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Risk factors for mortality in patients with tuberculosis admitted to intensive care units

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Abstract. – OBJECTIVE: The purpose of this study is to investigate the mortality of patients with tuberculosis (TB) who need to be admitted to the intensive care unit (ICU) and to analyze the risk factors for mortality.

PATIENTS AND METHODS: A retrospective analysis was conducted to collect clinical data of patients with TB who were hospitalized in the ICU at Hebei Chest Hospital between 2015 and 2020. Subsequent to data collection, a rigorous statistical analysis was conducted.

RESULTS: A total of 99 patients with TB were admitted to the ICU of Hebei Chest Hospital from 2015 to 2020. After 28 days, 78 of the 99 eligible participants in this study died, while 21 survived. The mortality rate of patients with TB in the ICU was 78.79%. There was a significant difference in the length of stay in ICU, shock, drug, acute physiology, and chronic health evaluation (APACHE) II, procalcitonin, C-reactive protein, and albumin ($p < 0.05$). Further analysis indicated that the length of stay in the ICU, shock, APACHE II, and albumin were considered independent risk factors for mortality.

CONCLUSIONS: In China, the mortality rate of patients with TB requiring admission to the ICU is very high. In these patients, a prolonged ICU stay, a high APACHE II score, the onset of shock in the ICU, and a low albumin level have a significant impact on the risk of mortality.

Key Words:
ICU, Mortality, Prediction, Risk factors, Treatment, Tuberculosis.

Introduction

As is widely acknowledged, tuberculosis (TB) stands as one of the 10 most prevalent infectious diseases globally, presenting a substantial threat to human health[1]. According to the October 2020 Global TB report[2], TB remains the infectious disease with the highest mortality. The incidence of tuberculosis has been on the rise in recent years worldwide[3]. In 2019, an estimated 10 million people developed TB, and an estimated 1.2 million people died as a result of TB among HIV-negative patients[4]. China is also one of the nations with the highest incidence of TB[4,5].

China has always been one of the countries with the most severe TB epidemics, with an annual average of 999,417 cases[6]. Previous studies[7] have shown that the mortality rate due to pulmonary tuberculosis was 4.38 per 100,000 population. According to the literature, about 3.4%[8]-16.7%[9] of hospitalized patients with TB may require admission to the intensive care unit (ICU) due to the severity of their condition. The mortality rate of patients with TB admitted to an ICU has been reported to be approximately 50%[10], while some studies[11] indicate that it is about 70%. A number of studies have analyzed risk factors for mortality in TB, including factors such as age, sex, bacterial status, comorbidities, host immunological and nutritional status, and drug abuse, but with varying conclusions[12-14]. Through this study, we intend to study the mortality rate of patients with TB in the ICU and further analyze its risk factors to better assess the condition of such patients.

Patients and Methods

The Ethics Committee of Hebei Provincial Chest Hospital approved this retrospective study. A waiver of written informed consent was granted due to the retrospective nature of the study and the anonymity of the data collection.

From 2015 to 2020, a total of 117 patients with TB were admitted to the ICU, but 18 were excluded due to incomplete data or certain other reasons. From January 2015 to December 2020, a retrospective observational study was conducted on 99 patients with TB admitted to the ICU of Hebei Chest Hospital. The specific research process is shown in Figure 1. The hospital is a provincial public referral hospital for TB, with

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the majority of admitted patients coming from the rural areas of Hebei Province. Patients were divided into a survival group and a death group based on their 28-day prognosis.

Inclusion Criteria

All patients were clearly diagnosed with TB and required ventilator assistance. All the enrolled patients were over 18 years old and had complete medical records. Exclusion criteria: patients with clearly diagnosed diseases that could significantly affect prognosis, such as severe trauma. Also, patients with incomplete medical records were excluded.

All of their general medical information, indicators of laboratory tests, scores related to disease severity, and the 28-day prognosis were recorded in detail.

Specific Indicators Observed

General information of patients admitted to ICU, including age, gender, length of admission to ICU, blood routine biochemical indicators, procalcitonin levels, acute physiology, chronic health evaluation (APACHE) II, and prognosis at 28 days.

Statistical Analysis

The SPSS 25.0 statistical software (IBM Corp., Armonk, NY, USA) was utilized for data processing, including conducting normality tests on the collected data. Data with normal distribution are represented as mean ± standard deviation (x±s). An individual sample *t*-test was used to compare two independent samples with variance homogeneity, while a rank sum test was used to compare variances. For measurement data that did not follow a normal distribution, the median (25^{th} percentile, 75^{th} percentile) was used. Non-parametric test was used for comparison between the two groups. For counting data, the Chi-squared (χ^2) test was used, while binary logistic regression was used to analyze the prognostic risk factors. A value of $p < 0.05$ was considered statistically significant.

Results

Patient Characteristics

A total of 99 patients were included in this study, of whom 82 were males and 17 were females. A total of 78 deaths were observed 28 days after admission to the ICU. Among these 78 patients, 63% were male. The age of patients included in this study ranged from 18 to 97, and the median age was 64 (50,79). The demographic, clinical, and laboratory characteristics of the enrolled patients are shown in Table I.

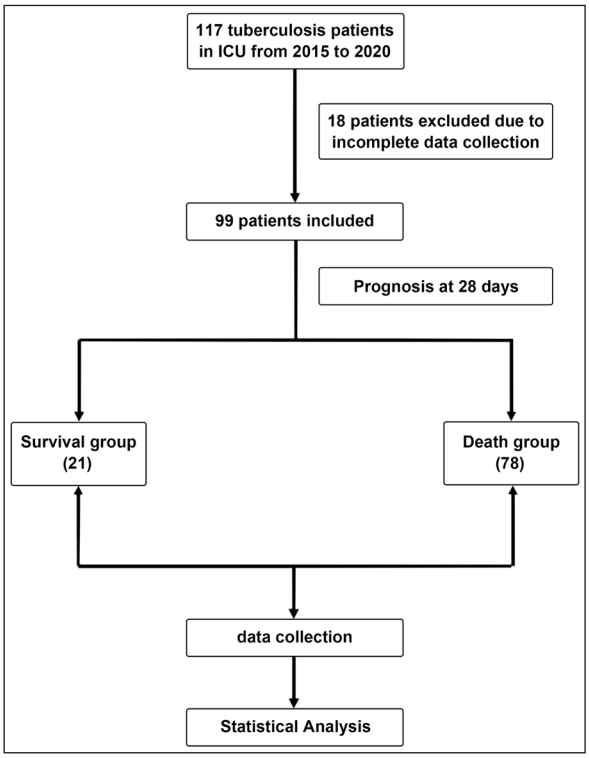

Figure 1. Flow chart of the study.

The results of this study showed that there were 21 patients in the survival group and 78 patients in the death group. The median age was 71 (55, 81.5) in the survival group and 64 (48, 79) in the death group, with no significant difference between the two groups ($p = 0.226$). There were 19 males in the survival group (accounting for 90.48%), and 63 males in the death group (accounting for 80.77%), showing no statistical difference between the two groups ($p = 0.243$). The median length of ICU stay was 24 (5, 81) days in the survival group and 6 (3,9.25) days in the death group, with a statistically significant difference ($p < 0.01$). The proportion of patients requiring mechanical ventilation was high in both groups, 85.71% and 94.87%, respectively, with no statistical difference ($p = 0.081$). In the two groups, the proportion of patients with TB receiving initial treatment was similar, 66.67% in the survival group and 62.82% in the death group, respectively, with no statistical difference ($p = 0.691$). In terms of TB in organs other than the lungs, the proportion of the two groups was 19.05% and 21.79%, respectively, with no statistical difference ($p = 1.0$). In the context of underlying medical

Table I. Demographic, clinical, and laboratory characteristics of the enrolled patients.

Variables	Survivals (n)	Death (n)	*p*-value
N	21	78	
Age (years)	71 (55,81.5)	64 (48,79)	0.226
Male	19 (90.48%)	63 (80.77%)	0.243
Time (day)	24 (5,81)	6 (3,9.25)	0.00*
Ventilation	18 (85.71%)	74 (94.87%)	0.081
Initial	14 (66.67%)	49 (62.82%)	0.691
Extra pulmonary	4 (19.05%)	17 (21.79%)	1.0
Structural disease	9 (42.86%)	34 (43.59%)	0.946
AKI	2 (9.52%)	22 (28.21%)	0.066
HF	9 (42.86%)	33 (42.31%)	0.959
Shock	4 (19.05%)	39 (50%)	0.006*
Drug	11 (52.38%)	64 (82.06%)	0.001*
DM	3 (14.29%)	17 (21.79%)	0.572
APACHE II	21.24 ± 7.314	26.72 ± 5.965	0.001*
WBC (10^9/L)	9.99 (7.87,14.2)	11.47 (7.225,17.1)	0.716
HGB (g/L)	100 (90,125)	101 (88.5,113)	0.590
PLT (10^9/L)	222.48 ± 116.93	216.62 ± 128.23	0.85
ALT (U/L)	15 (10,25)	19 (12,35)	0.255
AST (U/L)	21 (17,35)	32 (18,61)	0.205
TP (g/L)	56.4 (53,64)	53 (47,60.7)	0.073
ALB (g/L)	30.2 ± 4.76	26.18 ± 7.26	0.016*
TBIL	12 (8,17.9)	10.45 (6.1,14.5)	0.122
DBIL	6.4 (5.2,11.6)	6.05 (4.1,9.9)	0.467
UREA	5.8 (4.7,13.5)	8.6 (5.1,17.2)	0.371
CREA	42 (33,67)	51 (31,83)	0.543
GLU	6.81 (6.1,8.0)	6.62 (5.67,9.20)	0.898
Lac	1.0 (0.7,2.7)	1.7 (1.1,2.7)	0.054
PCT	0.343 (0.164,0.76)	1.185 (0.322,3.69)	0.011*
CRP	21.0 (1.09,93.31)	98.51 (53.9,191.9)	0.002*
Dimer	2.35 (0.83,6.57)	3.97 (1.88,8.23)	0.132
CK	38 (24.5,136.5)	61 (36,112)	0.178
CKMB	15.3 (12.4,28.9)	18.1 (13.8,29.3)	0.364
LDH	207.5 (157.5,381)	291.5 (224.0,445)	0.105
PT	13.2 (12.1,16.3)	13.2 (12.2,14.5)	0.905
APTT	30.5 (28.7,34.3)	32.65 (26.9,34.3)	0.962
Fib	3.78 (2.63,4,43)	3,7 (2.8,4,78)	0.867

*$p < 0.05$. Data are shown as mean ± standard deviation or median (25^{th} percentile, 75^{th} percentile). AKI: Acute kidney injury; HF: Heart failure; DM: Diabetes mellitus; APACHE II: Acute Physiology and Chronic Health Evaluation II; WBC: White blood cell count; HGB: Hemoglobin; PLT: Platelet; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; TP: TotalProtein; ALB: Albumin; TBIL: Total bilirubin; DBIL: Direct Bilirubin; CREA: Creatinine; GLU: Glutamate; Lac: Lactic Acid; PCT: Procalcitonin; CRP: C-reactive protein; CK: Creatine Kinase; CKMB: Creatine Kinase Isoenzyme; LDH: Lactate dehydrogenase; PT: Prothrombin time; APTT: Activated partial thromboplastin time; Fib: Fibrinogen.

conditions, there were no notable differences observed between the survival group and the death group. Specifically, structural lung disease was prevalent in 9 cases (42.86%) in the survival group and 34 cases (43.59%) in the death group. Acute kidney injury was noted in 2 cases (9.52%) in the survival group and 22 cases (28.21%) in the death group. Heart failure was reported in 9 cases (42.86%) in the survival group and 33 cases (42.31%) in the death group, while diabetes mellitus was present in 3 cases (14.29%) in the survival group and 17 cases (21.79%) in the death group. There was no statistical difference between the two groups in the above aspects, with $p > 0.05$. There were significant differences between the two groups in cases of septic shock or in cases where vasoactive drugs were administered. The difference between the survival group with septic shock and the death group was statistically significant ($p = 0.006$), with 4 patients surviving (19.05%) and 39 patients dying (50%) in the septic shock group. In the administration of vasoactive drugs, 11 (52.38%) patients survived, and 64 (82.06%) died, and the difference was statistically significant ($p = 0.001$). APACHE II scores at ICU admission were 21.24 ± 7.314

in the survival group and 26.72 ± 5.965 in the death group ($p = 0.001$). There were no significant differences between the two groups ($p > 0.05$) in most of the test indexes at the time of admission to the ICU, except for albumin (30.2 ± 4.76 and 26.18 ± 7.26, $p = 0.016$), procalcitonin [0.343 (0.164, 0.76) and 1.185 (0.322, 3.69), $p = 0.011$] and C-reactive protein [21.0 (1.09, 93.31) and 98.51 (53.9, 191.9), $p = 0.002$] levels.

Based on binary logistic regression analysis, it was found that the length of stay in the ICU, shock, APACHE II, and albumin were independent risk factors of mortality (Table II).

Table II. Logistic regression analysis of independent risk factors for death.

Variables	*p*-value	OR
Time	0.006	0.953
Shock	0.021	3.416
APACHE II	0.020	1.116
ALB	0.043	0.910

OR, odds ratio; ALB: Albumin; APACHE II: Acute Physiology and Chronic Health Evaluation II.

Discussion

Strengths and Limitations

This study has several strengths. First, it provides valuable data on mortality and its risk factors among critically ill patients with TB in China, a population for which data is scarce[15]. Second, the study was conducted at a hospital specializing in TB that has extensive experience managing this specific patient cohort[16]. Third, the sample size of 99 patients exceeds many similar single-center studies on patients with TB admitted to the ICU[17].

However, significant limitations must be acknowledged. The retrospective, single-center design and small sample size limit the generalizability of the findings[18]. Selection bias may have been present as this was not a randomized controlled trial. As a retrospective study, the collection of data was hampered by inaccurate or insufficient medical records. There was a lack of data on key variables like mechanical ventilation settings and antibiotic use. The long-term mortality following ICU discharge was not assessed. Finally, the effects of various therapeutic interventions in the ICU were not analyzed.

Comparison with Previous Studies

TB patients requiring admission to the ICU have been reported to have a high mortality rate[18]. The mortality rate in this study is consistent with other reports[19,20] on critically ill patients with TB in low-income and middle-income countries. Patients with TB in South Korea, however, had a lower ICU mortality rate of 62.7%, which may reflect regional differences in patient characteristics and ICU care[21].

Several risk factors identified in this study align with previous evidence, including shock[22], high APACHE II scores[23], and hypoalbuminemia[24]. However, the length of ICU stay was a risk factor in this study but not in the South Korean ICU cohort[20], while respiratory failure was a risk factor identified by Vincent et al[25], but not observed here. These discrepancies may be attributable to variations in the study population, sample size, and statistical methods. Moreover, the 2518A/G polymorphism in the monocyte chemotactic protein-1 gene has been shown to be associated with an increased risk of TB in the Chinese population[26]. In addition, the independent risk factors associated with recurrent TB included no use of directly observed therapy, short course, diabetes, smoking, and malnutrition[27]. Further investigations, including other potential risk factors, are warranted.

Previous studies[28,29] have also investigated the co-infection of other respiratory viruses among patients with TB. For instance, a high frequency of TB progression and complications has been observed among patients with seasonal influenza co-infection[28]. An observational case-control study has suggested that both active and latent TB is a risk factor for COVID-19 infection[29]. In addition, the application time of antibiotics and hormones has been associated with the risk of TB complicated with pulmonary aspergillosis[30]. Future studies are needed to explore the role of respiratory co-infection in TB patients admitted to ICU further.

Implications for Practice and Research

This study has made a contribution to the prognosis and management of critically ill patients with TB. Clinicians can better stratify the mortality risk of patients admitted to the ICU by recognizing key mortality factors[31]. Using evidence-based interventions to target modifiable factors, such as shock and hypoalbuminemia, may improve outcomes[31]. The findings can increase awareness among clinicians of the high risk of morbidity and mortality among patients with TB requiring intensive care[32].

However, the results of this study may not be fully applicable beyond the regional population studied. The effects of specific ICU treatments were not examined. Going forward, rigorous multi-center prospective cohort studies with larger, more diverse samples are needed to better elucidate prognostic factors and optimal management strategies for critically ill patients with TB[33,34]. Investigation of emerging therapies and models of care to reduce mortality in this vulnerable group represents an important area for future research[35].

Conclusions

Our study indicates a very high mortality rate among patients with TB requiring intensive care. The length of ICU stays, APACHE II score at admission to ICU, shock during ICU treatment, and serum protein level were all risk factors for mortality in these patients. These factors are extremely useful for assessing the prognosis of patients with TB in the ICU. Nonetheless, as this is a single-center study with a small sample size, more research is needed to confirm these findings.

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Conflict of Interest
The authors declare that they have no competing interests.

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Ethics Approval
The Ethics Committee of Hebei Chest Hospital approved this retrospective study (2023084).

Informed Consent
A waiver of written informed consent was granted due to the retrospective nature of the study and the anonymity of the data collection.

Availability of Data and Materials
All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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Authors' Contributions
Conception and design of the research: Gang Chen, Xin Wang, Ning Li. Acquisition of data: Yunxia Wei, Lijing Yan, Lijiao Shao. Analysis and interpretation of the data: Donglei Qie, Ning Li, Lijiao Shao. Statistical analysis: Yunxia Wei, Lijing Yan, Donglei Qie. Obtaining financing: None. Writing of the manuscript: Xin Wang, Yunxia Wei. Critical revision of the manuscript for intellectual content: Xin Wang, Gang Chen. All authors read and approved the final draft.

References

1) Khaliq A, Ravindran R, Afzal S, Jena PK, Akhtar MW, Ambreen A, Wan YY, Malik KA, Irfan M, Khan IH. Gut microbiome dysbiosis and correlation with blood biomarkers in active-tuberculosis in endemic setting. PLoS One 2021; 16: e0245534.
2) Chakaya J, Khan M, Ntoumi F, Aklillu E, Fatima R, Mwaba P, Kapata N, Mfinanga S, Hasnain SE, Katoto PDMC, Bulabula ANH, Sam-Agudu NA, Nachega JB, Tiberi S, McHugh TD, Abubakar I, Zumla A. Global Tuberculosis Report 2020 - Reflections on the Global TB burden, treatment and prevention efforts. Int J Infect Dis 2021; 113 Suppl 1: S7-S12.
3) Zhang J, Kern-Allely S, Yu T, Price RK. HIV and tuberculosis co-infection in East Asia and the Pacific from 1990 to 2017: results from the Global Burden of Disease Study 2017. J Thorac Dis 2019; 11: 3822-3835.
4) Zhong W, Bragazzi NL, Kong JD, Safiri S, Behzadifar M, Liu J, Liu X, Wang W. Burden of Respiratory Infection and Tuberculosis Among US States from 1990 to 2019. Clin Epidemiol 2021; 13: 503-514.
5) Zuo Z, Wang M, Cui H, Wang Y, Wu J, Qi J, Pan K, Sui D, Liu P, Xu A. Spatiotemporal characteristics and the epidemiology of tuberculosis in China from 2004 to 2017 by the nationwide sur-

veillance system. BMC Public Health 2020; 20: 1284.

6) Zhang H, Huang F, Chen W, DU X, Zhou MG, Hu J, Wang LX. Estimates of tuberculosis mortality rates in China using the disease surveillance point system, 2004-2010. Biomed Environ Sci 2012; 25: 483-488.
7) Muthu V, Agarwal R, Dhooria S, Aggarwal AN, Behera D, Sehgal IS. Outcome of Critically Ill Subjects With Tuberculosis: Systematic Review and Meta-Analysis. Respir Care 2018; 63: 1541-1554.
8) Silva DR, Menegotto DM, Schulz LF, Gazzana MB, Dalcin Pde T. Factors associated with mortality in hospitalized patients with newly diagnosed tuberculosis. Lung 2010; 188: 33-41.
9) Loh WJ, Yu Y, Loo CM, Low SY. Factors associated with mortality among patients with active pulmonary tuberculosis requiring intensive care. Singapore Med J 2017; 58: 656-659.
10) Erbes R, Oettel K, Raffenberg M, Mauch H, Schmidt-Ioanas M, Lode H. Characteristics and outcome of patients with active pulmonary tuberculosis requiring intensive care. Eur Respir J 2006; 27: 1223-1228.
11) Anton C, Lemos CX, Machado FD, Bernardi RM, Freitas AA, Silva DR. Tuberculosis in the intensive care unit: alternative treatment regimens and association with mortality. Trop Med Int Health 2021; 26: 111-114.
12) Zhang P, Xiong J, Zeng J, Zhan S, Chen T, Wang Y, Deng G. Clinical Evaluation of Active Tuberculosis-Related Deaths in Shenzhen, China: A Descriptive Study. Int J Gen Med 2021; 14: 237-242.
13) Lee CM, Lee MS, Cho YJ. Drug resistant tuberculosis in critically ill patients: clinical features and treatment outcomes. Crit Care 2019; 23: 109.
14) Mer M, Richards G. Towards an appropriate intensive care unit model of care for South African public hospitals. S Afr Med J 2017; 107: 991-993.
15) Jacob ST, Banura P, Baeten JM, Moore CC, Meya D, Nakiyingi L, Burke R, Horton CL, Iga B, Wald A, Reynolds SJ, Mayanja-Kizza H, Scheld WM; Promoting Resource-Limited Interventions for Sepsis Management in Uganda Study Group. The impact of early monitored management on survival in hospitalized adult Ugandan patients with severe sepsis: a prospective intervention study*. Crit Care Med 2012; 40: 2050-2058.
16) Leening MJ, Dawson R, Dent JM. Bias from combining exposure and outcome in medical research: an empirical study of EHR data examining associations between smoking and MI incidence. J Am Med Inform Assoc 2020; 27: 1246-1254.
17) Mehmood K, Zamir N, Nadeem SG, Saba N, Bana M. Frequency of multi-drug resistant tuberculosis in critically ill patients. Pak J Med Sci 2020; 36: 231-235.
18) Wang JL, Yin QY, Han C, Liu FL, Wang MS. Risk factors for death in tuberculosis patients requiring ICU care. Epidemiol Infect 2021; 149: e22.
19) Dramowski A, Mehtar S, Moultrie H. Characteristics and outcomes of critically ill HIV-infected patients with tuberculosis requiring admission to intensive care units in a high HIV/TB burden setting. J Acquir Immune Defic Syndr 2015; 68: 47-53.
20) Hurtado J, Coitinho C, Nin N, Buroni M, Hurtado FJ, Robello C, Greif G. Clinical and epidemiological features of tuberculosis isolated from critically ill patients. Rev Argent Microbiol 2022; 54: 43-47.
21) Lee S, Kim MJ, Lee SH, Kim HY, Kim HS, Oh IH. Comparison of Disability-Adjusted Life Years (DALYs) and Economic Burden on People With Drug-Susceptible Tuberculosis and Multidrug-Resistant Tuberculosis in Korea. Front Public Health 2022; 10: 848370.
22) Ranzani OT, Prina E, Menéndez R. New Sepsis Definition (Sepsis-3) and Community-acquired Pneumonia Mortality in Internal Medicine Wards. Am J Respir Crit Care Med 2017; 196: 307-310.
23) Nie W, Zhang Y, Jee SH, Jung KJ, Li B, Xiu Q. Obesity survival paradox in pneumonia: A meta-analysis. BMC Med 2014; 12: 61.
24) Lee S, Kim YW, Han SK. Risk factors for one-year mortality in patients with tuberculous destroyed lung. Int J Tuberc Lung Dis 2015; 19: 1487-1493.
25) Vincent JL, Rello J, Marshall J, Silva E, Anzueto A, Martin CD, Moreno R, Lipman J, Gomersall C, Sakr Y, Reinhart K; EPIC II Group of Investigators. International study of the prevalence and outcomes of infection in intensive care units. JAMA 2009; 302: 2323-2329.
26) Chen LM, Tong X, Li XB, Wu ZJ, Zhang YG. The association between the -2518A/G polymorphism in the MCP-1 gene and the risk of pulmonary tuberculosis in Sichuan Chinese population. Eur Rev Med Pharmacol Sci 2015; 19: 563-566.
27) Tian PW, Wang Y, Shen YC, Chen L, Wan C, Liao ZL, Wen FQ. Different risk factors of recurrent pulmonary tuberculosis between Tibetan and Han populations in Southwest China. Eur Rev Med Pharmacol Sci 2014; 18: 1482-1486.
28) Walaza S, Cohen C, Tempia S, Moyes J, Nguweneza A, Madhi SA, McMorrow M, Cohen AL. Influenza and tuberculosis co-infection: A systematic review. Influenza Other Respir Viruses 2020; 14: 77-91.
29) Chen Y, Wang YG, Fleming J, Yu YH, Gu Y, Liu C, Fan LC, Wang XD, Cheng MX, Bi LJ, Liu YY. Active or latent tuberculosis increases susceptibility to COVID-19 and disease severity. MedRxiv 2020: 2.
30) Teng GL, Huang Q, Xu L, Chi JY, Wang C, Hu H. Clinical features and risk factors of pulmonary tuberculosis complicated with pulmonary aspergillosis. Eur Rev Med Pharmacol Sci 2022; 26: 2692-2701.
31) Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M; Early Goal-Directed Therapy Collaborative

Group. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001; 345: 1368-1377.

32) Phua J, Ngerng W, See K, Tay C, Kiong T, Lim H, Chew M, Yip H, Tan A, Khalizah H, Capistrano R, Lee K, Mukhopadhyay A. Characteristics and outcomes of culture-negative versus culture-positive severe sepsis. Crit Care 2013; 17: R202.

33) Leening MJ, Dawson R, Dent JM. Bias from combining exposure and outcome in medical research: an empirical study of EHR data examining associations between smoking and MI incidence. J Am Med Inform Assoc 2020; 27: 1246-1254.

34) Rudd KE, Tutaryebwa LK, West TE. Presentation, management, and outcomes of sepsis in adults and children admitted to a rural Ugandan hospital: A prospective observational cohort study. PLoS One 2017; 12: e0171422.

35) Famous KR, Delucchi K, Ware LB. Acute Respiratory Distress Syndrome Subphenotypes Respond Differently to Randomized Fluid Management Strategy. Am J Respir Crit Care Med 2017; 195: 331-338.