positive sepsis has increased significantly(15, 16). A study of the epidemiology of sepsis in the United States (U.S.) found that the annual number of sepsis cases caused by fungal organisms increased by 207% between 1979 and 2000(11). Candida spp. positive occurs in up to 80% of critically ill patients after one week in intensive care(17). The Extended Prevalence of Infection in Intensive Care (EPIC II) study found that Candida spp. were the second most frequent cause of infection (18.2% of all infections) in North American intensive care units (ICUs)(18). In our retrospective study, 16.7% of patients with sepsis were fungal culture-positive. In short, fungal infection is still a big challenge(19).

Compared with fungal culture-negative in sepsis patients, positive patients had a worse outcome. After ICU admission, 1-year mortality was significantly higher in fungal culture-positive patients with sepsis with an APACHE II score less than 25 than in those with fungal culture-negative patients (66.7% versus 50.0%)(20). Some studies even gave a 30-day mortality of up to 60% for fungal positive patients, while mortality in septic shock was almost 90% in a retrospective case series from the USA(21). A lot of studies have shown that patients with positive fungus have more complications and long hospital stays, so we should pay attention to them(4).

However, antifungal treatments do not always work.(22) In a multicentre, randomized, double-blind clinical trial, empirical antifungal therapy in sepsis patients with nonneutropenic did not improve 28-day mortality.(23) Antifungal therapy also did not significantly improve prognosis in burn patients.(9)

Therefore, in the early stage of sepsis, antifungal agents had no significant effect on death regardless of the patients' fungal culture status.

This study has several limitations. First, sepsis patients are divided into two groups according to fungi culture status. In reality, both groups are a mixed bag of diagnoses. Culture-negative patients include many non-fungal sepsis or even non-septic patients. Second, bacteria are the main pathogenic microorganisms of sepsis, so both fungal positive and negative patients contain a large number of positive bacterial patients, so it is likely to affect the outcome. Third, the fungi species had not been subdivided, most of which were yeast, which affected further analysis. Fourth, there is no specific time for medication. The use of antifungal agents in this article is indicative of the presence of these agents throughout the treatment process. These can also affect the efficacy of antifungal drugs and our outcomes.

Conclusions

In conclusion, by the analysis of a large clinical database, our study shows that significant differences between fungi-positive and fungi-negative sepsis, with the former group having more comorbidities, worse severity of illness, longer hospitalizations, and higher mortality. Antifungal therapy does not affect hospital mortality. However, more research on this topic needs to be undertaken before the association between antifungal therapy and mortality is more clearly understood.

Declarations

Ethics approval and consent to participate:

We extracted the data from an online international database— Medical Information Mart for Intensive Care III (MIMIC III), with approval from the review boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center. We did not need informed consent because all the patients in the database were de-identified for privacy protection.

Consent for publication:

Written informed consent for publication was obtained from all participants.

Availability of data and materials:

One author (Zhiye Zou) obtained access to this database (certification number 35951237) and was responsible for data extraction.

Author Contributions:

Statistical analysis: Z Zou

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Obtained funding: M Wu

Conflict of Interest Disclosures:

The authors have no financial conflicts of interest. Each author has completed the conflict of interest form.

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Tables

Table 1 Characteristics at baseline and on day one of intensive care unit admission.

	Fungi-negative patients(N=4191)	Fungi-positive patients(N=836)	P value
Demographics			
Age (years)	66.1±16.9	65.4±16.6	0.33
Male, n(%)	2350 (56.1)	436 (52.2)	0.037
Obesity[a], n(%)	232(5.5)	47(5.6)	0.92
Ethnicity, n(%)			
White	3001 (71.6)	589 (70.5)	0.50
Black	369 (8.8)	59 (7.1)	0.098
Asian	119 (2.8)	28 (3.3)	0.42
Hispania /Latino	146 (3.5)	19 (2.3)	0.073
Others	556 (13.3)	141 (16.9)	0.006
Comorbid conditions, n(%)			
Hypertension	2061 (49.2)	348 (41.6)	<0.001
Congestive heart failure	1296 (30.9)	293 (35.0)	0.019
Diabetes mellitus	1221 (29.1)	227 (27.2)	0.25
Chronic pulmonary	813 (19.4)	190 (22.7)	0.028
Chronic kidney disease	772 (18.4)	128 (15.3)	0.032
Liver disease	754 (18.0)	183 (21.9)	0.008
Cancer	567 (13.5)	116 (13.9)	0.79
Emergency department, n(%)	3927 (93.7)	782 (93.5)	0.86
ICU type, n(%)			
MICU	2742 (65.4)	558 (66.7)	0.46
TSICU/SICU	839 (20.0)	102(21.3)	0.40
CCU/CSRU	610 (14.6)	100 (12.0)	0.05
Vital signs upon ICU admission			
Mean MAP(mmHg)	72.7 (67.0,80.0)	72.2(66.8, 79.1)	0.23
Maximum temperature(°C)	37.6(37.0, 38.3)	37.7(37.1, 38.4)	0.29
Maximum heart rate	110 (95, 126)	114 (98, 128)	0.003

Maximum respiratory rate	28 (24, 33)	29 (25, 34)	0.041
GCS score	15 (14, 15)	15 (14, 15)	0.053
Laboratory outcomes, median (IQR)			
Minimum white blood cell (109/L)	10.6(6.7, 15.4)	11.8(7.4, 17.5)	<0.001
Maximum white blood cell (109/L)	14.4(9.7, 20.65)	15.9 (10.6, 23.2)	<0.001
Neutrophils (%)	87.7 (81.0, 91.9)	89.0 (83.0, 92.7)	<0.001
CD4/CD8, ratio	0.40(0.2, 1.3)	0.35(0.1, 1.0)	0.66
Severity scores			
SOFA score, median (IQR)	6 (3, 9)	7 (4, 10)	<0.001
Renal replacement therapy on day 1, n(%)	259 (6.2)	70 (8.4)	0.019
Organ failure[b], n(%)			
Cardiovascular	1510 (36.0)	385 (46.1)	<0.001
Renal	988 (23.6)	224 (26.8)	0.047
Respiratory	955 (22.8)	347 (41.5)	<0.001
Central nervous system	442 (10.5)	106 (12.7)	0.071
Coagulation	332 (7.9)	61 (7.3)	0.54
Hepatic	322 (7.7)	93 (11.1)	<0.001
Antifungal agent, n(%)	1058 (25.2)	401 (48.0)	<0.001
Azole antifungals	757 (18.1)	316 (37.8)	<0.001
nystatin	432 (10.3)	114 (13.6)	0.005
Echinocandin	158 (3.8)	98 (11.7)	<0.001
Amphotericin	8 (0.2)	8 (1.0)	<0.001

[a]Obesity, body mass index(BMI) is over 30kg/m^2. [b]organ failure defined as Sequential Organ Failure Assessment (SOFA) score >2 for the specified organ. Abbreviations: ICU intensive care unit, MICU multiple intensive care unit, TSICU traumatic surgical intensive care unit, SICU surgical intensive care unit, CCU coronary care unit, CSRU cardiac surgery care unit, MAP Mean Blood Pressure, GCS Glasgow Coma Scale, SOFA Sequential Organ Failure Assessment, IQR, interquartile range.

Table 2 Source and species of fungi.

Type of culture[a]	Other yeast fungi(819), n	Candida spp.[b] (165), n	Aspergillus spp.[c] (30), n	cryptococcus neoformans (2), n	Fungi-positive patients (N=836) , n(%)	Hospital mortality, n(%)
Sputum	461	15	27	0	487 (58.3)	186(38.2)
Bronchoalveolar lavage	82	11	3	1	91 (10.9)	37(40.7)
Urine	232	13	0	0	238 (28.5)	101(42.4)
Blood	3	60	0	0	62 (7.4)	24(38.7)
Venous catheter	3	8	0	0	10 (1.2)	2（20.0）
Pleural fluid	0	5	0	0	5 (0.6)	3(60.0)
Peritoneal fluid	6	11	0	0	12 (1.4)	2(16.7)
Bile	0	8	0	0	8 (1.0)	2(25.0)
Soft tissue	0	6	0	0	6 (0.7)	2(33.3)
Cerebrospinal fluid	0	0	0	1	1 (0.1)	1(100.0)
Other fluid	3	9	0	0	11 (1.3)	4(36.4)
Other swab	29	19	0	0	46 (5.5)	15(32.6)

[a]Cultures collected within two days before and the two days after ICU admission were included, Some patients had more than one site of infection. [b]candida glabrata, candida albicans, candida guilliermondii, candida parapsilosis, candida tropicalis, candida krusei; [c]Aspergillus flavus, Aspergillus fumigatus.

Table 3. Factors Associated With Positive Fungi by univariable and multivariable logistic regression analyses.

Variable[a]	Univariable OR (95% CI)	P Value	Multivariable adjusted OR (95% CI)[b]	P Value
Age, per year	1.00(0.99, 1.00)	0.333	1.00(0.99, 1.00)	0.262
Male sex	0.85(0.74,0.99)	0.037	0.82(0.70,0.95)	0.009
Comorbid conditions				
Chronic pulmonary	1.22(1.02, 1.46)	0.028	1.25 (1.04, 1.49)	0.017
Congestive heart failure	1.21(1.03,1.41)	0.019	1.25(1.06, 1.47)	0.007
Neutrophils	1.012(1.005, 1.020)	0.001	1.015(1.008, 1.022)	<0.001
SOFA score	1.07(1.05, 1.09)	<0.001	1.05(1.03, 1.08)	<0.001
Organ failure				
Respiratory	2.40(2.06, 2.81)	<0.001	2.25(1.83, 2.66)	<0.001

[a]Only variables that were significantly associated with hospital mortality on univariable or multivariable analyses are shown. [b]Hosmer-Lemeshow test for goodness of fit for multivariable logistic regression model:χ^2 =13.186, degrees of freedom = 8, P = 0.11.

Table 4 Predictors of hospital mortality by univariable and multivariable logistic regression analyses.

Variable[a]	Univariable OR (95% CI)	P value	Multivariable adjusted OR (95% CI)	P value
Demographics				
Age, per year	1.020（1.016，1.024）	<0.001	1.025（1.020，1.029）	<0.001
Vital signs upon ICU admission				
Mean MAP	0.964(0.958,0.970)	<0.001	0.988(0.981,0.995)	0.001
Maximum temperature	0.70(0.66,0.75)	<0.001	0.75(0.70,0.81)	<0.001
Maximum respiratory rate	1.04（1.03，1.05）	<0.001	1.032(1.022,1.041)	<0.001
Comorbid conditions				
Congestive heart failure	1.32（1.16，1.50）	<0.001	1.20 (1.04, 1.40)	0.014
Liver disease	2.52（2.18，2.91）	<0.001	2.12（1.78，2.54）	<0.001
Neutrophils	0.98(0.97, 0.99)	<0.001	0.99(0.98, 0.99)	0.010
SOFA score	1.24（1.22，1.27）	<0.001	1.26（1.23，1.28）	<0.001
Organ failure				
Renal	3.40（2.97，3.89）	<0.001	1.54(1.30, 1.83)	<0.001
Coagulation	3.04（2.48，3.74）	<0.001	1.59(1.24, 2.03)	<0.001
Hepatic	2.82（2.31，3.45）	<0.001	1.29(1.02, 1.64)	0.035
Fungi positive	1.42(1.16, 1.73)	0.001	1.49(1.25, 1.78)	<0.001
Other yeast fungi	1.69(1.44, 1.99）	<0.001	1.50(1.25, 1.81)	<0.001
Aspergillus spp.	4.80(2.21, 10.43)	<0.001	3.33(1.44, 7.68)	0.005
Candida spp.	1.58(1.12, 2.24）	0.010	1.44(0.97, 2.15)	0.070
Type of culture				
Sputum's fungi	1.73(1.42, 2.10)	<0.001	1.39(1.12, 1.73)	0.003
Sputum's yeasts	1.65(1.35, 2.02)	<0.001	1.36(1.09, 1.70)	0.007
Sputum's aspergillus	4.53(2.07, 9.92)	<0.001	3.12(1.33, 7.28)	0.009
Bronchoalveolar lavage's fungi	1.83(1.20, 2.80)	0.005	1.90(1.20, 3.03)	0.007
Urine's fungi	2.02(1.55, 2.63)	<0.001	1.86(1.38, 2.51)	<0.001
Urine's yeasts	1.93(1.47, 2.52)	<0.001	1.78(1.31, 2.41)	<0.001
Antifungal agent	1.13(0.99, 1.29)	0.08	1.03(0.89, 1.20)	0.676

Azole antifungals			1.06(0.91, 1.23)	0.429	0.96(0.81, 1.13)	0.606
Nystatin			0.76(0.62, 0.93)	0.009	0.76(0.61,0.96)	0.019
Echinocandin			2.53(1.97, 3.25)	<0.001	2.24(1.68, 2.98)	1.69
Amphotericin			2.94(1.13, 7.65)	0.027	2.22(0.78, 6.27)	0.134
	Fungi-positive	antifungal				
Lung	Yes	Yes	1.45(1.11, 1.89)	0.006	1.21(0.90, 1.63)	0.201
		No	1.88(1.48, 2.39)	<0.001	1.56(1.19, 2.05)	0.001
	No	Yes	1.02(0.88, 1.17)	0.809	0.95(0.81, 1.11)	0.502
		No	0.74(0.66, 0.84)	<0.001	0.79(0.68, 0.90)	0.001
Urine	Yes	Yes	1.95(1.35, 2.82)	<0.001	1.85(1.22, 2.80)	0.004
		No	1.96(1.36, 2.83)	<0.001	1.71(1.13, 2.60)	0.011
	No	Yes	1.03(0.89, 1.78)	0.716	0.92(0.79, 1.08)	0.312
		No	0.80(0.71, 0.91)	0.001	0.83(0.72, 0.95)	0.009
Blood	Yes	Yes	1.35(0.71, 2.59)	0.359	1.35(0.65, 2.80)	0.425
		No	2.38(1.01, 5.61)	0.048	1.70(0.63, 4.55)	0.294
	No	Yes	1.10(0.96, 1.26)	0.170	0.99(0.85, 1.15)	0.879
		No	0.84(0.74, 0.96)	0.009	0.86(0.75, 1.00)	0.049

[a]Only variables that were significantly associated with hospital mortality on univariable or multivariable analyses are shown. [b]Hosmer-Lemeshow test for goodness of fit for multivariable logistic regression model:χ^2 =9.519, degrees of freedom = 8, P = 0.300;

Table 5 Outcomes.

	Fungi-negative patients(N=4191)	Fungi-positive patients(N=836)	P value
Duration of vasopressors(hours)	32.5(12.25,65.08)	37.28(16.0,71.75)	0.23
Duration of Mechanical ventilation(hours)	99.21(25.75,247.0)	138.58(57.0,279.0)	<0.001
Duration of ICU stay(days)	3.21 (1.77, 8.01)	6.65 (2.96, 13.12)	<0.001
Duration of hospital stay(days)	10.42(5.70, 20.25)	14.20(7.80, 24.56)	<0.001
28-day mortality	1028 (24.5)	291 (34.8)	<0.001
Hospital mortality	1069 (25.5)	312 (37.3)	<0.001
Mortality by the end of follow up	2382 (56.8)	599 (71.7)	<0.001

Table 6 Comparisons of the covariates after propensity score matching.

Variables	Fungi-negative patients(N=613)	Fungi-positive patients(N=613)	P value
Demographics			
Age (years)	67.9 (54.7, 80.2)	67.6(54.7, 79.6)	0.59
Male, n(%)	326 (53.2)	329 (53.7)	0.86
Obesity, n(%)	35 (5.7)	32 (5.2)	0.71
Comorbid conditions			
Hypertension	271 (44.2)	270 (44.0)	0.95
Congestive heart failure	205 (33.4)	202 (33.0)	0.86
Chronic pulmonary	135 (22.0)	131 (21.4)	0.78
Liver disease	135 (22.0)	123 (20.1)	0.40
Chronic kidney disease	95 (15.5)	101 (16.5)	0.64
SOFA score, median (IQR)	6 (4, 9)	7 (4, 10)	0.69
Clinical outcomes			
Renal replacement therapy on day1	36 (5.9)	50 (8.2)	0.12
Duration of vasopressors(hours)	25.8 (9.5, 47.8)	35.2 (13.0, 70.6)	0.071
Duration of Mechanical ventilation(hours)	72.2(23.0, 250.7)	136.4 (54.2, 277.8)	<0.001
Duration of ICU stay(days)	3.3(1.8, 7.8)	6.3(2.9, 12.3)	<0.001
Duration of hospital stay(days)	10.0(5.8, 21.1)	14.2(7.9, 23.8)	<0.001
28-day mortality	164 (26.8)	203 (33.1)	0.015
Hospital mortality	167 (27.2)	216 (35.2)	0.003
Mortality by the end of follow up	367 (59.9)	446 (72.8)	<0.001

Figures

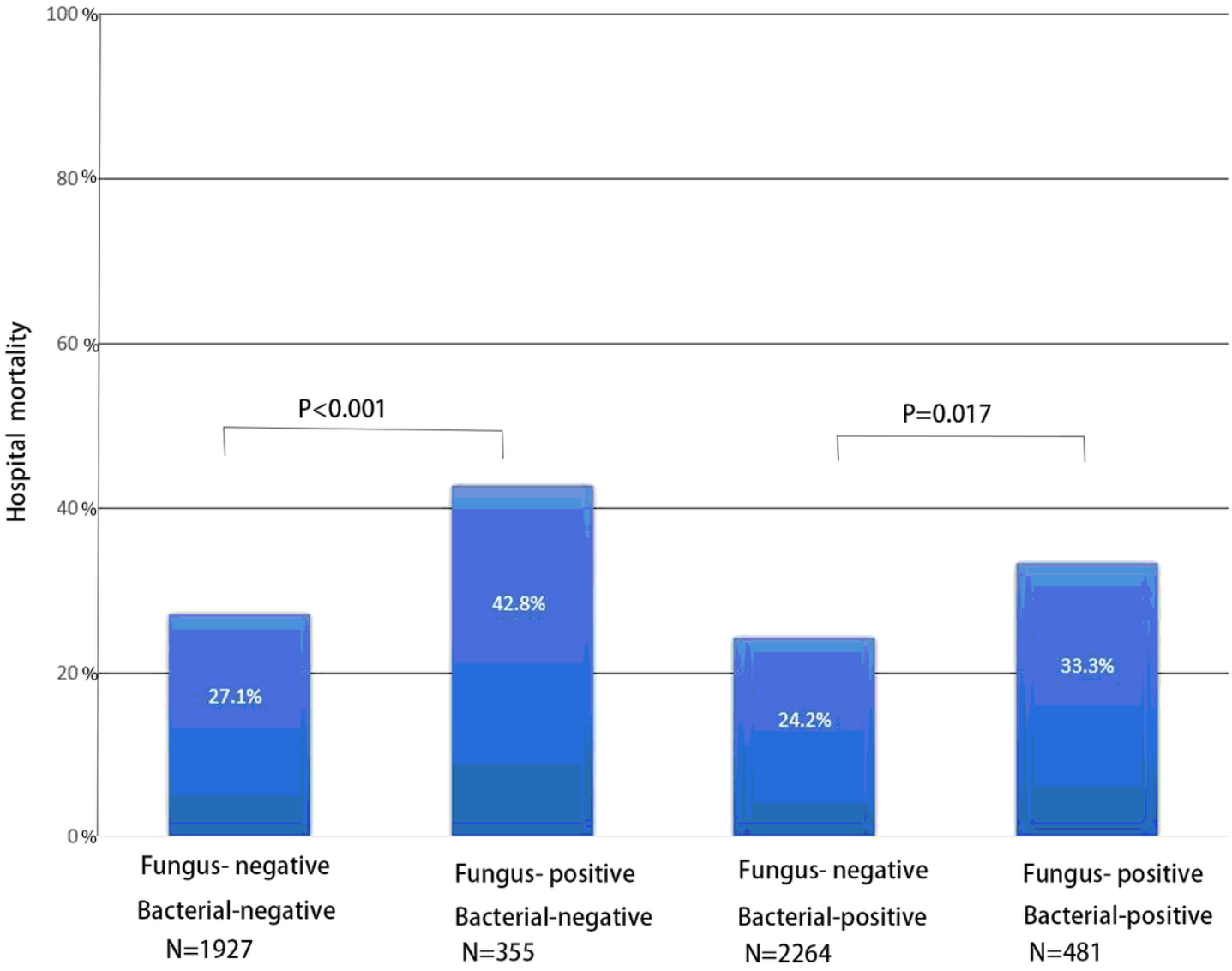

Figure 1

Hospital mortality for subgroups according to fungi and bacteremia.