

论著·临床研究

结核病合并基础疾病的抗结核治疗效果及肺部损伤分析

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[摘要] 目的 · 探讨结核病诊断时的合并症对患者预后及肺部损伤的影响。方法 · 采用回顾性队列研究, 选择2018年1月—12月上海市肺科医院涂片阳性的结核患者, 分为无合并症组和有合并症组(合并糖尿病、高血压、肝脏疾病、肾脏疾病和胆囊疾病)。利用 χ^2 检验比较无合并症组和有合并症组结核患者的总体治疗结果和肺部损伤情况, 并采用分层分析比较各合并症对结核患者预后及肺部损伤影响, 使用Kaplan-Meier分析合并症与结核病预后的时间相关性。结果 · 纳入450例结核患者, 男性323例(71.8%), 女性127例(28.2%), 中位年龄为33岁。其中, 173例患者有合并症: 糖尿病49例, 高血压23例, 肝脏疾病83例, 肾脏疾病35例, 胆囊疾病17例。无合并症的结核患者治愈率为80.5%, 显著高于有合并症组($P<0.05$)。诊断时患有糖尿病、高血压和肾脏疾病的结核患者治愈率显著降低是引起抗结核治疗失败的关键原因; 患有糖尿病和肝脏疾病的结核患者肺部载菌量更多、肺部损伤区域更大, 患有糖尿病和肾脏疾病的结核患者肺部空洞发生率更高。结论 · 糖尿病、高血压和肾脏疾病使肺部损伤加重导致结核病治愈率降低, 诊断时临床医生及早采取干预措施, 可提高结核患者的治愈率, 缩短治疗时间, 降低医疗成本。

[关键词] 结核病; 合并症; 预后; 肺部损伤

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Analysis of the effect of anti-tuberculosis treatment and lung injury in patients with tuberculosis combined with underlying disease

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[Abstract] Objective · To investigate the impact of complications on the prognosis and lung injury of patients with tuberculosis. Methods · A retrospective cohort study was used for analysis, to select a total of 450 smear-positive tuberculosis (TB) patients, 323 males (71.8%) and 127 females (28.2%), from January to December 2018 at Shanghai Pulmonary Hospital, Tongji University School of Medicine, which were divided into non-complication group and complication group (diabetes, hypertension, liver diseases, kidney diseases and gallbladder diseases). Overall treatment outcomes and lung injuries in TB patients with and without complications were analyzed by using χ^2 test. Stratified analysis of the impact of each comorbidity on the prognosis and lung injury of TB patients was performed. Kaplan-Meier analysis was used to analyze the temporal correlation between complications and tuberculosis prognosis. Results · Four hundred and fifty patients with a median age of 33 years were included, 173 of whom had complications: diabetes in 49 cases, hypertension in 23 cases, liver diseases in 83 cases, kidney diseases in 35 cases, and gallbladder diseases in 17 cases. The cure rate of TB patients without complications was 80.5%, which was significantly higher than that of the group with complications ($P<0.05$); the significantly lower cure rate of TB patients with diabetes, hypertension and kidney diseases at diagnosis was the key cause of anti-tuberculosis treatment failure; TB patients with diabetes and liver diseases had higher lung bacterial load and larger areas of lung damage, and TB patients with diabetes and kidney diseases had higher incidence of pulmonary cavity. Conclusion · Diabetes, hypertension and kidney diseases exacerbate lung damage and lead to lower TB cure rates. Early

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interventions by clinicians at the time of diagnosis can improve cure rates, shorten treatment time, and reduce medical costs for TB patients.

[Key words] tuberculosis; complication; prognosis; lung damage

结核病是由结核分枝杆菌引起的严重危害人类健康的慢性传染病，主要通过呼吸道飞沫传播，是传染病死亡的主要原因^[1-3]。空洞、胸腔积液和结节在结核患者影像学中较多见，是引起咳嗽、咯血等临床症状的常见原因，是评估结核病预后的主要指标^[4-6]。中国作为全球第3的结核病高负担国家^[7]，患者基数大，结核菌引起病症的同时常常伴有众多合并症，如糖尿病、高血压、肝脏和肾脏疾病等^[8-12]。我国结核病患者糖尿病的总体患病率为7.8%，其中东部沿海地区的患病率达到8.3%^[13]。我国高血压发病率逐年升高，一项横断面研究报道了结核患者的高血压患病率为15.2%^[14]。目前系统研究各种合并症对结核病预后的影响报道不多，本研究采用回顾性队列研究，对450例结核患者的治疗结果和肺部损伤进行分析，探讨结核病诊断时的合并症对结核预后的影响，以期引导临床医生重视合并症结核患者的差异化治疗。

1 资料与方法

1.1 研究对象

选择2018年1月1日—2018年12月31日在同济大学附属上海市肺科医院治疗的结核患者。分组标准：①在结核病诊断时无其他合并症的结核患者为无合并症组。②合并患有糖尿病、高血压、肝脏疾病、肾脏疾病和胆囊疾病的合并症结核患者为合并症组。

纳入标准：①符合肺结核诊断标准^[15]，结核病病原学检测阳性的患者。②患者痰标本涂片阳性或结核分枝杆菌培养阳性；临床疑似非结核分枝杆菌(nontuberculous mycobacteria, NTM)患者辅助检测GeneXpertMTB/RIF阳性判为结核的患者。排除标准：①年龄<18周岁和>70周岁的患者。②抗结核药物耐药患者。③病历资料不全的患者。

1.2 治疗结果的判断标准

依据世界卫生组织(World Health Organization,

WHO)发表的《结核病定义和报告框架》^[16]，完成治疗并且在治疗结束前至少2次涂片或培养呈阴性的患者判断为治愈，治疗方案需要终止或永久更改为新的方案或治疗策略的患者判断为治疗失败。

1.3 患者资料收集

通过同济大学附属上海市肺科医院信息处理数据库、电子病案系统收集结核患者的就诊资料，包括患者的人口学特征、临床症状、合并症、治疗结果以及影像学检测数据。收集2018年首次入院的CT资料，由2名经验丰富的影像学医师采用双盲法阅片，判断病灶分布、空洞积液和结节等情况，分析影像学特征。

1.4 统计学分析

采用SPSS25.0和GraphPad Prism 8软件进行统计分析。定量资料以 $M(Q_1, Q_3)$ 表示。定性资料以频数(百分率)表示，采用 χ^2 检验进行组间比较；当理论频数<5或总体样本量<40时，采用Fisher精确检验。采用Kaplan-Meier(K-M)分析计算生存曲线，并使用对数秩检验比较曲线之间的差异。 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 结核患者基本资料和临床特征

共纳入450例结核患者，中位年龄为33岁。患者的基本资料和临床特征如表1所示。

2.2 结核病诊断时的合并症对结核治疗结果的影响

450例结核患者中，343例治愈，107例未治愈。如表2所示，173例诊断时有合并症的结核患者中有53例(30.6%)未治愈，未治愈率高于诊断时无合并症的结核患者($P=0.007$)。诊断时有糖尿病、高血压和肾脏疾病的结核患者治愈率低于无合并症的结核患者，差异有统计学意义(均 $P<0.05$)；诊断时有肝脏



表1 结核患者基本资料和临床特征

Tab 1 General information and clinical characteristics of tuberculosis patients

Item	Tuberculosis patients
Age/year	33.00 (25.00, 51.25)
Gender/n(%)	
Male	323 (71.8)
Female	127 (28.2)
Fever/n(%)	117 (26.0)
Cough/n(%)	292 (64.9)
Hemoptysis/n(%)	52 (11.6)
Sweat/n(%)	23 (5.1)
Lose weight/n(%)	10 (2.2)
Complication/n(%)	
Diabetes	49 (10.9)
Hypertension	23 (5.1)
Liver disease	83 (18.4)
Kidney disease	35 (7.8)
Gallbladder disease	17 (3.8)
Grade of sputum smear/n(%)	
1+	356 (79.1)
2+	35 (7.8)
3+	44 (9.8)
4+	15 (3.3)

疾病和胆囊疾病的结核患者与无并发症的结核患者治愈率比较，差异均无统计学意义（均 $P>0.05$ ）。

为探讨单一并发症对结核预后的影响，进一步对单一并发症的结核患者进行了抗结核治疗的预后分析，结果如表3所示。诊断时患有糖尿病的结核患者治愈率低于无并发症的结核患者，差异有统计学意义 ($P=0.007$)；诊断时有高血压的结核患者治愈率也低于无并发症的结核患者，差异有统计学意义 ($P=0.001$)。

为分析糖尿病和高血压与结核病预后的时间相关性，使用K-M分析3年多时间的合并糖尿病和高血压与抗结核治疗的预后关系。结果表明，诊断时患有糖尿病的结核患者的治愈率低于诊断时无并发症的结核患者（Log-rank $P=0.003$ ，图1A）。诊断时患有高血压的结核患者的治愈率同样低于诊断时无并发症的结核患者（Log-rank $P=0.019$ ，图1B）。

2.3 结核病诊断时的并发症对结核患者肺部损伤的影响

如表4所示，无并发症的结核患者中117例（42.2%）

表2 诊断时有、无并发症的结核患者治疗结果的比较 [n(%)]

Tab 2 Comparison of treatment outcomes in TB patients with and without complications at diagnosis [n(%)]

Group	Cured	Not-cured	χ^2 value	P value
TB with/without complications			7.293	0.007
Without	223 (80.5)	54 (19.5)		
With	120 (69.4)	53 (30.6)		
TB with/without diabetes			5.646	0.017
Without	223 (80.5)	54 (19.5)		
With	32 (65.3)	17 (34.7)		
TB with/without hypertension			7.279	0.011
Without	223 (80.5)	54 (19.5)		
With	13 (56.5)	10 (43.5)		
TB with/without liver disease			0.456	0.500
Without	223 (80.5)	54 (19.5)		
With	64 (77.1)	19 (22.9)		
TB with/without kidney disease			5.739	0.017
Without	223 (80.5)	54 (19.5)		
With	22 (62.9)	13 (37.1)		
TB with/without gallbladder disease			2.461	0.126
Without	223 (80.5)	54 (19.5)		
With	11 (64.7)	6 (35.3)		

表3 诊断时仅患有1种并发症结核患者与无并发症患者治疗结果的比较 [n(%)]

Tab 3 Comparison of treatment outcomes between tuberculosis patients with only one complication at diagnosis and those without complication [n(%)]

Group	Cured	Not-cured	χ^2 value	P value
TB with/without diabetes			7.341	0.007
Without	223 (80.5)	54 (19.5)		
With	15 (57.7)	11 (42.3)		
TB with/without hypertension			14.413	0.001
Without	223 (80.5)	54 (19.5)		
With	2 (25.0)	6 (75.0)		
TB with/without liver disease			0.534	0.465
Without	223 (80.5)	54 (19.5)		
With	38 (76.0)	12 (24.0)		
TB with/without kidney disease			2.756	0.149
Without	223 (80.5)	54 (19.5)		
With	8 (61.5)	5 (38.4)		
TB with/without gallbladder disease			0.355	0.627
Without	223 (80.5)	54 (19.5)		
With	5 (71.4)	2 (28.5)		



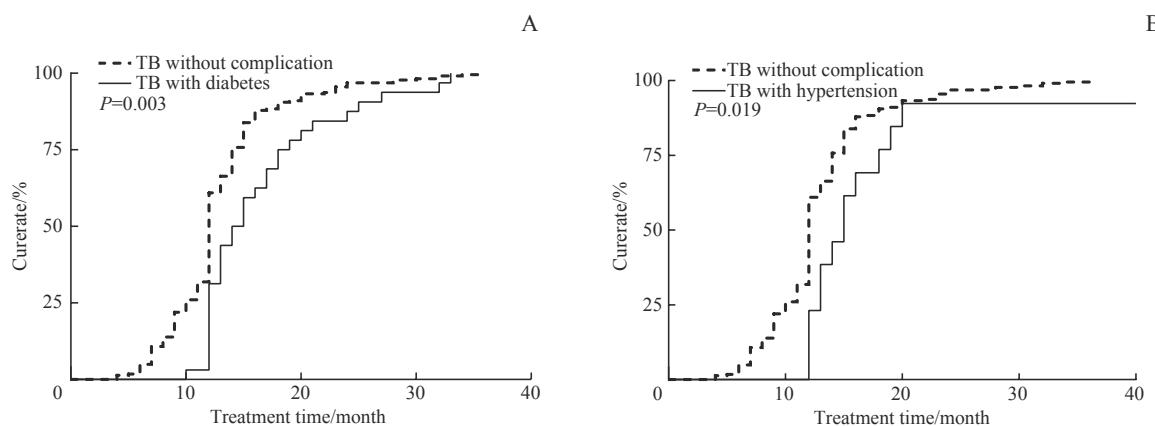


图1 诊断时患有糖尿病(A)与高血压(B)的结核患者与无合并症结核患者的生存曲线对比

Fig 1 Comparison of survival curve between tuberculosis patients with diabetes (A) and hypertension (B) at diagnosis and tuberculosis patients without complications

和诊断时有合并症的结核患者中101例(58.4%)双侧肺有损伤,差异有统计学意义($P=0.001$)。诊断时有合并症的结核患者空洞发生率是40.5%,比无合并症的结核患者高14.5%,差异有统计学意义($P=0.001$)。诊断时有合并症的结核患者肺部载菌量高于诊断时无合并症的结核患者,差异有统计学意义($P=0.007$)。

表4 诊断时有、无合并症的结核患者肺部损伤的比较[n(%)]

Tab 4 Comparison of lung injury in tuberculosis patients with and without complications at diagnosis [n(%)]

Lung injury	TB without complications	TB with complications	χ^2	P value
Area of lung injury		11.112	0.001	
Bilateral lung	117 (42.2)	101 (58.4)		
Unilateral lung	160 (57.8)	72 (41.6)		
Cavity		10.323	0.001	
Yes	72 (26.0)	70 (40.5)		
No	205 (74.0)	103 (59.5)		
Effusion		0.606	0.436	
Yes	46 (16.6)	24 (13.9)		
No	231 (83.4)	149 (86.1)		
Nodule		0.793	0.373	
Yes	88 (31.8)	62 (35.8)		
No	189 (68.2)	111 (64.2)		
Grade of sputum smear		11.968	0.007	
1+	227 (81.9)	129 (74.6)		
2+	20 (7.2)	15 (8.7)		
3+	27 (9.8)	17 (9.8)		
4+	3 (1.1)	12 (6.9)		

有合并症的结核患者肺部损伤分布在双侧肺的比例高于诊断时无合并症的结核患者($P=0.001$),进一步细分发现仅糖尿病和肝脏疾病合并结核感染时影响

肺部损伤。如表5所示,诊断时患有糖尿病的结核患者肺部损伤分布在双侧肺的比例高于诊断时无合并症的结核患者,差异有统计学意义($P=0.003$);诊断时患有肝脏疾病的结核患者肺部损伤分布在双侧肺的比例高于诊断时无合并症的结核患者,差异有统计学意义($P=0.002$)。

表5 诊断时有、无合并症的结核患者肺部损伤区域的比较[n(%)]

Tab 5 Comparison of areas of lung injury in tuberculosis patients with and without complications at diagnosis [n(%)]

Group	Area of lung injury		χ^2 value	P value
	Bilateral lung	Unilateral lung		
TB with/without complications			11.112	0.001
Without	117 (42.2)	160 (57.8)		
With	101 (58.4)	72 (41.6)		
TB with/without diabetes			8.928	0.003
Without	117 (42.2)	160 (57.8)		
With	32 (65.3)	17 (34.7)		
TB with/without hypertension			2.997	0.083
Without	117 (42.2)	160 (57.8)		
With	14 (60.9)	9 (39.1)		
TB with/without liver disease			9.467	0.002
Without	117 (42.2)	160 (57.8)		
With	51 (61.5)	32 (38.5)		
TB with/without kidney disease			0.509	0.476
Without	117 (42.2)	160 (57.8)		
With	17 (48.6)	18 (51.4)		
TB with/without gallbladder disease			3.289	0.070
Without	117 (42.2)	160 (57.8)		
With	11 (64.7)	6 (35.3)		



如表6所示,有并发症的结核患者肺部空洞发生率高于诊断时无并发症的结核患者。分层分析发现患有糖尿病的结核患者中33例(67.4%)发生空洞,患

有肾脏疾病的结核患者中16例(45.7%)发生空洞,空洞发生率均高于无并发症的结核患者,差异有统计学意义(均 $P<0.05$)。

表6 诊断时有、无并发症的结核患者肺部空洞的比较[n(%)]

Tab 6 Comparison of pulmonary cavities in tuberculosis patients with and without complications at diagnosis [n(%)]

Group	Cavity		χ^2 value	P value	Group	Cavity		χ^2 value	P value
	Yes	No				Yes	No		
TB with/without complications			10.323	0.001	TB with/without liver disease			1.369	0.242
Without	72 (26.0)	205 (74.0)			Without	72 (26.0)	205 (74.0)		
With	70 (40.5)	103 (59.5)			With	27 (32.5)	56 (67.5)		
TB with/without diabetes			32.610	0.000	TB with/without kidney disease			5.968	0.015
Without	72 (26.0)	205 (74.0)			Without	72 (26.0)	205 (74.0)		
With	33 (67.4)	16 (32.6)			With	16 (45.7)	19 (54.3)		
TB with/without hypertension			0.000	0.992	TB with/without gallbladder disease			3.589	0.088
Without	72 (26.0)	205 (74.0)			Without	72 (26.0)	205 (74.0)		
With	6 (26.1)	17 (73.9)			With	8 (47.1)	9 (52.9)		

如表7所示,并发症结核患者肺部载菌量更高且差异有统计学意义($P=0.007$)。分层分析发现,患有糖尿病的结核患者肺部载菌量高于无并发症的结核患者,差异有统计学意义($P=0.000$);患有肝脏疾病的结核

患者肺部载菌量也高于无并发症的结核患者,差异有统计学意义($P=0.004$)。诊断时合并患有高血压、肾脏疾病和胆囊疾病的结核患者肺部载菌量与无并发症的结核患者相比,差异均无统计学意义(均 $P>0.05$)。

表7 诊断时有、无并发症的结核患者肺部载菌量情况比较[n(%)]

Tab 7 Comparison of pulmonary bacterial load between tuberculosis patients with and without complications at diagnosis [n(%)]

Group	Grade of sputum smear				χ^2 value	P value
	1+	2+	3+	4+		
TB with complications					11.968	0.007
Without	227 (81.9)	20 (7.2)	27 (9.8)	3 (1.1)		
With	129 (74.6)	15 (8.7)	17 (9.8)	12 (6.9)		
TB with diabetes					27.877	0.000
Without	227 (81.9)	20 (7.2)	27 (9.8)	3 (1.1)		
With	28 (57.1)	4 (8.2)	11 (22.4)	6 (12.3)		
TB with hypertension					7.640	0.083
Without	227 (81.9)	20 (7.2)	27 (9.8)	3 (1.1)		
With	17 (73.9)	2 (8.7)	2 (8.7)	2 (8.7)		
TB with liver disease					13.597	0.004
Without	227 (81.9)	20 (7.2)	27 (9.8)	3 (1.1)		
With	66 (79.5)	5 (6.0)	5 (6.0)	7 (8.5)		
TB with kidney disease					4.369	0.224
Without	227 (81.9)	20 (7.2)	27 (9.8)	3 (1.1)		
With	27 (77.1)	3 (8.6)	3 (8.6)	2 (5.7)		
TB with gallbladder disease					3.474	0.302
Without	227 (81.9)	20 (7.2)	27 (9.8)	3 (1.1)		
With	12 (70.6)	2 (11.8)	2 (11.8)	1 (5.8)		

3 讨论

据WHO全球结核病报告^[7],2021年我国约有78万人患结核病,每10万人中约55人患有结核病。

糖尿病、高血压、肝脏疾病和肾脏疾病等非传染性疾病是结核患者诊断时常见的并发症^[8-12]。本研究分析450名结核菌阳性患者中,38.4%(173/450)患者在结核诊断时患有并发症,其中糖尿病49例,高血压



23例，肝脏疾病83例，肾脏疾病35例，胆囊疾病17例。目前在一项研究中系统分析各合并症对结核病的预后影响报道很少。本研究回顾性分析了诊断时患有合并症的结核患者预后情况，探讨各合并症对结核患者治疗结果及肺部损伤的影响。

结核病的高危险因素中，糖尿病位居第4位^[7]，罹患糖尿病会增加结核患者肺部损伤范围，增加治疗失败的风险^[17-18]。本研究痰涂片结果显示，患有糖尿病的结核患者肺部载菌量高于无合并症的结核患者，糖尿病引起的免疫系统紊乱，导致抗结核菌感染的免疫功能障碍，减弱患者机体抗感染和修复能力，促进患者体内结核菌的生长和繁殖^[19]。一项多中心横断面研究^[20]表明，患有糖尿病的结核患者治疗失败的风险是无合并症患者的3.25倍，空洞发生的风险是无合并症患者的3.89倍。这与本研究的结果一致：患有糖尿病的结核患者未治愈率（34.7%）高于无合并症患者（19.5%），其空洞发生率（67.4%）高于无合并症患者（26.0%）。

高血压是我国发病率较高的疾病，且患病率持续升高^[21]。高血压与全身炎症相关^[22]，与血压正常的患者相比，高血压患者的C反应蛋白水平升高^[23]。C反应蛋白与活动性结核显著相关，结核病不良治疗结局也与诊断时高C反应蛋白水平相关^[24]。因此，高血压与结核病不良治疗结局之间存在相关性。本研究中，结核病诊断时患有高血压的患者治愈率降低，这与几内亚比绍一项回顾性队列研究^[25]的结果一致。

肝脏是药物代谢的主要器官，药物性肝损伤是抗结核治疗过程中常见的不良反应，会使治疗中断^[10]。严重药物肝损伤患者的痰涂片转阴率显著低于轻中度药物肝损伤患者，造成不良的治疗结果^[26]。然而，很少有研究探讨结核诊断时肝脏疾病对结核治疗结果的影响。本研究发现诊断时患有肝脏疾病的结核患者肺部损伤区域更大，肺部载菌量更多，说明肝脏疾病同样会引起患者免疫力降低，增加结核菌对患者的损伤程度，使抗结核治疗失败。

我国的一项回顾性研究^[11]分析了慢性肾脏疾病合并结核病的基本特征，数据显示慢性肾脏病患者的结核病发病率和死亡率明显高于普通人群，说明肾脏疾病会影响结核病的进展，但未探讨肾脏疾病对结核患者肺部损伤及预后的影响。本研究发现诊断时患有肾脏疾病的结核患者治愈率更低，空洞发生率更高，

证明结核诊断时患有肾脏疾病会影响结核患者的预后，增加结核患者的肺部损伤。

本研究有一定的局限性。首先，本研究属于回顾性研究，存在选择偏倚。其次，纳入的样本量相对较少，在分析患有合并症的结核患者肺部损伤时，可能不能代表研究对象全貌。最后，本研究仅分析了诊断时结核患者的肺部损伤，未进一步分析抗结核治疗过程中肺部损伤情况。

总体来说，诊断时患有糖尿病、高血压和肾脏疾病的结核患者治愈率更低，患有糖尿病和肝脏疾病的结核患者肺部载菌量更多、肺部损伤区域更大，患有糖尿病和肾脏疾病的结核患者肺部空洞发生率更高。结核病诊断时的合并症对结核预后的不同影响，提示临床医生应重视合并症结核患者的差异化治疗，了解合并症对结核病的预后影响，方便及早采取干预措施，提高结核患者的治愈率，缩短治疗时间，降低医疗成本。

利益冲突声明/Conflict of Interests

所有作者声明不存在利益冲突。

All authors disclose no relevant conflict of interests.

伦理批准和知情同意/Ethics Approval and Patient Consent

本研究涉及的所有操作均已获得同济大学医学院上海肺科医院伦理委员会（中国上海）批准（文件号：K19-060Y）。受试对象或其亲属已经签署知情同意书。

All the protocols in this study were reviewed and approved by the Ethics Committee of Shanghai Pulmonary Hospital, Tongji University School of Medicine (Shanghai, China) (Approval Letter No. K19-060Y). The consent letters have been signed by the research participants or their relatives.

作者贡献/Authors' Contributions

骆梦醒负责数据分析和论文撰写，参与研究设计；邹欣和高雅娴参与数据整理和数据统计；吴小翠和余方友参与数据整理；胡洋参与论文修改；曾奇兵和刘忠华负责研究设计和论文修改。所有作者均阅读并同意最终稿件的提交。

LUO Mengxing performed the statistical analysis and drafted the manuscript, contributing to the study design. ZOU Xin and GAO Yaxian participated in data collation and data statistics. WU Xiaocui and YU Fangyong participated in data collation. HU Yang was involved in the revision of the manuscript. ZENG Qibing and LIU Zhonghua were responsible for the study design and revised the manuscript. All the authors have read the last version of paper and consented for submission.

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