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MAJOR ARTICLE

Aspartate Aminotransferase/Platelet Ratio Index Upon Admission Predicts 24-Week Mortality in Patients With HIV-Associated *Talaromyces marneffei*

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Background. A high aspartate aminotransferase/platelet ratio index (APRI) predicts mortality in patients with severe infection. This study aims to assess the potential of APRI as a predictor for mortality in patients with HIV-associated *Talaromyces marneffei* (HTM).

Methods. Associations between APRI and CD4 count, white blood cell count, C-reactive protein (CRP) level, procalcitonin (PCT) level, and cytokines were assessed in 119 patients. Univariate and multivariate Cox regression models were used to predict APRI on 24-week mortality.

Results. APRI was positively associated with CRP ($r = 0.190$, $P = .039$), PCT ($r = 0.220$, $P = .018$), interleukin 6 ($r = 0.723$, $P < .001$), interleukin 10 ($r = 0.416$, $P = .006$), and tumor necrosis factor α ($r = 0.575$, $P < .001$) and negatively associated with CD4 count ($r = -0.234$, $P = .011$). In total, 20.2% (24/119) of patients died within the 24-week follow-up. The 24-week survival rate was 88.0% for patients with APRI <5.6% and 61.1% for those with APRI ≥5.6 (log-rank $P < .001$). After adjustment for sex, age, body mass index, and CD4 count, as well as serum levels of hemoglobin, APRI ≥5.6 (adjusted hazard ratio [95% CI]; 3.0 [1.2–7.1], $P = .015$), PCT ≥1.7 ng/mL (3.7 [1.5–9.6], $P = .006$), and non–amphotericin B deoxycholate treatment (2.8 [1.2–6.6], $P = .018$) were independent risk factors for 24-week mortality.

Conclusions. For patients with HTM, APRI is associated with severity and is an independent risk factor for 24-week mortality.

Keywords. APRI; HIV; prognostic analysis; talaromycosis.

Talaromyces marneffei is an important dimorphic fungus that causes severe infection in people living with HIV in Southeast Asia, Southern China, and Northeastern India [1–3]. The mortality rate of talaromycosis is as high as 50.6% in patients without antifungal treatment. Although effective antifungal medicine is administrated, the mortality rate of patients with HIV-associated *T marneffei* (HTM) remains at approximately 25% [4]. Thus, it is pivotal to identify the patients at high risk of death to reduce mortality.

Nearly 75.0% of patients with HTM had increased aspartate aminotransferase (AST) levels, and more than half had thrombocytopenia [5]. Meanwhile, the clinical significance of these abnormal laboratory results was unclear. The AST/platelet ratio index (APRI) is used to evaluate the level of liver fibrosis among patients with chronic liver disease [6], including chronic viral hepatitis, nonalcoholic fatty liver disease, and liver cancer [7–9]. APRI is currently identified as an independent risk factor for mortality in patients with systemic infections, such as COVID-19, malaria, dengue, and sepsis [10–13]. *T marneffei* can lead to systemic and disseminated infection [14] and manifest with fever, lymphadenopathy, splenomegaly, increased AST, and thrombocytopenia [5, 15, 16]. Therefore, we wonder whether APRI could be used as a surrogate marker for the prognosis of patients with HTM.

The present study examined the relationship of APRI to cytokines and CD4, aiming to evaluate whether APRI is associated with the progression and prognosis of patients with HTM.

METHODS

Study Cohort and Patient Enrollment

Between January 2013 and December 2022, 141 patients with HTM at the First Affiliated Hospital, College of Medicine, Zhejiang University, were enrolled in this retrospective study. Patients with the following criteria were included: a seropositive HIV result; age ≥18 years; and diagnosis of *T marneffei*

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infection by culture, histopathologic, or next-generation sequencing (NGS). The exclusion criteria included a seronegative HIV result, age <18 years, and missing the necessary laboratory and therapeutic records. Seventeen patients who were HIV uninfected, 2 patients <18 years old, and 3 patients with HTM without laboratory results and therapy information were excluded from the analyses. Finally, 119 patients were included in the study (Supplementary 1).

Diagnosis of Talaromycosis

Talaromycosis was diagnosed with any one of the following criteria: (1) a positive culture of *T marneffei* by blood, bronchoalveolar lavage fluid (BALF), body fluids, or tissue biopsy, characterized by dimorphic fungi that grew as a mold at 25 °C or a yeast at 37 °C; (2) characteristic yeast cells (2–3 μm in diameter with oval, round, or sausage-like shapes and cells that divided by fission) observed in the tissue sections by periodic acid–Schiff staining or Wright staining; and (3) *T marneffei* sequences identified by NGS from the blood, BALF, body fluids, or tissue biopsy [17, 18].

Initial Induction Therapy

Antifungal therapy was administered to all patients immediately after the diagnosis of talaromycosis. The initial induction therapy involved intravenous amphotericin B (0.7 mg/kg/d) for 93 (78.2%) patients, voriconazole (8 mg/kg/d; divided into 2 doses) for 21 (17.6%), and itraconazole (400 mg/d; divided into 2 doses) for 5 (4.2%). Of those, 18 (15.1%) patients were treated with amphotericin B for <1 week, 9 (7.6%) with voriconazole for <1 week, and 1 (0.8%) with itraconazole for <1 week during induction therapy for intolerable side effects (Figure 1).

Laboratory Tests

Patients underwent routine laboratory screening within 24 hours after admission. The following measurement was done: complete blood count, CRP, ferritin, PCT, liver function tests, and kidney function tests. The initial laboratory test results after hospitalization were used for analyses. APRI was calculated as follows: [(AST/upper limit of normal) / platelet count $\times 10^9$/L] $\times$ 100 [19]. The CD4 count was measured by a flow cytometer (Becton Dickinson) with fluorescein isothiocyanate–conjugated antihuman CD4 (Becton Dickinson). Levels of cytokines were measured by enzyme-linked immunosorbent assay (Human Platinum ELISA Kit; eBioscience): interleukins 2, 4, 6, 10, and 17 (IL-2, IL-4, IL-6, IL-10, and IL-17), as well as tumor necrosis factor α (TNF-α) and interferon γ (IFN-γ).

Follow-up and Collection of Clinical Data

Basic medical information was recorded for all patients, such as age, sex, body mass index (BMI), blood test results, treatments, and follow-up, and saved in the electronic medical record system of the hospital. Patient information was collected by the hospital and local staff from the local Center for Disease Control and Prevention at treatment initiation, at each follow-up visit, at each regimen change, and again at treatment termination. Patients were followed up from the first day of admission until 24 weeks or death.

Statistical Analyses

The Shapiro-Wilk test was used to evaluate the normal distribution of data. Continuous normally distributed variables are presented as mean and SD. Continuous nonnormally distributed variables are presented as median and IQR. The receiver operating characteristic curve with Youden index was used to find the optimal cutoff for age, BMI, hemoglobin, albumin, PCT, CRP, ferritin, white blood cell (WBC) count, CD4 count, and APRI for categorical analysis. Receiver operating characteristic curve analysis for 24-week mortality following TM infection yielded an area under the curve of 0.69 (95% CI, .56–.79; $P = .004$). The APRI's optimal cutoff was established at 5.6, resulting in sensitivity and specificity values of 61.9% and 76.5%, respectively (Supplementary 2). Categorical variables are presented as number and percentage. Variables were compared by Student *t* test, Mann-Whitney *U* test, χ^2 analysis, or Fisher exact test. Patient survival was analyzed by the Kaplan-Meier method. Multivariable Cox regression models were used to analyze risk factors associated with 24-week mortality. *T marneffei*–related death was defined as an "event." The data of the patients were censored at the date of the final visit (for those alive at the end of follow-up) and the date last known to be alive (for those with unknown vital signs). Data not available were defined as "missing data." Univariate Cox regression models were fit for each covariate, and covariates with *P* values <.15 in the univariate model were selected for the multivariate Cox proportional hazards model per the forward likelihood ratio method. Data were analyzed with SPSS version 21.0 (IBM) and Prism version 9 (GraphPad).

Patient Consent Statement

This study was conducted in accordance with the 1975 Declaration of Helsinki and was approved by the Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University (No. 2021-599). The committee waived the requirement for written informed consent from the participants.

RESULTS

Patient Characteristics and Demographic Information

A total of 119 patients were enrolled in this study: 107 (89.9%) male and 12 (10.1%) female. The mean age was 38.2 ± 11.4 years. The median CD4 count was 8.0 cells/μL (IQR, 3.8–23.5). Twelve (10.1%) patients had liver disease: 9 with chronic hepatitis B, 2 with hepatic cirrhosis, and 1 with steatohepatitis. In total 97 (81.5%) patients had positive blood cultures, 17 (14.3%) had positive bone marrow cultures, 13 (10.9%) had

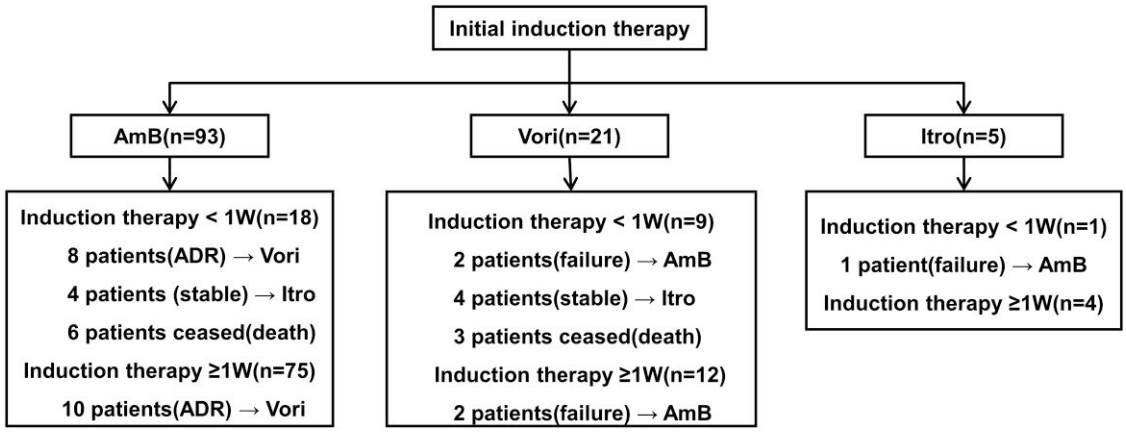

Figure 1. Initial induction treatment therapy of patients with HIV-associated *Talaromyces marneffei*. ADR, adverse drug reaction; AmB, amphotericin B deoxycholate; Itro, itraconazole; Vori, voriconazole.

Table 1. Baseline Characteristics and Outcome (N = 119)

Characteristic	Result
Age, y, mean ± SD	38.2 ± 11.4
Sex: male [No.(%)]	107 (89.9)
Body mass index, kg/m^2, mean ± SD	20.0 ± 3.4
CD4+, cell/μL, median (IQR)	8.0 (3.8–23.5)[a]
Comorbidities[No.(%)]	
Liver disease	12 (10.1)
Chronic pulmonary disease	5 (4.2)
Malignancies	4 (3.4)
Diabetes	3 (2.5)
Syphilis	2 (1.7)
Hypertension	1 (0.8)
Other	2 (1.7)
ART	38 (31.9)
Diagnosis	
Blood culture	97 (81.5)
Bone marrow culture	17 (14.3)
NGS	13 (10.9)
Histopathology	3 (2.5)
BALF culture	3 (2.5)
Skin culture	2 (1.7)
Urine culture	1 (0.8)
24-wk mortality [No.(5)]	24 (20.2)

Abbreviations: ART, antiretroviral therapy; BALF, bronchoalveolar lavage fluid; NGS, next-generation sequencing.

[a]Data available in 117 patients.

tested positive NGS results, 3 (2.5%) had positive histopathology results, 3 (2.5%) had positive cultures from BALF, 2 (1.7%) had positive skin cultures, and 1 (0.8%) had a positive urine culture. Of those patients, 13 were diagnosed by a method of blood culture with bone marrow culture, 3 by blood culture with NGS, and 1 by blood culture with BALF culture. Overall mortality was 20.2% (24/119) within 24 weeks. Patient characteristics and mortality are listed in Table 1.

APRI Was Correlated With CD4 Count and Serum Cytokine Concentration

The CD4 count was used to assay HIV/AIDS progression. We found that APRI was negatively correlated with CD4 count ($r = -0.234$, $P = .011$; Figure 2). We also assessed the relationships between APRI and PCT as well as WBC and CRP. Pearson correlation analyses suggested that an increased APRI was positively correlated with the PCT level ($r = 0.220$, $P = .018$) and CRP level ($r = 0.190$, $P = .039$; Figure 3*A* and 3*B*). No statistically significant correlation was found between APRI and WBC count ($P = .094$). Furthermore, relationships were studied between APRI and cytokines IL-2, IL-4, IL-6, IL-10, IL-17, TNF-α, and IFN-γ. Correlation analyses suggested that the level of APRI was associated with anti-inflammatory cytokines IL-4 ($r = 0.318$, $P = .038$) and IL-10 ($r = 0.416$, $P = .006$) (Figure 3*C* and 3*D*)and proinflammatory cytokines IL-6 ($r = 0.723$, $P < .001$) and TNF-α ($r = 0.575$, $P < .001$) (Figure 3*E* and 3*F*). There were no significant correlations between IL-2, IL-17, and IFN-γ and APRI ($P = .173$, $P = .386$, and $P = .359$, respectively).

APRI Predicted 24-Week Mortality of Patients With HTM

We assessed the prognostic factors that might affect the survival of patients with HTM. Patients were stratified according to the following criteria: age (<50.0 and ≥50.0 years), BMI (<19.0 and ≥19.0 kg/m^2), and antiretroviral therapy (on and off); serum levels of hemoglobin (<100.0 and ≥100.0 g/L), albumin (<35.0 and ≥35.0 g/L), PCT (<1.7 and ≥1.7 ng/mL), CR5P (<50.0 and ≥50.0 mg/L), and ferritin (<5000.0 and ≥5000.0 ng/mL); WBC count (<5.0 and ≥5.0 ×10^9/L) and CD4 count (<50.0 and ≥50.0 cells/μL); APRI (<5.6 and ≥5.6); and initial induction antifungal therapy (amphotericin B deoxycholate [AmB] and non-AmB [ie, AmB not included in the initial induction therapy]).

Of the 119 patients enrolled in our study, 20.2% (24/119) had died at the 24-week follow-up, including 10 (8.4%) with APRI

<5.6 and 14 (11.8%) with APRI ≥5.6. Risk factors associated with 24-week mortality were identified in our study. In the unadjusted model, we found that APRI ≥5.6 (hazard ratio [95% CI]; 4.0 [1.8–9.0], $P = .001$) PCT ≥1.7 ng/mL (4.9 [2.0–11.8], $P < .001$) and non-AmB treatment (2.5 [1.1–5.6], $P = .033$) were closely associated with 24-week mortality. Moreover, ferritin ≥5000.0 ng/mL (2.1 [0.8–5.4], $P = .114$) manifested trends toward association with 24-week mortality, albeit statistically nonsignificant.

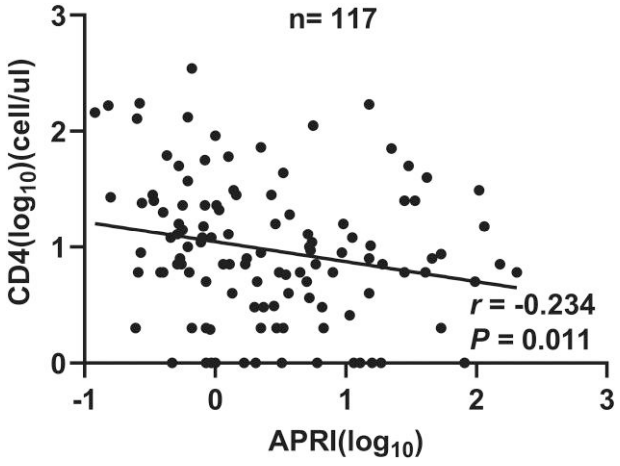

Figure 2. Correlation analysis of the APRI with CD4 count ($r = -0.234$, $P = .011$). APRI, aminotransferase/platelet ratio index.

In the adjusted model, our study indicated that APRI ≥5.6 (adjusted hazard ratio [95% CI]: 3.0 [1.2–7.1], $P = .015$), PCT ≥1.7 ng/mL (3.7 [1.5–9.6], $P = .006$), and non-AmB treatment (2.8 [1.2–6.6], $P = .018$) were independent risk factors for 24-week mortality in patients with HTM (Table 2). The 24-week survival rate was 88.0% for patients with HTM and APRI <5.6 and 61.1% for those with APRI ≥5.6 (log-rank $P < .001$; Figure 4*A*); 83.9% for patients treated with AmB and 65.4% for those treated with a non-AmB regimen (log-rank $P = .025$; Figure 4*B*); and 90.3% for patients with PCT <1.7 ng/mL and 61.4% for those with PCT ≥1.7 ng/mL (log-rank $P < .001$; Figure 4*C*).

DISCUSSION

T marneffei is an endemic opportunistic fungus leading to multiorgan damage and poor prognosis in people living with HIV. Among 119 patients with HTM, 20.2% died within the 24-week follow-up from the first day of hospitalization, even though all patients were administered with an antifungal regimen immediately after diagnosis. The mortality rate in our study is similar to that in research published by Sun et al in 2021 [20]. In our study, we found that APRI was negatively associated with CD4 count and positively associated with proinflammatory indicators (CRP, PCT, IL-6, TNF-α) and anti-inflammatory indicators (IL-4, IL-10). More important, a high APRI level was closely associated with a high risk of 24-week mortality. Even after adjustment for sex, age, BMI, and CD4 count as well as serum levels of hemoglobin, albumin, WBC count, CRP, PCT,

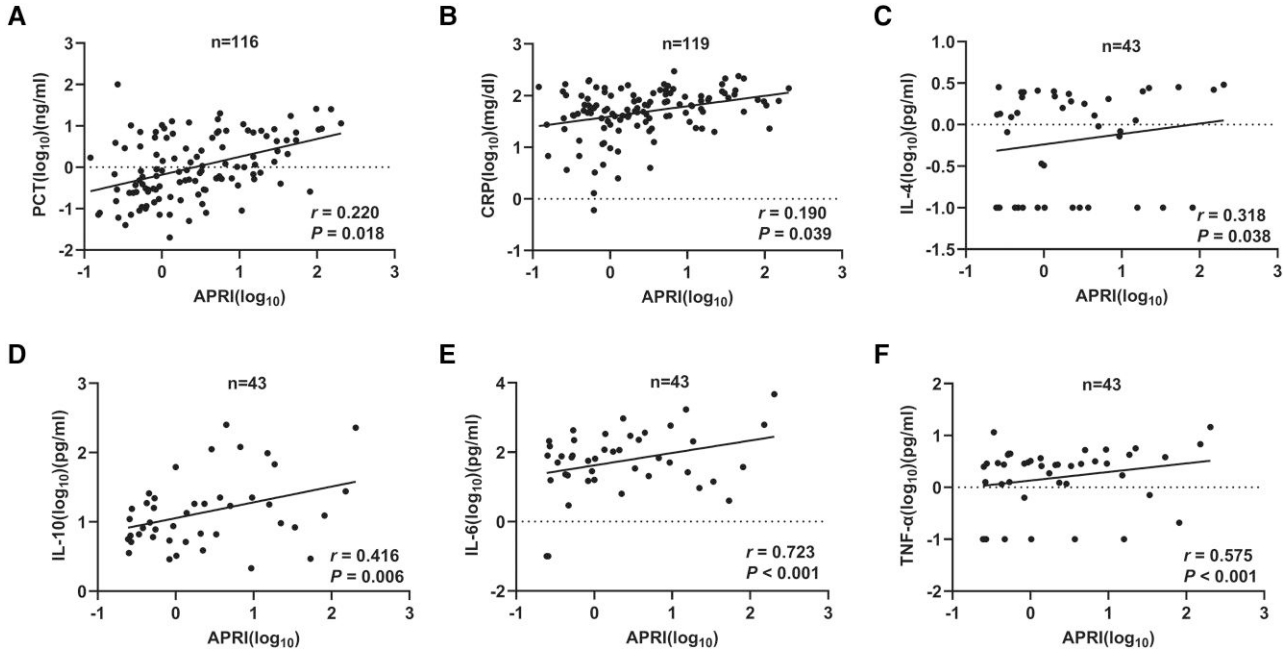

Figure 3. Correlation analysis of the APRI with PCT and CRP levels, as well as IL-4, IL-6, IL-10, and TNF-α. *A*, PCT ($r = 0.220$, $P = .018$). *B*, CRP ($r = 0.190$, $P = .039$). *C*, IL-4 ($r = 0.318$, $P = .038$). *D*, IL-10 ($r = 0.416$, $P = .006$). *E*, IL-6 ($r = 0.723$, $P < .001$). *F*, TNF-α ($r = 0.575$, $P < .001$). APRI, aminotransferase/platelet ratio index; CRP, C-reactive protein; IL, interleukin; PCT, procalcitonin; TNF-α, tumor necrosis factor α.

Table 2. Risk Factors for Mortality in Patients With HIV-Associated *Talaromyces marneffei*: Univariate and Multivariate Cox Proportional Hazard Models

		Risk Factors for 24-wk Mortality (N = 119)			
		Univariate		Multivariate	
Factor	Deaths (n = 24)	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Sex					
Male	21/107	1 [Reference]			…
Female	3/12	1.3 (.4–4.4)	.667		
Age, y					
<50.0	19/99	1 [Reference]			
≥50.0	5/20	1.4 (.5–3.7)	.511		…
BMI, kg/m^2					
<19.0	12/46	1.6 (.7–3.7)	.225		…
≥19.0	12/73	1 [Reference]			
Serum albumin, g/L					
<35.0	22/101	2.1 (.5–8.8)	.322	…	…
≥35.0	2/18	1 [Reference]			
WBC, ×10^9/L					
<5.0	15/86	1 [Reference]			
≥5.0	9/33	1.7 (.7–3.8)	.230		…
Hemoglobin, g/L					
<100.0	15/62	1.7 (.7–3.8)	.232		…
≥100.0	9/57	1 [Reference]			
C-reactive protein, mg/L					
<50.0	8/54	1 [Reference]			
≥50.0	16/65	1.8 (.8–4.3)	.167		…
Predisposing disease					
Yes	7/29	1 [Reference]			
No	17/90	1.3 (.5–3.0)	.624		
ART					
On	10/38	1.7 (.8–3.8)	.211		…
Off	14/81	1 [Reference]			
Procalcitonin, ng/mL					
Missing data	3	1 [Reference]			
<1.7	7/72			1 [Reference]	
≥1.7	17/44	4.9 (2.0–11.8)	.000	3.7 (1.5–9.6)	.006
Ferritin, ng/mL					
Missing data	1/6	…			
<5000.0	9/61	1 [Reference]	.114		…
≥5000.0	14/52	2.1 (.8–5.4)			
CD4 count, cells/μL					
Missing data	1/2	…			
<50.0	19/103	0.6 (.2–1.8)	.368		…
≥50.0	4/14	1 [Reference]			
APRI					
<5.6	10/83	1 [Reference]		1 [Reference]	
≥5.6	14/36	4.0 (1.8–9.0)	.001	3.0 (1.2–7.1)	.015
Initial treatment					
AmB	15/93	1 [Reference]		1 [Reference]	
Non-AmB treatment	9/26	2.5 (1.1–5.6)	.033	2.8 (1.2–6.6)	.018

Abbreviations: AmB, amphotericin B deoxycholate; APRI, aminotransferase/platelet ratio index; ART, antiretroviral therapy; BMI, body mass index; HR, hazard ratio; WBC, white blood cell.

and ferritin, APRI ≥5.6 was associated with a 3-fold higher risk of death in patients with HTM in the multivariate model. Thus, APRI may be a useful surrogate to predict clinical outcomes in patients with HTM.

AST is mainly expressed in liver and muscle. Infectious diseases involving the liver might increase serum AST levels. A study indicated that liver injury was common in critical cases of HTM and that a higher AST level was associated with increased morbidity and mortality [21]. In addition, patients with HTM and thrombocytopenia had a higher mortality as compared with those with normal platelet levels [1]. Although APRI is widely used to predict severity and mortality of

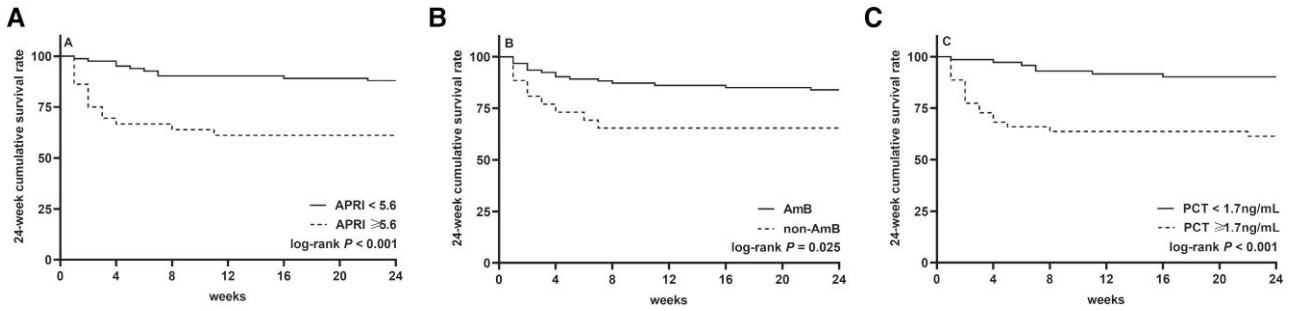

Figure 4. Factors associated with survival of patients. *A*, The 24-week culmulative survival rate was 88.0% for patients with APRI <5.6% and 61.1% for patients with APRI ≥5.6 ($P < .001$). *B*, The 24-week culmulative survival rate was 83.9% for patients treated with AmB and 65.4% for patients treated with non-AmB ($P = .025$). *C*, The 24-week culmulative survival rate was 90.3% for patients with PCT <1.7ng/mL and 61.4% for patients with PCT ≥1.7 ng/mL ($P < .001$). AmB, amphotericin B deoxycholate; APRI, aminotransferase/platelet ratio index; PCT, procalcitonin.

COVID-19, dengue, and malaria [11, 22, 23], its utility on HTM is undeterminable. Interestingly, our results showed that APRI was a surrogate to predict the mortality of patients with HTM. When compared with those with APRI <5.6 on admission, patients with HTM with APRI ≥5.6 had a 3-fold risk of 24-week mortality even after adjustment for PCT and treatment.

Complex factors predispose to an increased APRI in patients with HTM. First, HIV-associated factors may directly or indirectly affect APRI. HIV infection is associated with elevated liver enzymes and thrombocytopenia [24–26]. Both processes contribute to increased APRI levels. A previous study reported that a significantly higher APRI was found in 8.0% of patients who were HIV monoinfected without liver steatosis [27]. Furthermore, a lower CD4 count (especially ≤200 cells/μL) was associated with a greater likelihood of a higher APRI [28, 29]. Consistent with those studies, we found that APRI was closely associated with CD4 counts in our data. Second, liver and bone marrow involvement might affect APRI. Hepatic involvement by *T marneffei* is common in patients with AIDS [5]. *T marneffei* induces pyroptosis in hepatocytes through activation of the AIM2–caspase-1/4–GSDMD axis, which may lead to hepatocyte damage [30]. In addition, microbial infection can reduce platelet production by inhibiting bone marrow function [31]. Some studies found that pathogens can directly infect megakaryocytes and alter the bone marrow microenvironment, resulting in low production of platelets in the bone marrow [32]. Third, inflammatory and anti-inflammatory reactions accentuate higher APRI. Several reports have indicated that proinflammatory cytokines (IL-6, TNF-α) have a positive relationship with APRI [33, 34]. Our results confirmed the association between APRI and proinflammatory cytokines. We also found that anti-inflammatory cytokines (IL-4, IL-10) had a weak correlation with APRI, which is in line with previous research [35]. It seemed that the imbalance between pro- and anti-inflammatory cytokines contributed to elevated APRI. This may be the result of polarized macrophages, induced by IL-6, secreting anti-inflammatory cytokines [36]. Overall, our results clearly show that APRI was associated with severity and mortality of HTM. Since APRI is a readily available indicator via routine laboratory blood tests, it should be considered a simple and convenient parameter to evaluate the severity of disease and the risk of mortality in this population.

In our study, the correlation coefficients of APRI with PCT and CRP were low, yet IL-6 and TNF-α showed high correlations with APRI. The possible reason was that PCT and CRP were not specific inflammatory markers solely related to *T marneffei* infection [37], whereas IL-6 and TNF-α are cytokines that participate in the modulation of infection, inflammation, and hepatic function [38].

There are several limitations in our study. First, it is a retrospective cohort study with a small sample size; as such, a large cohort study is needed to confirm our conclusions. Second, the relationships between cytokines and patient outcomes were not fully discussed because cytokine assay was not performed in all patients. Third, the impacts of some liver diseases, such as cirrhosis, were not fully discussed due to the few patients with liver disease in our study. Fourth, we did not analyze the dynamic changes of APRI because some individuals accepted antithrombocytopenia treatment during hospitalization.

In summary, our data suggest that elevated APRI is associated with poor outcomes among patients with HTM. APRI level could serve as a surrogate for the degree of inflammation and is an independent risk factor for increased mortality in patients with HTM.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Acknowledgments

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Author contributions. Q. W. performed the study and prepared the drafted manuscript. H. Z. collected the data. Y. T., J. Q., and M. Z. performed the follow-up. L. X. designed the study and revised manuscript.

Ethical approval. This study was conducted in accordance with the 1975 Declaration of Helsinki and was performed under the auspices of protocols that were approved by the Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University (Hangzhou, China; No. 2021-599). All electronic data analyzed were anonymous.

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Potential conflicts of interest. All authors: No reported conflicts.

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