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Letter to the Editor

Association between caspofungin treatment and mortality in non-HIV *Pneumocystis jirovecii* pneumonia: A multicenter, retrospective study

To the Editor,

In our previous study, we reported the epidemiological characteristics of *Pneumocystis jirovecii* (*P. jirovecii*) pneumonia (PJP).[1] Trimethoprim-sulfamethoxazole (TMP-SMX) remains the first-line treatment for PJP.[2] Despite the availability of antifungal therapies, in-hospital mortality remains high, ranging from 25% to 35%.[3,4] Several studies have suggested the potential of caspofungin as an adjunctive treatment for PJP. In this observational cohort study, we aimed to compare the clinical effectiveness of TMP-SMX versus TMP-SMX combined with caspofungin in non-HIV-infected PJP patients admitted to the ICU.

We retrospectively reviewed the medical records of PJP patients without HIV across 16 ICUs in China from October 2019 to September 2023. Among them, 95 PJP patients came from previously reported studies.[1,5–7] The diagnostic criteria for PJP were: 1. clinical symptoms with fever, cough, or acute onset of dyspnea; 2. diffuse interstitial infiltration of both lungs with ground-glass changes on chest computed tomography (CT); 3. Metagenomic next-generation sequencing test of bronchoalveolar lavage fluid showed the positivity of *P. jirovecii* as described before.[5,8] Clinical data were collected, and the patients were divided into two groups: those who received TMP-SMX monotherapy and those who received TMP-SMX plus caspofungin treatment. The primary outcome was 28-day mortality from the date of ICU admission.

All data were tested for normality. Continuous variables are presented as medians and interquartile ranges (median [Q1-Q3]), while categorical variables are presented as percentages. Statistical significance was assessed using Kruskal-Wallis for continuous variables and the $\chi 2$ or Fisher's exact test for categorical variables. A two-sided p-value less than 0.05 was considered statistically significant. All statistical analyses were performed using R software (v4.2.1) or Python (v3.9.13). To investigate the association between the 28-day mortality rate and TMP-SMX monotherapy or TMP-SMX plus caspofungin, univariate and multivariate Cox proportional hazard regression analyses were performed. We used the inverse probability of treatment weighting (IPTW) method to balance the baseline characteristics between the two groups. The standardized mean difference (SMD) less than 0.2 was considered an acceptable threshold. The primary outcome was further verified in the IPTW-adjusted model. Sensitive analysis was performed. 28-day mortality after mNGS testing was reported in this study.

In the results, a total of 120 PJP patients were included in the final cohort: 31 received TMP-SMX monotherapy, and 89 received TMP-SMX combined with caspofungin. Cohort characteristics are summarized in Table 1. Compared to the combination group, the monotherapy group had higher rates of solid tumors (32.3% vs. 12.4%, p=0.025) and pulmonary aspergillosis co-infection (38.7% vs. 14.6%, p=0.010), but a lower rate of organ transplantation (3.2% vs. 22.5%, p=0.031). The median time from TMP-SMX initiation to ICU admission was 1 day in the monotherapy group and 0 days in the combination group; median treatment durations were 8 and 16 days, respectively. TMP-SMX was continued throughout treatment unless discontinued due to adverse effects. No significant differences were observed between groups in sex, other comorbidities, prior therapies, laboratory findings, disease severity, mNGS-to-ICU interval, radiological features, or post-ICU interventions.

The overall 28-day mortality rate was 43.3%. Mortality was significantly higher in the TMP-SMX monotherapy group (61.3%) compared to the combination group (37.1%, P=0.033). Cox regression analysis showed that monotherapy was associated with increased mortality (adj HR = 2.37, 95% CI: 1.12–5.05, P=0.024) (Table S1). After adjusting for potential confounders including sex, age, CKD, solid tumors, CT findings, SOFA score, time from TMP-SMX initiation to ICU admission, mechanical ventilation, and corticosteroid use, covariate balance was achieved (Fig. S1), and monotherapy remained significantly associated with higher mortality (HR=2.97, 95% CI: 1.68–5.25, P < 0.001) (Fig. 1).

In multivariate Cox regression for the unadjusted cohort, 28-day mortality after mNGS testing in sensitivity analyses showed that no combined with caspofungin was associated with higher mortality (HR = 2.37, P = 0.044, Table S2). Before and after matching confounding factors using the same IPTW method (Fig. S2), it led to the same conclusion: patients in the TMP-SMX plus caspofungin group had lower 28-day mortality after mNGS testing (Fig. S3).

Caspofungin, an antifungal agent, inhibits β-D-glucan (BDG) synthesis in fungal cell walls, disrupting the integrity of cystic forms of Pneumocystis, which are rich in BDG. This suggests its potential as an adjunctive therapy for PJP. This study's 28-day mortality was significantly lower in the TMP-SMX plus caspofungin group. This

Abbreviations: ICHs, Immunocompromised hosts; PJP, *Pneumocystis jirovecii* pneumonia; TMP-SMX, Trimethoprim-sulfamethoxazole; ICU, intensive care unit; CT, computed tomography; mNGS, metagenomic next-generation sequencing; IPTW, inverse probability of treatment weighting; SOFA, sequential organ failure assessment; OR, odds ratio; CI, confidence interval; HR, hazard ratio; HIV, human immunodeficiency virus; BAL, broncho-alveolar lavage; CHD, coronary atherosclerotic heart disease; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; CTD, connective tissue disease; PCT, procalcitonin; CRP, C-reactive protein; BDG, 1, 3-β-D-glucan; CRRT, continuous renal replacement therapy; LOS, length of stay; ARDS, acute respiratory distress syndrome; APACHE II, Acute Physiology and Chronic Health Evaluation II

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Table 1
Characteristics of 120 PJP patients without HIV in the final cohort.

Variables	All	TMP-SMX monotherapy	TMP-SMX plus caspofungin	P-value	Missing data (%)
N Variables	120	31	89		NA
Male, n (%)	76 (63.3)	20 (64.5)	56 (62.9)	1.000	0.0
Age, year, median (IQR)	62.5 [51.0,72.2]	66.0 [57.0,74.5]	60.0 [51.0,72.0]	0.087	0.0
Underlying diseases, n (%)					
Diabetes mellitus	25 (20.8)	7 (22.6)	18 (20.2)	0.983	0.0
CHD	4 (3.3)	0 (0.0)	4 (4.5)	0.535	0.0
COPD	17 (14.2)	7 (22.6)	10 (11.2)	0.207	0.0
Liver disease	15 (12.5)	5 (16.1)	10 (11.2)	0.693	0.0
CKD	38 (31.7)	10 (32.3)	28 (31.5)	1.000	0.0
Cerebrovascular disease	7 (5.8)	1 (3.2)	6 (6.7)	0.784	0.0
CTD	18 (15.0)	5 (16.1)	13 (14.6)	1.000	0.0
Solid tumor	21 (17.5)	10 (32.3)	11 (12.4)	0.025	0.0
Hematologic neoplasms	18 (15.0)	5 (16.1)	13 (14.6)	1.000	0.0
Organ transplantation	21 (17.5)	1 (3.2)	20 (22.5)	0.031	0.0
PJP prophylaxis	1 (4.8)	0 (0)	1 (5.0)	1.000	0.0
Treatment (Within a month)					
Radiotherapy	8 (6.7)	3 (9.7)	5 (5.6)	0.717	0.0
Chemotherapy	22 (18.3)	9 (29.0)	13 (14.6)	0.129	0.0
Immunosuppressive drug	85 (70.8)	18 (58.1)	67 (75.3)	0.113	0.0
Laboratory tests, median (IQR)					
White blood cell	9.4 [6.2,13.6]	10.9 [5.9,15.1]	9.2 [6.2,12.9]	0.325	0.0
Limphocyte	0.4 [0.2,0.7]	0.4 [0.2,1.0]	0.4 [0.2,0.7]	0.340	0.0
Neutrophil	8.6 [5.1,12.6]	9.0 [5.2,14.2]	8.2 [5.1,12.0]	0.427	0.0
CRP	79.5 [45.3159.1]	105.3 [60.8169.4]	70.2 [43.0158.1]	0.295	1.7
PCT	0.7 [0.2,3.3]	0.6 [0.4,4.7]	0.7 [0.2,2.4]	0.318	3.3
(1, 3) β-D-Glucan value, pg/mL	100.6 [10.0240.0]	89.4 [10.0229.8]	100.6 [10.0245.9]	0.442	17.5
SOFA score at ICU admission, median (IQR)	7.1 ± 2.7	6.8 ± 2.3	7.2 ± 2.9	0.434	0.0
Respiration	2.9 ± 0.8	2.8 ± 1.0	3.0 ± 0.8	0.248	0.0
Coagulation	0.9 ± 1.2	0.9 ± 1.0	1.0 ± 1.2	0.735	0.0
Hepatic	0.2 ± 0.6	0.3 ± 0.7	0.2 ± 0.6	0.465	0.0
Cardiovascular	1.4 ± 1.0	1.6 ± 0.9	1.4 ± 1.0	0.376	0.0
Neurologic	0.6 ± 1.1	0.5 ± 0.9	0.6 ± 1.1	0.398	0.0
Kidney	1.0 ± 1.4	0.8 ± 1.0	1.0 ± 1.5	0.362	0.0
CT shows diffuse interstitial changes in both lungs, n (%)	76 (63.3)	17 (54.8)	59 (66.3)	0.356	0.0
Coinfections, n (%)					
Pulmonary aspergillosis	25 (20.8)	12 (38.7)	13 (14.6)	0.010	0.0
Possible	11 (9.2)	2 (6.5)	9 (10.1)	0.726	0.0
Probable	14 (11.7)	10 (32.3)	4 (4.5)	< 0.001	0.0
Use of voriconazole	18 (72.0)	10 (83.3)	8 (61.5)	0.443	0.0
Interventions					
Mechanical ventilation	99 (82.5)	26 (83.9)	73 (82.0)	1.000	0.0
CRRT	37 (30.8)	9 (29.0)	28 (31.5)	0.979	0.0
Corticosteroid	108 (90.0)	26 (83.9)	82 (92.1)	0.330	0.0
Time from hospital admission to ICU	0.0 [0.0,4.0]	0.0 [0.0,1.0]	0.0 [0.0,5.0]	0.085	0.0
Time from mNGS to hospital admission	4.0 [2.0,8.0]	3.0 [2.0,6.0]	4.0 [2.0,8.0]	0.210	0.0
Time from mNGS to ICU admission	2.0 [1.0,3.2]	2.0 [1.5,3.0]	2.0 [1.0,4.0]	0.980	0.0
Time from TMP-SMX use hospital admission	1.5 [0.0,4.2]	1.0 [0.0,9.0]	2.0 [0.0,3.0]	0.425	0.0
Time from TMP-SMX use ICU admission	0.0 [−1.0,2.0]	1.0 [0.0,5.0]	0.0 [−1.0,2.0]	0.033	0.0
Duration of TMP-SMX, days	14.5 [7.0,21.0]	8.0 [4.0,16.0]	16.0 [10.0,23.0]	0.001	0.0
Hospital LOS, median (IQR)	20.9 [12.5,41.0]	17.0 [10.5,23.5]	22.1 [14.0,41.0]	0.098	0.0
ICU LOS, median (IQR)	12.0 [6.4,21.0]	9.0 [5.5,16.5]	12.0 [7.0,21.7]	0.147	0.0
28 day-mortality, n (%)	52 (43.3)	19 (61.3)	33 (37.1)	0.033	0.0

Abbreviations: TMP-SMX= trimethoprim/sulfamethoxazole; IQR= interquartile range; CHD= coronary atherosclerotic heart disease; COPD= chronic obstructive pulmonary disease; CKD= chronic kidney disease; CTD= connective tissue disease; CRP=C-reactive protein; PCT= procalcitonin; SOFA=sequential organ failure assessment; ICU=intensive care unit; mNGS= metagenomic next-generation sequencing; CT= computed tomography; CRRT=continuous renal replacement therapy; LOS= length of stay.

finding remained consistent across IPTW-adjusted models and sensitivity analyses. Our results align with Tian et al.'s findings in HIV-positive patients, who showed higher response rates and lower mortality with combination therapy.[4] We extend this evidence to non-HIV populations.

The timing of caspofungin may be critical, as early use could disrupt the life cycle of Pneumocystis by targeting cyst forms, preventing progression to trophozoites. This mechanism resembles influenza treatment using neuraminidase inhibitors. Moreover, co-infection with pulmonary aspergillosis is common in PJP patients, and caspofungin may also mitigate aspergillus-related mortality.[1,5,9] Elevated BDG levels (≥800 pg/mL) may predict a better response to caspofungin, though our cohort had a lower median BDG (100.6 pg/mL).[10]

Limitations of this study include its retrospective, multicenter design, potential data loss, selection bias in caspofungin use, and limited sample size. Nonetheless, our findings raise important questions about the dual role of caspofungin in treating PJP and preventing aspergillosis, warranting further prospective validation.

In conclusion, the use of TMP-SMX plus caspofungin is associated with lower 28-day mortality compared to TMP-SMX monotherapy in PJP patients without HIV. Further randomized trials are needed.

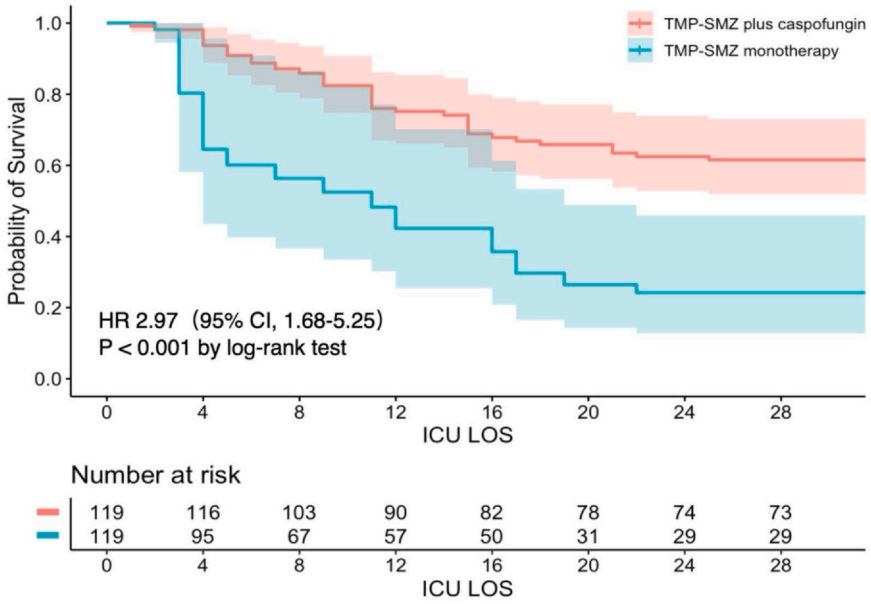

Fig. 1. Kaplan–Meier Estimates of Death from Any Cause at 28 Days. Shown is the risk of death at 28 days (the primary endpoint) among patients with PJP in the TMP-SMX monotherapy group and the TMP-SMX plus caspofungin group in the IPTW-adjusted model.

Ethics approval and consent to participate

This study was performed in accordance with the Declaration of Helsinki and relevant guidelines and regulations. The study has been approved by the ethics committees of the first affiliated hospital, Zhejiang University School of Medicine (id: IIT20240251A) and other participating hospitals. As a retrospective study, informed consent was waived.

Consent for publication

Not applicable.

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Author contributions

Hongliu Cai and Lingtong Huang designed the study and reviewed the final manuscript. All investigators participated in the discussion and agreed with the final version of the manuscript.

Data availability

The datasets generated and/or analyzed during the current study are not publicly available because the individual privacy of patients could be compromised, but are available from the corresponding author on reasonable request.

Declaration of Competing Interest

The authors declare no conflict of interest.

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Not applicable.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2025.106548.

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