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ORIGINAL ARTICLE

The joint impact of smoking plus alcohol drinking on treatment of pulmonary tuberculosis

Y. Ma [1,2,3] · N.-Y. Che [1,2,3] · Y.-H. Liu [1,2,3] · W. Shu [1,2,3] · J. Du [1,2,3] · S.-H. Xie [1,2,3] · Liang Li [1,2,3]

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Abstract

Tuberculosis, smoking, and alcohol drinking are major public health and social issues worldwide. We investigated the joint effect of smoking plus alcohol drinking on TB treatment. Retrospective study was conducted among TB patients in 49 units from eight provinces in China. All patients enrolled were classified into four groups according to their smoking and/or alcohol status. Current smokers plus drinkers belonged to group 1; ex-smokers plus ex-drinkers were in group 2; current smokers and ex-drinkers, current smokers and never drinkers, ex-smokers and current drinkers, ex-smokers and never drinkers, never smokers and current drinkers, and never smokers and ex-drinkers belonged to group 3; while the never smokers plus never drinkers were in group 4. We used a chi-square test to compare adverse drug reaction, lesions absorption and cavities of lung, sputum culture at the end of the second month, and treatment outcomes among the four groups. Among the 1256 participants enrolled in the study, 6.1% (76/1256) were current smokers plus drinkers; 25.9% (325/1256) were ex-smokers plus drinkers; 29.1% (366/1256) were current/never/ex-smokers and/or drinkers, and 38.9% (489/1256) were never smokers plus drinkers, respectively. Compared to the never smokers and drinkers, smoker plus drinker TB patients were more likely to experience adverse drug reaction (x^2 = 8.480, P = 0.037), less proportion of lesions absorption in lungs (x^2 = 10.330, P = 0.016), lower proportion of culture conversion (x^2 = 18.83, P = 0.04), and more unfavorable outcomes. Smoking plus alcohol drinking adversely affect response against TB treatment, which increase adverse drug reactions, sputum culture–positive rate at the end of the second month, and failure rate of pulmonary tuberculosis patients.

Keywords Tuberculosis · Smoking · Alcohol · Epidemiology · Treatment outcome

TB remains a major public health problem globally and is the ninth leading cause of deaths. World Health Organization (WHO) reported an estimated 10.4 million new TB cases and about 1.67 million deaths due to TB in 2016. China has ~ 895,000 TB patients which is the third highest in the world and 37,000 deaths [1]. Tobacco smoking and alcohol drinking are a major public health and social issue worldwide. As described in *WHO global report on trends in prevalence of tobacco smoking 2015*, tobacco use kills about 6 million people across the world each year [2]; 95% of the TB cases and 80% of the tobacco users reside in low- and middle-income countries, and an estimated 17.6% of the TB cases and 15.2% of TB mortality were attributed to smoking [3]. China is the largest producer and consumer of tobacco in the world and suffers more than 1 million deaths from tobacco-related diseases annually. The current smoking rate was 27.7% among aged 15 and above people during 2015 while the number of smokers reached 316 million [4]. Moreover, alcohol is a psychoactive substance with dependence-producing properties that has been widely used in many cultures for centuries. WHO revealed that ~ 3.3 million deaths, or 5.9% of all the deaths, were attributable to alcohol consumption globally in 2012 [5]. A meta-analysis published highlighted that approximately 10% of the TB patients were estimated to be attributable to alcohol globally [6]. Studies published from Russia,

Y. Ma and N.-Y. Che contributed equally to this work.

✉ Liang Li
liliang@tb123.org

[1] Beijing Chest Hospital, Capital Medical University, Machang Road, No. 97, Beijing 101149, China

[2] Beijing Tuberculosis and Thoracic Tumor Research Institute, Beijing 101149, China

[3] Administration Office, Clinical Center on Tuberculosis, China CDC, Beijing 101149, China

Canada, USA, Switzerland, and Australia revealed that 10–50% of the TB patients had alcohol usage disorders [7, 8]. Therefore, smoking and drinking cause social and economic burden in societies. Previous studies reported that tobacco use or alcohol consumption is more likely to increase the risk of tuberculosis [8–13]. Furthermore, tobacco consumption or drinking hampers the treatment outcomes [14–18] in contrast with the TB patients without drinking and smoking. However, these studies only described the association smoking or drinking and TB but did not demonstrate the impact of smoking plus alcohol drinking on TB treatment. In our study, we collected large number of samples from different centers in eight provinces to understand the effect of smoking plus alcohol drinking on TB treatment in China.

Methods

Study setting and case enrollment

A retrospective study was conducted among TB patients in 49 units between 2008 and 2011 (including TB dispensaries or designated hospitals) from eight provinces in China i.e., Tianjin, Chongqing, Shanghai, Guangdong, Guangxi, Hebei, Henan, and Yunnan, respectively. All of the enrolled patients met the following inclusion criteria: (1) aged 15 and above, (2) sputum culture-positive, and (3) provided informed consent. The patients were excluded if they had any of the following: (1) non-tuberculous mycobacterium, (2) sputum culture–negative, (3) drug resistance, and (4) retreatment. All cases completed treatment in 2011.

Microbiological examination

Sputum smear and solid mycobacterial culture were performed according to standard methods in the guidelines of China's National TB Control Program (NTP) [19]. Cultures for *Mycobacterium tuberculosis* were grown using Lowenstein–Jensen media; drug-susceptibility testing was performed using proportional methods.

Study definitions and criteria

The definitions of treatment outcome in our study followed China's NTP [19]. Cured: a patient who has completed prescriptive treatment, is sputum smear–negative with continuing two-time and at least one after completed. Completed treatment: a patient who has completed treatment, is sputum smear–negative once at the end of intensive phase, none or once in continuing phase of the treatment, and did not do sputum smear in the last month during treatment. Treatment success included cured and completed treatment in our study. Failure: a smear-positive patient is still sputum smear–positive at 5 months. Defaulted (interrupted treatment): a patient whose treatment was interrupted for 2 months or more, doctors did their best but the patient did not continue the treatment. Transferred out: a patient who has been transferred to another TB control unit.

Assessment of patients on smoking or drinking status at the time of enrolment: smokers are defined as the individuals who have smoked continuously or for 6 months and above during their lifetime. Patients were classified into three categories according to their smoking status. (1) Current smoker was defined as the individual who have been smoking for 6 months or above, or who was still smoking or had stopped smoking for less than 6 months when enrolled for the study. (2) Ex-smoker was defined as the smoker who had stopped smoking for at least 6 months before the current TB diagnosed. (3) Non-smoker was defined as the person who had never smoked. Similarly, drinkers are defined as those who have been drinking continuously or accumulated for 6 months and above during their lifetime. Patients were classified into three categories according to their drinking status. (1) Current drinker was defined as those who have been drinking for 6 months or above, or who were still drinking or had stopped drinking for less than 6 months when enrolled for the study. (2) Ex-drinker was defined as the drinker who had stopped drinking for at least 6 months before the current TB diagnosed. (3) Non-drinker was defined as the individual who had never drunk. In our study, patients were classified into four groups as follows: group 1 included TB patients with current smokers plus drinkers; group 2 included ex-smokers plus ex-drinkers; group 3 included current smokers and ex-drinkers, current smokers and never-drinkers, ex-smokers and current drinkers, ex-smokers and never drinkers, never smokers and current drinkers, and never smokers and ex-drinkers; group 4 included never smokers plus never drinkers (as shown in Table 1).

Adverse drug reactions (ADRs) was defined as "an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product" [20].

Assessment of chest X-rays

In the present study, we assessed manifestations of chest X-rays among patients when they completed treatment episode, including lesions and cavities of the lungs. Criteria of assessment followed the "Tuberculosis Fascicle, Guideline on Clinical Diagnosis and Treatment" [21]. (1) Lesions. significant absorption: absorption of all lesions $\geq 1/2$ of primary lesion; absorption: absorption of all lesions $< 1/2$ of primary lesion; no change: no significant change of all lesions; deterioration: lesions enlarge or spread. (2) Cavities. Decreased:

Table 1 Categories of smoking and/or alcohol drinking among TB patients

Crude group	Categories		Number	Percent	Adjusted group	Number	Percent
	Smoking	Drinking					
1	Current smokers	Current drinkers	76	6.1	Group 1:current smokers plus drinkers	76	6.1
2	Current smokers	Ex-drinkers	74	5.9	Group 2: ex-smokers plus drinkers	325	25.9
3	Current smokers	Never drinkers	79	6.3	Group 3: current/never/ex-smokers and/or drinkers include crude group 2, 3,4,6,7, and 8	366	29.1
4	Ex-smokers	Current drinkers	21	1.7	Group 4: never smokers plus never drinkers	489	38.9
5	Ex-smokers	Ex-drinkers	325	25.9			
6	Ex-smokers	Never drinkers	121	9.6			
7	Never smokers	Current drinkers	5	0.4			
8	Never smokers	Ex-drinkers	66	5.2			
9	Never smokers	Never drinkers	489	38.9			
Total			1256	100.0	Total	1256	100.0

cavities decreased ≥ 1/2 of primary cavities diameter; no change: cavities decreased or increased < 1/2 of primary cavities diameter; increase: cavities increased > 1/2 of primary cavities diameter.

Statistical analysis

Characteristics of the participants were analyzed descriptively. We used a chi-square test to compare ADR, lesions absorption and cavities of lung, sputum culture at the end of the second month, and treatment outcome among different four groups. A two-sided *P* value of 0.05 was considered statistically significant. All analyses in the study were performed using SAS version 9.1.3 (SAS Institute, Cary, NC).

Results

Demographic characteristics of study participants

The demographic characteristics of participants are shown in the Table 2. A total of 1256 participants were enrolled, that aged 15 (minimum) and 91 (maximum) with an average age of 45.2 ± 12.5, respectively. Nearly more than one third of the participants (36.7%) were between age 25–44; more than two thirds of whom were male (72.9%); 54.6% had a BMI value between 18.5 and 24; 55.8% had completed junior middle and high school; 52.8% were farmers and migrant workers; 27.2% were unmarried, and 29.1% were not registered with the local population. Additionally, the current smokers and drinkers, ex-smokers and drinkers, Current/non-/ex-smokers and/or drinkers, non-smokers and drinkers accounted for 6.1% (76/1256), 25.9% (325/1256), 29.1% (366/1256), 38.9% (489/1256), respectively. Notably, smokers and drinkers were more likely to be male, aged 45–64, BMI (18.5–24), junior middle and high school educated, farmers and migrant workers, and married and the local population registered. Univariate analysis also revealed that sex, age, degree of education, profession, marriage, and census registration were significantly different among the four groups.

Adverse drug reaction

ADR among four groups are presented in Table 3. Out of the 1256 participants, the overall rate of ADR was 21.6%. ADR rate among the current smokers and drinkers was 27.6%, higher than other three groups; adverse events yielded significant difference ($P = 0.037$).

Lesions absorption and cavity closure

As shown in Table 4, a significantly higher proportion of lesion absorption was observed among the non-smokers and drinkers group compared with the other three groups, and showed significant difference ($P = 0.016$). Furthermore, we compared cavities among the four groups, higher proportion of deterioration; no change was found among the current smokers and drinkers. However, no significant difference was identified in the cavities among the four groups ($P = 0.248$).

Sputum culture at the end of the second month and treatment outcome

As shown in Table 5, the overall culture conversion rate at the end of the second month of treatment was 87.1%. As expected, the smokers and drinkers had lower proportion of culture conversion in contrast with the non-smokers and drinkers i.e., 82.1% in the current smoker and drinker

Table 2 Demographic characteristics of the study participants

Demographic characteristics	Total *n* (%)	Current smokers and drinkers *n* (%)	Ex-smokers and drinkers *n* (%)	Current/non-/ex-smokers and/or drinkers *n* (%)	Non-smokers and drinkers *n* (%)	χ^2	*P*
Sex						487.79	< 0.001
Male	915 (72.9)	74 (97.4)	317 (97.5)	337 (92.1)	187 (38.2)		
Female	341 (27.1)	2 (2.6)	8 (2.5)	29 (7.9)	302 (61.8)		
Age						115.956	< 0.001
15–24	266 (21.2)	3 (4.0)	39 (12.0)	56 (15.3)	168 (34.4)		
25–44	461 (36.7)	30 (39.5)	114 (35.1)	137 (37.4)	180 (36.8)		
45–64	361 (28.7)	36 (47.3)	121 (37.2)	120 (32.8)	84 (17.2)		
65–	168 (13.4)	7 (9.2)	51 (15.7)	53 (14.5)	57 (11.6)		
BMI						10.359	0.11
< 18.5	497 (39.6)	27 (35.5)	122 (37.5)	135 (36.9)	213 (43.6)		
18.5~	686 (54.6)	46 (60.5)	183 (56.3)	215 (58.7)	242 (49.5)		
≥ 24.0	73 (5.8)	3 (4.0)	20 (6.2)	16 (4.4)	34 (6.9)		
Level of education						80.20	< 0.001
Illiteracy	109 (8.7)	7 (9.2)	24 (7.4)	29 (7.9)	49 (10.0)		
Primary school	312 (24.8)	21 (27.6)	119 (36.6)	75 (20.5)	97 (19.9)		
Junior middle and high school	701 (55.8)	46 (60.6)	164 (50.5)	237 (64.8)	254 (51.9)		
College degree and above	134 (10.7)	2 (2.6)	18 (5.5)	25 (6.8)	89 (18.2)		
Profession						65.642	< 0.001
Farmers and migrant workers	663 (52.8)	41 (53.9)	205 (63.1)	194 (53.0)	223 (45.6)		
Employees	171 (13.6)	7 (9.2)	24 (7.4)	29 (7.9)	111 (22.7)		
Others	422 (33.6)	28 (36.9)	96 (29.5)	143 (39.1)	155 (31.7)		
Marriage						59.658	< 0.001
Unmarried	342 (27.2)	9 (11.9)	59 (18.2)	86 (23.5)	188 (38.4)		
Married	865 (68.9)	65 (85.5)	247 (76.0)	268 (73.2)	285 (58.3)		
Others	49 (3.9)	2 (2.6)	19 (5.8)	12 (3.3)	16 (3.3)		
Census register						23.781	< 0.001
The local population registered	890 (70.9)	62 (81.6)	258 (79.4)	250 (68.3)	320 (65.4)		
Not local population registered	366 (29.1)	14 (18.4)	67 (20.6)	116 (31.7)	169 (34.6)		

group while 81.4% in the ex-smoker and drinker group. However, the culture conversion rate among patients with non-smokers and drinkers reached up to 90.7%; statistically significant difference was found in the four groups ($P = 0.004$). We further compared treatment outcome among 1256 subjects. The overall rate of favorable outcomes (cured or completed treatment) was 81.4%; for the ex-smokers and drinkers, it was 77.5%, which is the lowest compared to other three groups. For the non-smokers and drinkers, the rate of favorable outcomes was the highest (85.7%). Nevertheless, TB outcomes did not significantly differ among the four groups ($P = 0.076$).

Discussion

In the current study, we found that the rate of smoking or drinking among TB patients was relatively higher. Smokers

Table 3 Analysis of adverse drug reaction among four groups

ADR	Total *n* (%)	Current smokers and drinkers *n* (%)	Ex-smokers and drinkers *n* (%)	Current/non-/ex-smokers and/or drinkers *n* (%)	Non-smokers and drinkers *n* (%)	χ^2	*P*
Yes	271 (21.6)	21 (27.6)	71 (21.8)	93 (25.4)	88 (18.0)	8.480	0.037
No	985 (78.4)	55 (72.4)	254 (78.2)	273 (74.6)	401 (82.0)		

Table 4 Analysis of the lesions absorption and cavity closure

Variable	Total *n* (%)	Current smokers and drinkers *n* (%)	Ex-smokers and drinkers *n* (%)	Current/non-/ex-smokers and/or drinkers *n* (%)	Non-smokers and drinkers *n* (%)	χ^2	*P*
Lesions						10.330	0.016
Deterioration/no change	69 (7.2)	4 (7.1)	26 (9.1)	24 (8.7)	15 (4.0)		
Absorption	891 (92.8)	52 (92.9)	221 (90.9)	261 (91.3)	357 (96.0)		
Cavities						4.129	0.248
Increase/no change	41 (10.3)	5 (20.9)	12 (12.2)	12 (9.0)	12 (8.3)		
Decrease/closure	358 (89.7)	19 (79.1)	86 (87.8)	121 (91.0)	132 (91.7)		

Absorption include significant absorption and absorption

accounted for 55.5%, including current (18.3%) and ex-smokers (37.2%). We found similar smoking rate among TB patients reported by Wang et al. (54.6%) [22] and Kanda R et al. (57%) [16] whereas higher than the reported rate from a study from Spain (39.3%) [23] and Malaysia (40.3%) [24]. In addition, 45.1% of the TB patients were drinkers that included current (8.1%) and ex-drinkers (37.0%); however, a study from the Russian Federation showed that 62.2% TB patients were drinkers [25], while 31% had alcohol use disorders in India [26]. Zetola et al. revealed that MDR-TB cases had a lifetime prevalence of alcohol use of 35.1% [27]. Moreover, in the present study, we found a higher rate (32.0%) of smoking plus drinking among TB patients, including current smoker and drinker (6.1%) and ex-smoker and drinker (25.9%). The data from our study demonstrated that smoking and drinking brought more unfavorable treatment effects when compared with cases without drinking and smoking.

We observed that smoking and drinking increased the ADR rate which was significantly different between groups. Higher ADR rate has been reported among drinkers than non-drinkers [24, 25] which could result due to effect of alcohol on the liver during treatment. Miller et al. reported higher ADR rate; however, no significant differences were demonstrated between drinkers and non-drinkers. Hence, further work is required to establish whether drinking could increase ADR rate or not. In addition, we also observed the effects of smoking and drinking on lesions and cavitation using chest radiography after treatment. We found a higher proportion of lung lesions and cavities among TB patients that were current smokers and drinkers and ex-smokers and drinkers. Previous studies revealed that smoker TB patients had higher frequency of cavities in contrast with the non-smokers [28–31]. Similarly, literature published has demonstrated that alcohol use was associated with higher frequency of lung cavitation [32, 33]. However, they explored the effects of smoking or alcohol consumption on lesions and cavities among TB patients, respectively, rather than TB cases with smokers as well as drinkers. To the best of our knowledge, our study is the first to discuss the association between smoking/drinking and lesions/cavities.

As reported in previous studies [34, 35], tobacco smoke contains various harmful substances such as nicotine and carbon monoxide. When smoked, it causes damage to the respiratory mucosa and the airway of epithelial cell cilia

Table 5 Sputum culture at the end of the second month and outcome among four groups

Variable	Total *n* (%)	Currentsmokers and drinkers *n* (%)	Ex-smokers and drinkers *n* (%)	Current/non-/ex-smokers and/or drinkers *n* (%)	Non-smokers and drinkers *n* (%)	χ^2	*P*
Sputum-culture of the end of second month						18.83	0.004
Negative	881 (87.1)	46 (82.1)	210 (81.4)	256 (88.3)	369 (90.7)		
Positive	130 (12.9)	10 (17.9)	48 (18.6)	34 (11.7)	38 (9.3)		
Treatment outcome						15.590	0.076
Treatment success	1023 (81.4)	60 (78.9)	252 (77.5)	291 (79.5)	419 (85.7)		
Failure	70 (5.6)	5 (6.6)	25 (7.7)	24 (6.6)	16 (3.3)		
Died	25 (2.0)	2 (2.6)	7 (2.2)	11 (3.0)	5 (1.0)		
Others	138 (11.0)	9 (11.8)	41 (12.6)	40 (10.9)	49 (10.0)		

Others include defaulted and transferred out cases

that causes an increase in the internal inflammatory cells; later, it affects the function of phagocytes and reduces the toxicity of phagocytic cells and increases the lethality of *M. tuberculosis*. Furthermore, alcohol consumption impairs the immune system; hence, smoking and drinking may impact the treatment effect of anti-tuberculosis drugs. As expected, our findings revealed that smoker and drinker TB patients had lower rate of sputum culture conversion. Studies from Japan, Brazil, and India have also confirmed that smoking adversely affected the culture conversion [14, 16, 17, 29]. In addition, literature has highlighted that alcohol use was associated with lower rate of sputum culture conversion [18]. We also demonstrated that both smoking and drinking have more unfavorable outcomes with higher failure and death rate, which was in agreement with other studies [15, 18, 26, 36].

Strengths and limitations

There are some notable strengths in the present study. To the best of our knowledge, this is the first study to investigate response of smoking plus drinking on treatment effect of TB patients in China. In addition, the study is multicenter, with large number of samples. Our results demonstrated that both smokers and drinkers among TB patients had higher proportion. Additionally, our data further confirmed that current and ex-smokers and drinkers had higher ADR rate, increased lung cavitation and lesions, lower rate of sputum culture conversion and more unfavorable treatment outcomes, compared to the never smokers and drinkers.

Despite the strengths of the present study, there are some limitations. Firstly, statuses of cigarette smoking and drinking were self-reported by the patients and are therefore prone to recall bias. Secondly, we know that dose−response effects of smoking and drinking on treatment effect of patients can be further analyzed, which may be better. Unfortunately, it is because the data were incomplete, and were not assessed in the study. Thirdly, because there was no follow-up after treatment of patients was completed, the relationship between TB relapse and smoking and drinking was not analyzed.

In conclusion, our data revealed that smoking and drinking brought worse treatment effects among the TB patients. Further studies should be conducted to confirm the relationship between smoking, drinking, and treatment effect. In addition, alcohol use and drinking intervention strategies should be recommended to improve favorable treatment outcome, and further control tuberculosis.

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Compliance with ethical standards Ethics approval was granted by the Institutional Ethics Review Committee of Beijing Tuberculosis and Thoracic Tumor Research Institute, and the eight provincial TB Control and Prevention Centers (TB special hospital). A written informed consent was obtained from eligible patients prior to interview.

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

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