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ORIGINAL RESEARCH

Association Between Age and the 28-Day All-Cause Mortality in Tuberculosis Complicated by Sepsis in ICU Patients: A Retrospective Cohort Study

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Purpose: Age is considered a vital factor in intensive care units (ICUs) because of its association with physiological frailty, comorbidities, and immune system function. Previous studies have examined the association between age and prognosis in patients with tuberculosis (TB) or sepsis; however, the association between age and prognosis in ICU patients with TB complicated by sepsis is rare. This study aimed to assess the association between age and the prognosis of patients in the ICU with TB complicated by sepsis.

Patients and Methods: Data from the ICU of the Public Health Clinical Center of Chengdu were analyzed using the multivariable Cox regression model, stratified analysis with interaction, restricted cubic spline (RCS), and threshold effect analysis to investigate the association between age and 28-day all-cause mortality in patients with TB complicated by sepsis.

Results: In total, 520 patients diagnosed with TB and sepsis were enrolled (120 women [23.1%]; median age, 64 years). The association between age and risk of death exhibited a J-shaped curve on the RCS (P for nonlinearity = 0.001). In the threshold analysis, the hazard ratio for the risk of death was 1.104 (95% confidence interval, 1.05–1.16) in participants aged ≥66.2 years. The risk of death increased by 10.4% with every 1-year increase in age in patients with TB complicated by sepsis. No significant association was found between age and 28-day all-cause mortality in patients aged <66.2 years.

Conclusion: A nonlinear relationship was observed between age and short-term all-cause mortality in patients in the ICU with TB complicated by sepsis. Patients with a higher age at admission may have a higher risk of death and require focused attention, close monitoring, and early treatment to reduce mortality.

Keywords: sepsis, tuberculosis, age, 28-day all-cause mortality, intensive care unit

Introduction

Tuberculosis (TB) is a chronic infectious disease caused by *Mycobacterium tuberculosis*. The World Health Organization reported a total of 10.6 million new cases of TB and 1.3 million deaths worldwide in 2022, making it one of the leading infectious disease killers globally.[1] Sepsis is a severe organ dysfunction caused by an inadequate or dysregulated response to infection.[2] According to an analysis of the global burden of sepsis from 1990 to 2017,[3] approximately 48.9 million cases of sepsis and 11 million deaths worldwide were documented in 2017. A meta-analysis based on modeling or prospective studies in 2023 reported that the annual incidence of sepsis worldwide was 276–678 per 100,000, with a fatality rate of 22.5–26.7%;[4] however, the study data only represented some regions worldwide. Another epidemiological study on sepsis in China showed that the annual incidence of sepsis was approximately 421.85/100,000 in 2019, of which 57.5% occurred in individuals aged >65 years and the hospital fatality rate was approximately 30%.[5] TB complicated by sepsis involves chronic and acute infections, contributing to the increased complexity of the condition and resulting in an unfavorable prognosis. Therefore, exploring the factors related to the prognosis in this patient group is of paramount importance.

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Rapidly aging populations pose a huge challenge to the global allocation of limited health care resources. Age is a crucial indicator of immune function and physiology. With increasing age, the immune system undergoes a series of changes, including a decline in the immune response, alterations in the inflammatory response, and a decrease in disease tolerance,[6] leading to significant differences in clinical manifestations and therapeutic outcomes in patients of different ages. An increasing number of studies have focused on the changes in organ function, increased frailty, and decreased activities of daily living in older patients that lead to increased intensive care unit (ICU) admissions and mortality.[7,8] Several studies have shown that older patients are at an increased risk of developing active TB due to waning immunity and combined chronic diseases.[9,10] They may exhibit atypical symptoms, delayed diagnosis, and experience more severe forms of the disease. It is well known that advanced age is a risk factor for developing sepsis, and older adults are more prone to severe sepsis and have a higher mortality rate compared to younger patients.[5,11] However, few studies have assessed the association between age and prognosis in patients admitted to the ICU with sepsis-complicated TB. This study aimed to investigate whether age is independently associated with 28-day all-cause mortality in patients admitted to the ICU with TB complicated by sepsis. This exploration is crucial for a more comprehensive assessment of patient prognosis and development of strategies for graded management.

Materials and Methods

Study Design and Participants

This retrospective single-center analysis used the data of consecutive patients who were diagnosed with TB complicated by sepsis in the ICU at the Public Health Clinical Center of Chengdu (Sichuan Province, China, between January 1, 2019, and February 1, 2023. This study was conducted in accordance with the principles of the Declaration of Helsinki (revised in Brazil, 2013) and was approved by the Ethics Review Board of the Public Health Clinical Center of Chengdu (YJ-K2022-16-01). Due to the retrospective nature of the study, no intervention was involved, anonymous patient data were used, and the requirement for obtaining informed consent was waived. This study was conducted following the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[12]

TB was diagnosed using the International Classification of Disease, Tenth Revision (ICD-10),[13] based on the results of etiological (including bacteriology and molecular biology) examination, epidemiological history, clinical manifestations, imaging findings, auxiliary examination results, and differential diagnosis; a comprehensive analysis was used for diagnosis.[14] Sepsis was defined as an infection combined with evidence of organ dysfunction based on the third international consensus definition.[2] Additionally, ICD-10 criteria were used to diagnose the infection. Organ dysfunction was characterized by an increased sequential organ failure assessment (SOFA) score of ≥2 points.[13,15] The baseline SOFA score of all patients in the ICU was presumed to be 0.[16] In addition, the diagnoses and treatments of all patients admitted to the ICU were discussed by at least two critical care physicians.

Upon admission to the ICU, all participants underwent a comprehensive assessment and standardized medical history data collection, including physical and laboratory examinations, and collection of demographic and health-related data. In cases in which a patient's critical condition impeded the direct acquisition of standardized medical history data, information was obtained from immediate family members.

Inclusion and Exclusion Criteria

Patients who, (1) required special monitoring and treatment in the ICU, (2) met the diagnostic criteria for TB complicated by sepsis, (3) were aged between 18 and 80 years, and (4) were admitted to the ICU for at least 24 h, were selected. Pregnant women, patients with tumors, and patients with HIV infections were excluded. The inclusion and exclusion criteria are shown in Figure 1.

Data Collection

The data used in this study were extracted from the hospital's electronic information management system. First, the population included in the study was determined based on the inclusion and exclusion criteria. The demographic information of the patients was extracted, and an Excel database was established.

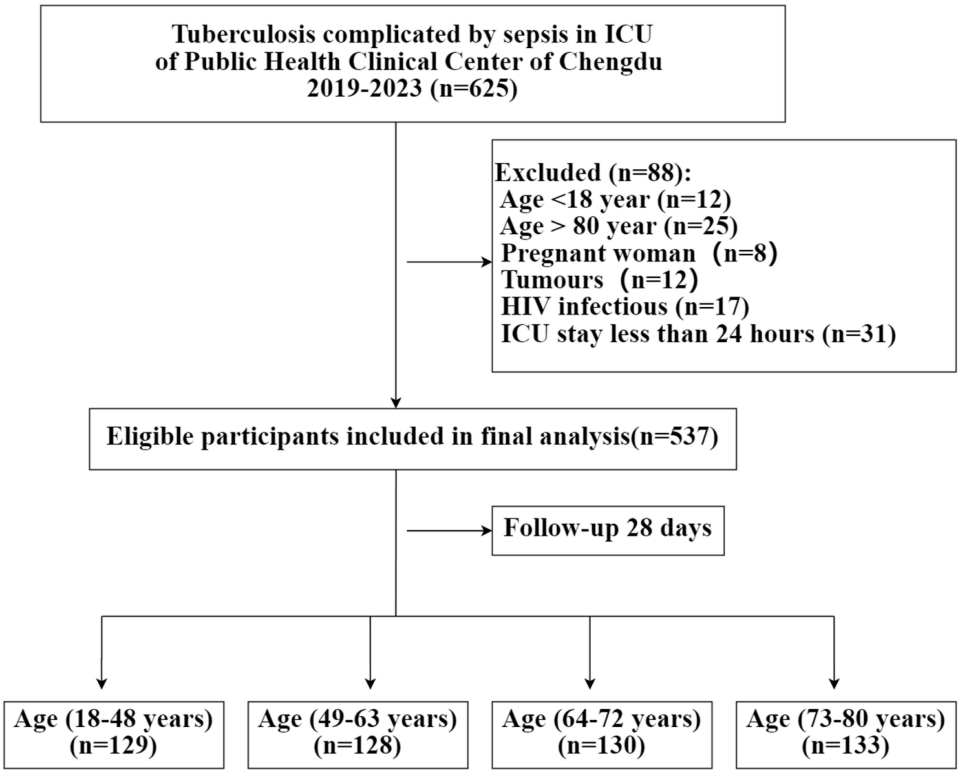

Figure 1 Flow chart of participants included in this analysis.

Demographic information included age, gender, race, smoking status, alcohol use, body mass index (BMI), and severity at admission as measured by the Acute Physiology and Chronic Health Evaluation (APACHE) II and SOFA scores. We categorized the participants into two races: Han Chinese and others (including Tibetans and Yis).

Previous studies have confirmed that age, BMI, hypertension, diabetes, intra-abdominal infection, hypotension, and lactate and hemoglobin (HGB) levels are prognostic risk factors for TB or sepsis.[17–19] To further investigate the association between age and risk of 28-day all-cause mortality in patients admitted to the ICU with TB complicated by sepsis, our study also included indicators such as immunosuppressive therapy, drug-resistant tuberculosis, primary site of infection (intra-abdominal infection and urinary tract infection), primary site of tuberculosis infection (pulmonary tuberculosis, tuberculous meningitis [TBM], intra-abdominal tuberculosis, urinary system tuberculosis, and tuberculosis in other parts of the body), comorbidities (chronic obstructive pulmonary disease [COPD], chronic kidney disease [CKD], chronic liver disease, systemic lupus erythematosus [SLE], rheumatoid arthritis [RA], and pneumothorax), vital signs (temperature, heart rate, respiratory rate, and mean arterial pressure [MAP]), laboratory test indicators (including count of white blood cells [WBC], red blood cells, and platelets, platelet count [PLT], and levels of HGB, procalcitonin level, C-reactive protein, and lactate), and interventions (invasive mechanical ventilation and vasopressor use). Based on the small number of patients with bone, laryngeal, skin, and genital tuberculosis in our study, we collected them into one group named tuberculosis in other parts of the body.

Demographic characteristics and vital signs were obtained at the time of ICU admission, and comorbidities were primarily identified through patient self-reports or previous diagnoses. Laboratory tests were performed using blood samples collected within 24 h of admission to the ICU. APACHE II and SOFA scores were obtained within 24 h of ICU admission. Patients were considered to have an intervention (invasive mechanical ventilation, vasopressor use) if it occurred within 24 h of admission to the ICU.

Outcome

The primary outcome of this study was the 28-day all-cause mortality from the day of ICU admission. Due to the retrospective nature of this study, endpoint events were determined by collecting patient information.

Statistical Analysis

This study aimed to determine the association between age and 28-day all-cause mortality in patients with TB complicated by sepsis. To gain a more detailed understanding of the characteristics of the study population at different ages, the patients were divided into four groups based on age quantiles, rather than the unevenly distributed tertiles, and a descriptive analysis was performed (Supplementary Table 1). Continuous data with a skewed distribution were expressed as medians and interquartile ranges. Categorical variables were expressed as proportions (%). Baseline characteristics across age quartile groups were compared using one-way analysis of variance for continuous variables and Pearson's chi-square test or Fisher's exact test for categorical variables. Survival curves for different age groups were plotted using the Kaplan–Meier method and compared statistically using the Log rank test.

Cox hazard regression models were used to determine the hazard ratios (HR) and 95% confidence intervals (95% CIs) for the relationship between age and 28 d mortality. Model I was unadjusted. Model II was adjusted for gender and comorbidities (hypertension, diabetes mellitus, COPD, chronic liver disease, SLE, RA, and pneumothorax). Model III was adjusted for model II plus drug-resistant tuberculosis, primary site of infection (intra-abdominal and urinary tract infections), and primary site of tuberculosis infection (pulmonary tuberculosis, TBM, intra-abdominal tuberculosis, urinary system tuberculosis, and tuberculosis in other parts of the body). In model IV, we selected these covariables based on their association with the outcomes of interest or a change-in-effect estimate >10%, which included BMI, hypertension, COPD, heart rate, mechanical ventilation, and vasopressor use (Supplementary Table 2).[20] Model V was adjusted for gender and the variables with P values <0.05 in the univariate Cox regression model (including immunosuppressive therapy, BMI, intra-abdominal infection, urinary tract infection, hypertension, diabetes, CKD, temperature, heart rate, MAP, HGB and lactate levels, PLT count, mechanical ventilation, and vasopressor use) (Supplementary Table 3).[21]

In addition, RCS regression was performed with four knots at the 5th, 35th, 65th, and 95th percentiles of age to assess linearity and examine the dose-response curve between age and 28-day all-cause mortality in TB complicated by sepsis after adjusting for the variables in model V.

If the relationship was nonlinear, we used a two-piecewise Cox regression model with smoothing to analyze the association threshold between age and 28-day all-cause mortality after adjusting for the variables in Model V. The likelihood-ratio test and bootstrap resampling method were used to determine inflection points.

Furthermore, potential modifications to the relationship between age and 28 d mortality were assessed, including gender, immunosuppressive therapy, drug-resistant tuberculosis, hypertension, diabetes, COPD, CKD, pneumothorax, mechanical ventilation, and vasopressor use. Heterogeneity among the subgroups was assessed using multivariate Cox hazard regression, and interactions between the subgroups and age were examined using likelihood ratio testing.

All analyses were performed using R Statistical Software (version 4.2.2, http://www.R-project.org) and the Free Statistics analysis platform (Version 1.8). A two-tailed test was performed, and a P value of <0.05 was considered significant.

Results

Patient Selection

Six hundred and twenty-five patients with TB who developed sepsis were identified according to the third international consensus definition. After screening based on the inclusion and exclusion criteria, the final cohort included 520 patients. A flowchart of the patient selection process is shown in Figure 1.

Patient Baseline Characteristics

The baseline patient characteristics are presented in Table 1. The enrolled patients were divided into four groups by the quartiles of age: Q1 group, 18–48 years; Q2 group, 49–63 years; Q3 group, 64–72 years; and Q4 group, 73–80 years. The median age of all participants was 64.0 (49.0, 73.0) years, and 23.1% were female. Participants with a higher age were more likely to have higher APACHE II scores, higher mortality, male, Han Chinese ethnicity, alcohol use, hypertension, diabetes, and COPD, be smokers, and were less likely to have drug-resistant tuberculosis and chronic liver disease

Table 1 Baseline Characteristics of the Study Participants by Age Quartiles

	Overall	Age(Years)				*P*-value	Statistic
		Q1 (18–48)	Q2 (49–63)	Q3 (64–72)	Q4 (73–80)		
No.	520	129	128	130	133		
Age	64.0 (49.0, 73.0)	37.0 (27.0, 44.0)	56.0 (53.0, 60.0)	68.0 (66.0, 70.0)	77.0 (75.0, 80.0)	< 0.001	486.952
Gender (Female)	120 (23.1)	52 (40.3)	19 (14.8)	24 (18.5)	25 (18.8)	< 0.001	29.402
Race						< 0.001	39.738
Han Chinese	419 (80.6)	80 (62)	106 (82.8)	114 (87.7)	119 (89.5)		
Other[a]	101 (19.4)	49 (38)	22 (17.2)	16 (12.3)	14 (10.5)		
Smoking	291 (56.0)	48 (37.2)	87 (68)	83 (63.8)	73 (54.9)	< 0.001	29.236
Alcohol use	195 (37.5)	28 (21.7)	63 (49.2)	60 (46.2)	44 (33.1)	< 0.001	26.492
Immunosuppressive therapy[b]	34 (6.5)	6 (4.7)	11 (8.6)	8 (6.2)	9 (6.8)	0.641	1.68
BMI	19.0 (18.3, 21.3)	19.3 (18.5, 23.0)	19.1 (18.3, 21.3)	19.0 (18.3, 20.1)	19.0 (18.2, 21.0)	0.222	4.391
Drug resistant tuberculosis	86 (16.5)	39 (30.2)	21 (16.4)	18 (13.8)	8 (6)	< 0.001	28.88
Severity of illness							
APACHE II score	17.0 (13.0, 21.0)	15.0 (13.0, 20.0)	17.0 (12.0, 21.0)	17.0 (15.0, 21.0)	18.0 (16.0, 23.0)	< 0.001	23.18
SOFA score	4.0 (3.0, 6.0)	4.0 (3.0, 5.0)	4.0 (3.0, 6.0)	4.0 (3.0, 6.0)	4.0 (3.0, 6.0)	0.203	4.603
Main site of infection							
Intra-abdominal infection	28 (5.4)	6 (4.7)	6 (4.7)	7 (5.4)	9 (6.8)	0.86	0.757
Urinary tract infection	2 (0.4)	0 (0)	1 (0.8)	0 (0)	1 (0.8)	0.745[d]	Fisher
Main site of tuberculosis infection							
Pulmonary tuberculosis	480 (92.3)	121 (93.8)	118 (92.2)	119 (91.5)	122 (91.7)	0.902	0.577
TBM	46 (8.8)	15 (11.6)	9 (7)	10 (7.7)	12 (9)	0.576	1.981
Intra-abdominal tuberculosis	59 (11.3)	15 (11.6)	16 (12.5)	15 (11.5)	13 (9.8)	0.916	0.511
Urinary system tuberculosis	11 (2.1)	4 (3.1)	4 (3.1)	1 (0.8)	2 (1.5)	0.46[d]	Fisher
Tuberculosis in other parts of the body[c]	28 (5.4)	8 (6.2)	9 (7)	6 (4.6)	5 (3.8)	0.639	1.691
Comorbidities							
Hypertension	113 (21.7)	2 (1.6)	22 (17.2)	30 (23.1)	59 (44.4)	< 0.001	72.625
Diabetes	102 (19.6)	12 (9.3)	30 (23.4)	31 (23.8)	29 (21.8)	0.008	11.767
COPD	109 (21.0)	4 (3.1)	11 (8.6)	44 (33.8)	50 (37.6)	< 0.001	71.89
CKD	33 (6.3)	3 (2.3)	8 (6.2)	9 (6.9)	13 (9.8)	0.102	6.213
Chronic liver disease	29 (5.6)	5 (3.9)	15 (11.7)	7 (5.4)	2 (1.5)	0.003	14.077
SLE	7 (1.3)	3 (2.3)	1 (0.8)	0 (0)	3 (2.3)	0.297[d]	Fisher
RA	12 (2.3)	0 (0)	3 (2.3)	5 (3.8)	4 (3)	0.154[d]	Fisher
Pneumothorax	31 (6.0)	13 (10.1)	7 (5.5)	4 (3.1)	7 (5.3)	0.112	5.999
Vital signs							
Temperature	36.8 (36.5, 37.5)	36.9 (36.6, 38.0)	36.7 (36.5, 37.6)	37.0 (36.6, 37.7)	36.8 (36.5, 37.1)	0.013	10.751
Heart rate	115.0 (100.0, 130.0)	126.0 (113.0, 140.0)	117.0 (97.8, 131.2)	112.5 (99.0, 125.8)	109.0 (98.0, 122.0)	< 0.001	41.877
Respiratory rate	32.0 (30.0, 35.0)	35.0 (31.0, 40.0)	32.0 (30.0, 35.0)	32.0 (30.0, 33.8)	32.0 (30.0, 34.0)	< 0.001	27.099
MAP	91.5 (78.0, 102.0)	88.0 (77.0, 101.0)	92.5 (78.8, 104.2)	95.0 (79.2, 104.0)	92.0 (77.0, 101.0)	0.250	4.11

(*Continued*)

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Table 1 (Continued).

	Overall	Age(Years)				*P*-value	Statistic
		Q1 (18–48)	Q2 (49–63)	Q3 (64–72)	Q4 (73–80)		
Laboratory test indicators							
WBC	8.4 (6.0, 11.7)	9.3 (6.7, 13.3)	7.9 (5.5, 11.7)	8.1 (6.2, 10.8)	8.0 (5.9, 11.4)	0.083	6.688
RBC	3.9 (3.3, 4.5)	4.0 (3.6, 4.7)	3.9 (3.2, 4.6)	3.8 (3.3, 4.4)	3.7 (3.1, 4.2)	0.003	14.095
HGB	108.0 (91.0, 125.0)	110.0 (92.0, 126.0)	109.0 (91.0, 131.0)	109.0 (92.0, 123.0)	101.0 (86.0, 123.0)	0.130	5.654
PLT	201.0 (124.5, 281.0)	235.0 (146.0, 314.0)	185.0 (105.0, 274.8)	193.5 (111.0, 271.5)	197.0 (126.0, 265.0)	0.025	9.308
PCT	0.5 (0.2, 1.5)	0.6 (0.2, 2.4)	0.5 (0.1, 1.4)	0.4 (0.1, 1.2)	0.4 (0.1, 1.3)	0.484	2.451
CRP	89.4 (51.0, 137.0)	83.7 (43.0, 124.9)	85.9 (51.0, 137.0)	96.1 (52.2, 144.2)	89.7 (53.9, 144.0)	0.425	2.79
Lactate	2.0 (1.5, 2.8)	2.1 (1.5, 2.9)	2.3 (1.5, 3.3)	1.9 (1.4, 2.6)	2.0 (1.6, 2.5)	0.121	5.812
Interventions							
Invasive mechanical ventilation use	107 (20.6)	35 (27.1)	24 (18.8)	22 (16.9)	26 (19.5)	0.187	4.801
Vasopressor use	132 (25.4)	38 (29.5)	32 (25)	24 (18.5)	38 (28.6)	0.162	5.142
Outcome							
28day los (Days)	19.5 (7.0, 28.0)	28.0 (9.0, 28.0)	22.0 (7.0, 28.0)	24.0 (8.0, 28.0)	12.0 (4.0, 28.0)	< 0.001	17.552
28-day mortality (Death)	241 (46.3)	52 (40.3)	53 (41.4)	51 (39.2)	85 (63.9)	< 0.001	22.292

Notes: Values are presented as median (interquartile range, IQR) for continuous variables of non-normal distribution and number (percentage) for categorical variables. [a]Including 98 Tibetans and 3 Yi ethnics; [b]Take immunosuppressants for more than 2 weeks before staying in ICU. [C]There were 17 cases of bone tuberculosis, 6 cases of laryngeal tuberculosis, 3 cases of skin tuberculosis (1 case with bone tuberculosis) and 3 cases of genital tuberculosis; [d]Fisher's exact test.

Abbreviations: BMI, body mass index; APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment; TBM, tuberculous meningitis; COPD, obstructive pulmonary disease; CKD, chronic kidney disease; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; MAP, mean arterial pressure; WBC, white blood cell; RBC, red blood cell; HGB, hemoglobin; PLT, platelet; PCT, procalcitonin; CRP, C-reactive protein.

compared with participants in the lowest age quartile. Additionally, significant differences in other indicators were observed between the groups, with participants in the highest age quartile having a lower temperature, heart and respiratory rates, WBC and PLT counts, and HGB level than those in the lowest age quartile.

Outcomes

The overall 28-day all-cause mortality rate was 46.3%. The 28-day all-cause mortality rates of patients in the lowest to highest age quartile (18–48, 49–63, 64–72, and 73–80) were 40.3, 41.4, 39.2, and 63.9%, respectively (Table 1). Kaplan–Meier curves showed that patients in the higher age quartile had a higher risk of 28-day all-cause mortality (Log rank test, P <0.0001, Figure 2).

Association between age and 28-day all-cause mortality

We constructed five multivariate Cox regression models to investigate the independent association between age and mortality risk in patients with TB complicated by sepsis (Table 2). In model I, which was not adjusted for covariables, age was positively associated with 28-day all-cause mortality (HR, 1.016; 95% CI, 1.007–1.024). Even after adjusting for various covariates in models II–V, mortality still increased by 1.2–1.8% for every 1-year increase in age (Table 2).

When age was entered as a categorical variable in each adjusted model, the changing trend of the effective value in different age groups was non-equidistant. After adjusting for gender, immunosuppressive therapy, BMI, intra-abdominal infection, urinary tract infection, hypertension, diabetes, CKD, temperature, heart rate, MAP, HGB and lactate levels, PLT count, invasive mechanical ventilation, and vasopressor use in model V, the multivariate-adjusted HR and 95% CI from lowest to highest age quartile (18–48, 49–63, 64–72, and 73–80) were 1.00 (reference), 0.97 (0.64, 1.46), 0.99 (0.64, 1.55), and 1.83 (1.21, 2.77), respectively, for the risk of 28-day all-cause mortality (P = 0.001) (Table 2).

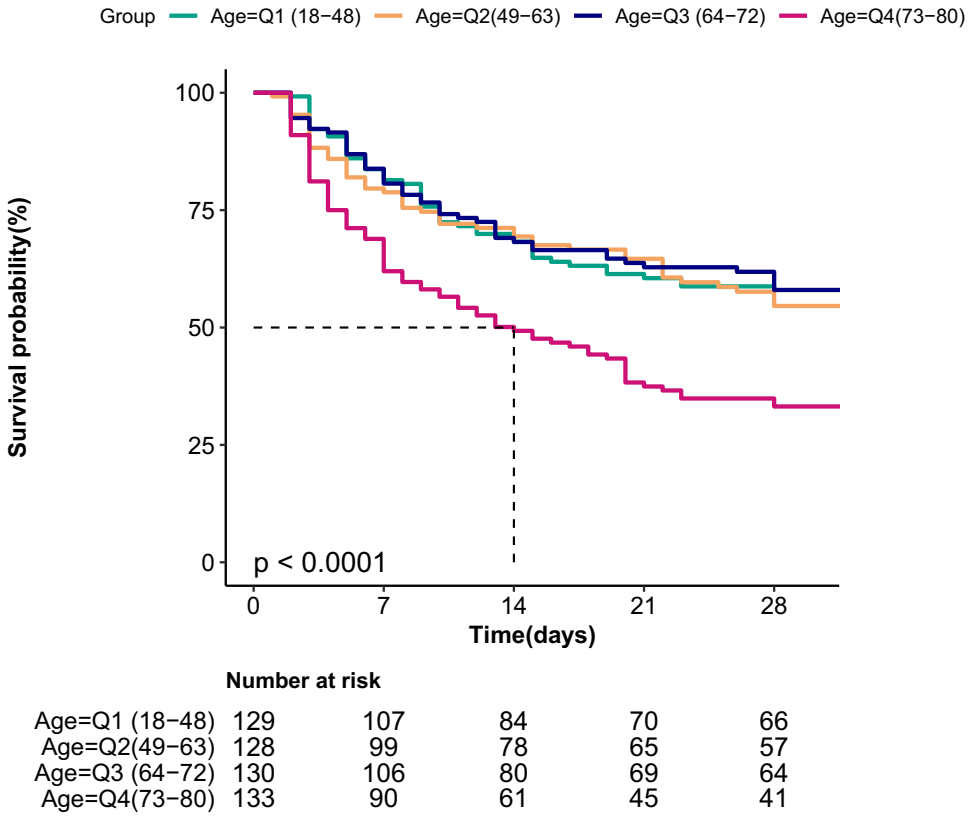

Figure 2 Kaplan-Meier survival curve for 28-day mortality of tuberculosis complicated by sepsis in different age groups.
Notes: Log rank X^2 = 26.43, df = 3, P < 0.001.

Table 2 Association Between Age and the 28-Day All-Cause Mortality in Tuberculosis Complicated by Sepsis ICU Patients

Exposure	Model I		Model II		Model III		Model IV		Model V	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age(years)	1.016 (1.007~1.024)	<0.001	1.013 (1.003~1.023)	0.0093	1.012 (1.002~1.022)	0.0162	1.018 (1.008~1.028)	0.001	1.013 (1.003~1.023)	0.008
Age tertiles (years)										
Q1 (18–48)	1(Ref)		1(Ref)		1(Ref)		1(Ref)		1(Ref)	
Q2(49–63)	1.09 (0.74~1.6)	0.665	1.01 (0.67~1.5)	0.975	0.99 (0.66~1.48)	0.958	1.11 (0.74~1.67)	0.599	0.97 (0.64~1.46)	0.882
Q3 (64–72)	0.99 (0.67~1.46)	0.956	0.88 (0.58~1.34)	0.565	0.87 (0.57~1.33)	0.516	1.16 (0.75~1.8)	0.506	0.99 (0.64~1.55)	0.978
Q4(73–80)	2.02 (1.43~2.86)	<0.001	1.75 (1.18~2.6)	0.006	1.72 (1.15~2.59)	0.009	2.15 (1.43~3.24)	<0.001	1.83 (1.21~2.77)	0.004
P for trend	1.25 (1.11~1.41)	<0.001	1.2 (1.05~1.37)	0.006	1.2 (1.04~1.37)	0.011	1.31 (1.14~1.5)	<0.001	1.25 (1.09~1.43)	0.001

Notes: Model I = not adjusted for covariables; Model II = adjusted for gender + comorbidities (hypertension, diabetes, COPD, CKD, chronic liver disease, SLE, RA, and pneumothorax); Model III = adjusted for model II +drug resistant tuberculosis+Main site of infection(intral-abdominal infection, urinary tract infection) +main site of tuberculosis infection(Pulmonary tuberculosis, TBM, intra-abdominal tuberculosis, urinary system tuberculosis, and tuberculosis in other parts of the body); Model IV =adjusted for gender, BMI, hypertension, COPD, Heart rate, invasive mechanical ventilation use, and vasopressor use; Model V = adjusted for gender, immunosuppressive therapy, BMI, intra-abdominal infection, urinary tract infection, hypertension, diabetes, CKD, temperature, heart rate, MAP, HGB, PLT, lactate, invasive mechanical ventilation use, and vasopressor use.

Abbreviations: HR, hazard ratio; CI, confidence interval; HR, hazard ratio, Ref, reference.

Dose-Response Relationship Between Age and Mortality

As a previous multivariate Cox regression analysis indicated a nonlinear relationship between baseline age and the risk of 28-day all-cause mortality in patients with TB complicated by sepsis, we employed a Cox proportional hazards regression model with RCS analysis to further investigate the correlation. Multivariate-adjusted RCS analyses suggested J-shaped associations between age and 28-day all-cause mortality in patients with TB complicated by sepsis (P for nonlinearity = 0.001, Figure 3). Similarly, the unadjusted RCS analysis yielded consistent results (nonlinear $P < 0.001$, Figure 5). Based on the threshold effect analysis, we identified the inflection age for the 28-day all-cause mortality as 66.2 years (Table 3). Beyond this threshold, the 28-day all-cause mortality demonstrated a rapid increase with a multivariable adjusted HR of 1.104 (95% CI, 1.05–1.16; Table 3); below this threshold, the estimated dose-response curve remained consistent with a approximately horizontal line with a multivariable adjusted HR of 0.996 (95% CI, 0.980–1.012; Table 3). This finding suggests that the 28-day all-cause mortality risk increased by 10.4% every year after the age of 66.2 years. However, the risk of mortality did not increase with advancing age when age was <66.2 years.

Subgroup Analysis

The results of the subgroup analyses are shown in Figure 4. Except for COPD, no significant interactions were observed in the subgroups (P = 0.023). Additional factors associated with mortality in patients with TB and sepsis admitted to the

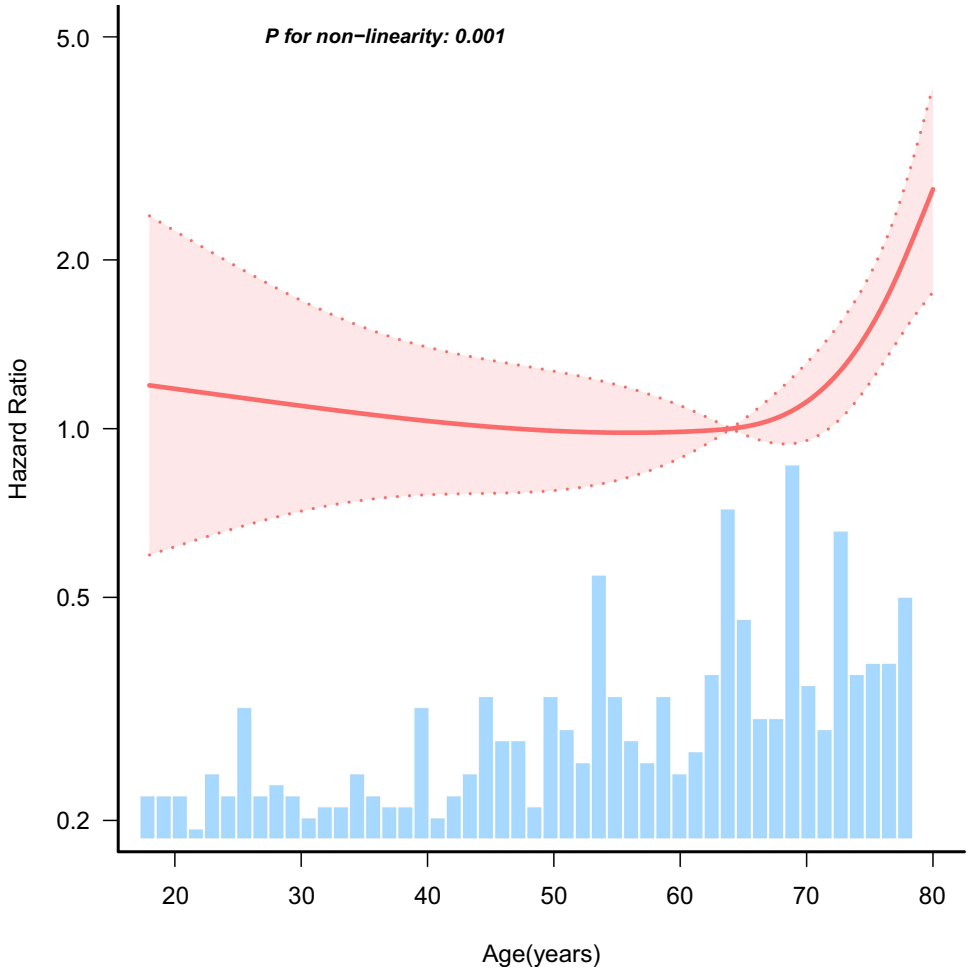

Figure 3 The nonlinear relationship of age and the risk of 28-day mortality fit by Cox proportional hazards regression models with multivariate-adjusted RCS analyses.
Notes: Solid and dashed lines represent the predicted value and 95% confidence intervals. It was adjusted for gender, immunosuppressive therapy, BMI, intra-abdominal infection, urinary tract infection, hypertension, diabetes, CKD, temperature, heart rate, MAP, HGB, PLT, lactate, invasive mechanical ventilation use, and vasopressor use. All of the data was displayed.

Table 3 Threshold Effect Analysis of the Association of Age and the 28-Day All-Cause Mortality in Tuberculosis with Sepsis ICU Patients

Age (year)	No.	Adjusted Model	
		HR(95% CI)	*P*-value
<66.2	307	0.996 (0.980, 1.012)	0.586
≥66.2	213	1.104 (1.05, 1.16)	< 0.001
Likelihood Ratio test			< 0.001

Notes: Adjusted for gender, immunosuppressive therapy, BMI, intra-abdominal infection, urinary tract infection, hypertension, diabetes, CKD, temperature, heart rate, MAP, HGB, PLT, lactate, invasive mechanical ventilation use, and vasopressor use. All the data are displayed.
Abbreviations: HR, hazard ratio, CI, confidence interval.

ICU included gender, immunosuppressive therapy, drug resistant tuberculosis, hypertension, diabetes, COPD, CKD, pneumothorax, invasive mechanical ventilation, and vasopressor use (Figure 4).

Discussion

In this retrospective cohort study, we observed a J-shaped association between age and 28-day all-cause mortality in patients diagnosed with sepsis-complicated tuberculosis. The subgroup analysis indicated that the age-related risk of

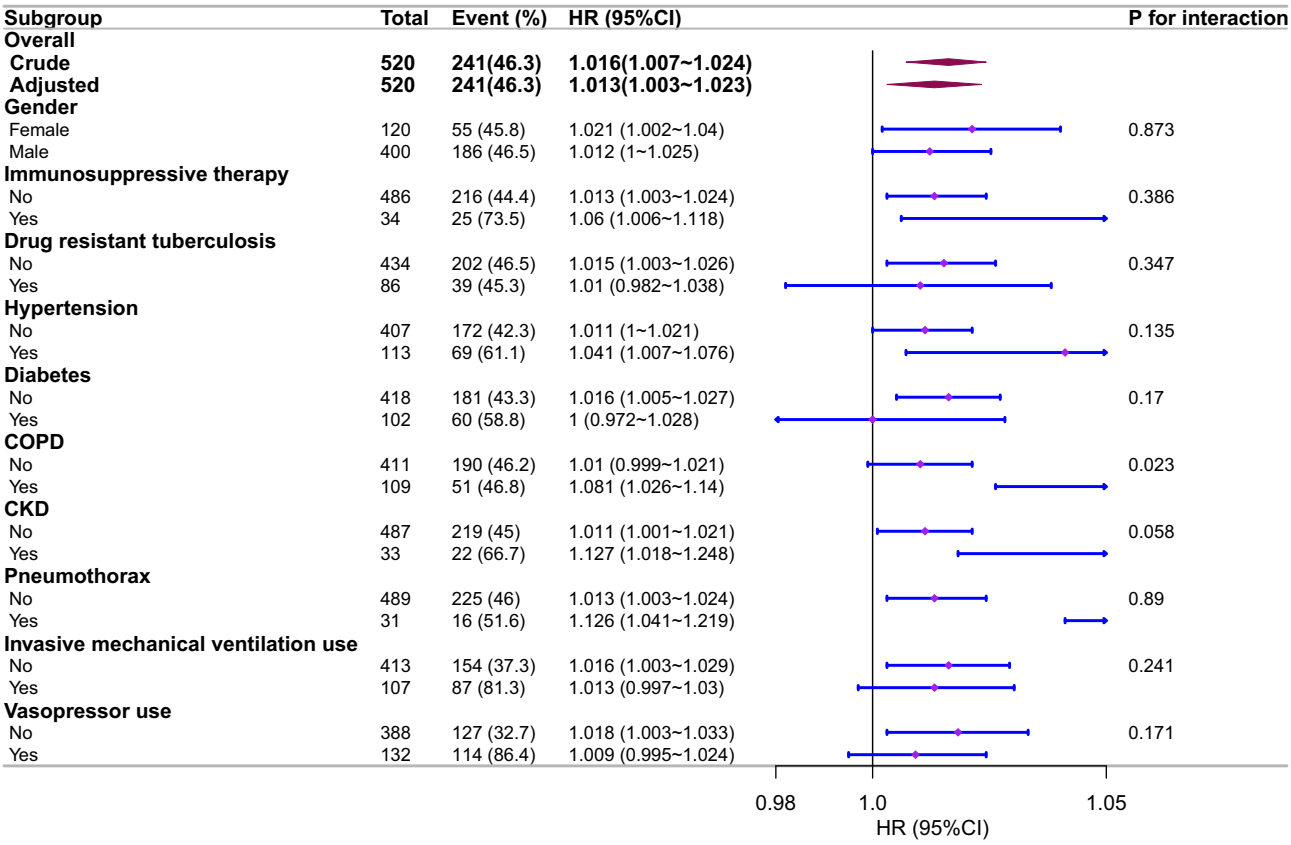

Figure 4 The relationship between age and the 28-day all-cause mortality in the subgroup analysis based on the tuberculosis complicated by sepsis ICU patients.
Notes: Each stratification was adjusted for gender, immunosuppressive therapy, BMI, intra-abdominal infection, urinary tract infection, hypertension, diabetes, CKD, temperature, heart rate, MAP, HGB, PLT, lactate, invasive mechanical ventilation use, and vasopressor use; Diamonds indicate odds ratios (ORs), with horizontal lines indicating 95%.
Abbreviations: HR, hazard ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease.

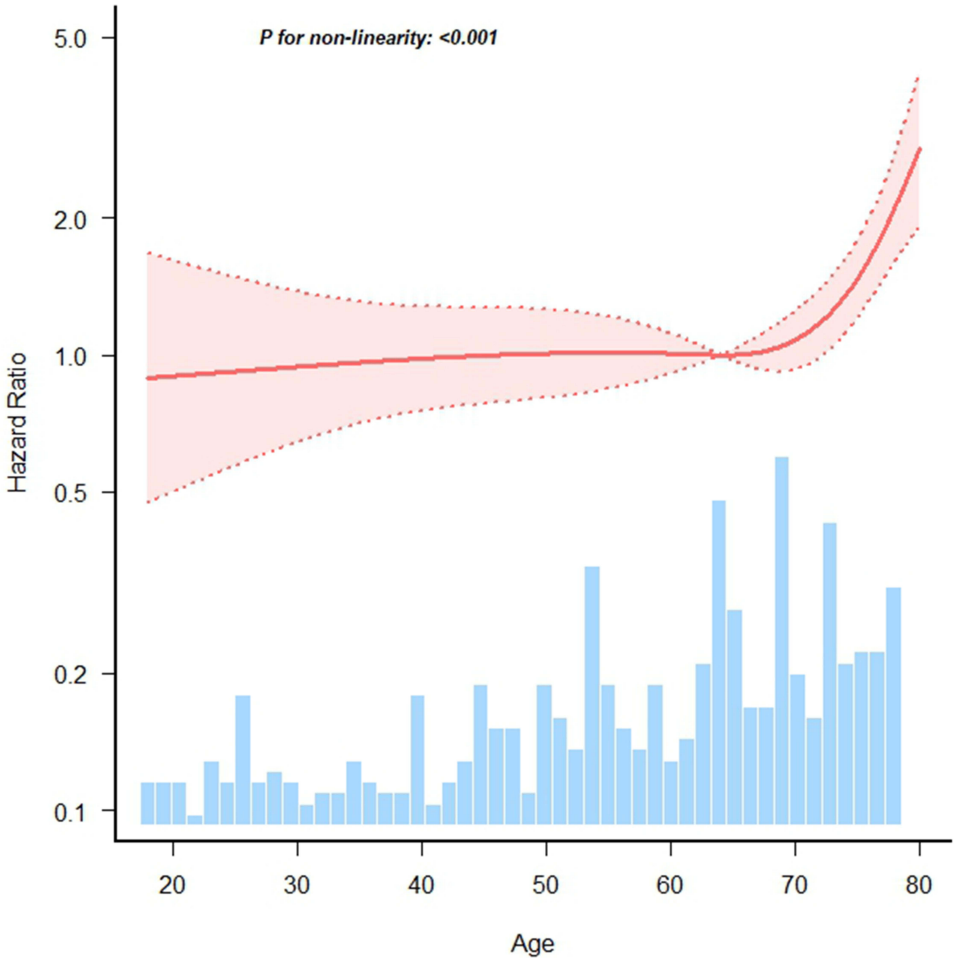

Figure 5 The nonlinear relationship of age and the risk of 28-day mortality fit by Cox proportional hazards regression models with unadjusted RCS analyses.
Notes: Solid and dashed lines represent the predicted value and 95% confidence intervals. It was adjusted for model I. All of the data was displayed.

mortality was higher among patients with hypertension, COPD, CKD, and pneumothorax. We confirmed by threshold analysis that the age-related risk of mortality was 1.093 in participants aged ≥66.2 years, whereas there was no significant association between age and the risk of mortality when the age was <66.2 years.

It is well established that advanced age is a prominent risk factor for COPD, hypertension, diabetes, and CKD.[22] Similarly, in our study, hypertension, diabetes, and COPD were mainly distributed among older people, but no similar distribution trend was observed for CKD or chronic liver disease, which may be related to the small sample size of our study population. When exploring the relationship between the age of patients with TB complicated by sepsis and chronic comorbidities, we observed a significant interaction in the COPD subgroup, which may have modified the impact of age on mortality. This may be due to the fact that patients with COPD usually have age-related factors such as decreased immunity, airway inflammation, and an abnormal immune response.[23,24] This condition accelerates the progression of COPD,[25] TB,[26] and sepsis[27] when combined with other infections. However, the underlying pathophysiological mechanisms must be confirmed in further studies.

The nonlinear association between age and adverse prognosis extends across various diseases. Xie et al reported a U-shaped association between age and the prognosis of breast cancer in women.[28] Zhang et al reported a J-shaped association between maternal age and spontaneous abortion.[29] Thompson et al reported a J- or U-shaped association between parental age, neonatal morbidity, and mortality.[30] Similarly, our study confirmed a J-shaped association between age and mortality, which could support the hierarchical management of patients.

Previous clinical studies have confirmed that age is an important factor in the prognosis of TB and sepsis.[31,32] Similarly, our study found that older patients with TB complicated by sepsis had the highest mortality rate among the groups, and the

risk of death increased with age after age ≥66.2 years. This result confirms that the older population is at high risk for death among patients with TB complicated by sepsis and require significant attention. Medical resources are very limited, and to reduce mortality in TB complicated by sepsis, it is necessary for older patients to take active and effective measures. First, early and close monitoring, timely intervention, and treatment in the case of disease changes. Second, a comprehensive assessment of physical status and disease was conducted to formulate a scientific treatment plan, and professional nursing care and rehabilitation exercises were provided to promote psychological and physical recovery.

This study had some limitations. First, as in all observational studies, potentially uncontrolled confounding factors may exist. Despite efforts to adjust for covariates and substantiate the robust association between age and 28-day all-cause mortality, validation through a large-sample study is warranted. Second, our study was retrospective and the parameters included in the study were tested only at baseline, which may vary with disease changes. Residual or unmeasured confounding factors or some of the factors that affect the prognosis of TB or sepsis that were not included may have impacted the study. This may have weakened our results. We will include more parameters related to patient prognosis and conduct a prospective study to validate our results. Finally, our study population was derived exclusively from Western China, which introduced an inevitable selection bias. The results of this study should be further verified through multicenter trials.

Conclusions

This study revealed a nonlinear relationship between age and short-term all-cause mortality in patients admitted to the ICU with sepsis-complicated TB. Age is an important prognostic factor in older patients. Stratified management of TB complicated by sepsis according to age, with a focus on older patients for whom close monitoring and early treatment could reduce mortality rates, is appropriate.

Data Sharing Statement

The data supporting the findings of this study are available from the first author, Kunping Cui, upon reasonable request.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that this study was conducted in the absence of any commercial or financial associations that could be construed as potential conflicts of interest.

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