Primary Drug-Resistant Tuberculosis in the Elderly in Shandong,China,from 2004 - 2019.

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Abstract

Background: With an aging population, China is facing a huge burden of elderly patients with drug resistant tuberculosis (DR-TB), which has become an significant obstacle for the global TB control targets. There is still few study on DR-TB among China so far. Thus, more researches on the epidemiological characteristics and trend of primary DR-TB among the elderly will be necessary.

Methods: A retrospective study was conducted in Shandong, China from 2004-2019, 12661 primary TB and 4368 elderly (≥ 60 years of age) primary TB cases were involved. Clinical characteristics including age, sex, Cavity, Smoking, drinking, comorbidity and drug susceptibility data were included. [Descriptive statistical](#) analysis, Chi-square and linear regression were used for analyzing.

Results: Among 4368 elderly patients with primary TB, the DR-TB and MDR-TB accounted for 17.19% and 2.29% respectively. During 2004 to 2019, the proportions of MDR-TB, PDR-TB, RFP-resistance increased by 160.00%, 18.18%, 231.82%, and the rate of DR-TB among elderly patients with primary cavitary TB increased by 255%. Among the elderly with primary DR-TB, the proportion of male (from 85.19 to 89.06), cavity (from 7.41 to 46.88), RFP (from 3.70 to 21.88), SM (from 37.04 to 62.5) increased significantly ($P < 0.05$). And the proportion of female (from 14.81 to 10.94), non-cavity (from 92.59 to 32.81), INH (from 66.67 to 57.81) decreased significantly. ($P < 0.05$).

Conclusion: Among the elderly, the proportions of MDR-TB, PDR-TB, RFP-resistance and cavitary DR-TB increased significantly. The pattern of DR-TB changed from female, non-cavity and INH-resistant groups to male, cavity and RFP, SM-resistant groups. For a better control on the elderly DR-TB in the future, we should pay more attention to, male, smoking, drinking, COPD and diabetes subgroups.

Introduction:

Tuberculosis is one of the top 10 causes of death and the mainly cause from an infectious disease around the world. Millions of people go on falling sick with TB each year. Drug-resistant TB plays an important role in the public health. The world health organization (WHO) estimated that around the world, there were an estimated 484 000 (range, 417 000–556 000) incident cases of MDR/RR-TB in 2018. China was one of countries accounted for almost half of the world's cases of MDR/RR-TB, which accounted for 14%. [1],[2] Global Burden of Diseases, Injuries, and Risk Factors data for tuberculosis (1990–2016) show that if current trends in tuberculosis incidence continue, few countries are likely to meet the SDG (Sustainable Development Goal) target to end the tuberculosis epidemic by 2030. [3] MDR tuberculosis, XDR tuberculosis, and resistance beyond XDR tuberculosis was a mainly threat to global tuberculosis control. [4]

China has the world's largest population, and is facing population aging. Until the end of 2012, the elderly population (≥ 60 years of age) in China were 194 million, which accounted for 14.3% of total population. By 2030, the elderly population in China is predicted to reach 400 million. [5] With the population aging, there will be many problems that China must face, including the health of aging people. TB plays an important role in the health of the old adults. [6] A study showed that tuberculosis deaths were higher among old adults than younger. [7] Meanwhile some studies showed that patients older was a significant risk factor for developing MDR. [8] Older adults provide society's carers, community leaders and mentors, and are important in educating the younger generation. Attaching importance to TB prevention, active TB cases finding and treatment will exert positive cascading influence through families, communities and societies. [6] DR-TB is still a crisis globally, especially multidrug resistant tuberculosis. [9] Besides, The rate of primary drug resistance is regarded as an epidemiological indicator for long-term surveillance of the quality of tuberculosis treatment in the community. [10] The primary DR-TB is very important in the transmission of TB. It means that we should put our sights on the primary tuberculosis among the elderly, especially the primary drug resistant tuberculosis to face the problem which the population aging will bring. Nevertheless, the studies on drug resistant tuberculosis in the elderly are few.

We collected 12661 primary TB cases with drug susceptibility test results. Meanwhile, Chi-square and linear regression were carried out to assess the epidemiological characteristics and trend of primary DR-TB among the elderly in Shandong, China, from 2004–2019. Otherwise, we divided the primary DR-TB among the elderly into some groups separated by drug-resistant profiles, sex, smoking, drinking, cavity and diabetes for further analysis.

Materials And Methods Ethics Statement

The study was approved by the Ethics Committee of Shandong, Provincial Hospital (SPH), affiliated with Shandong University and the Ethic Committee of Shandong Provincial Chest Hospital (SPCH), China. All patients' data were rendered anonymous before analysis.

Study Population And Data Collection

The study acquired these cases from 36 TB prevention and control institutions of Shandong Province, China, Jan. 1, 2004 to Dec. 31, 2019. 2 province-level hospitals (Shandong Provincial Hospital and Shandong Provincial Chest Hospital), 13 municipal-level and 21 county-level local health departments were engaged in monitoring of DR-TB from 2004 to 2019. All mycobacterium tuberculosis cases involved in this study were consecutive culture-confirmed, susceptibility to first line anti-TB drugs (isoniazid, rifampin, ethambutol, and streptomycin) was identified by DST. Data on demographic and clinic information (sex, smoking, drinking, cavity and diabetes) were collected. Smoker (or drinker) refers to the people who have been smoking (or drinking) for 6 months or above, or those who were still smoking (or drinking) or had stopped smoking (or drinking) for less than 6 months before TB diagnosis. Non-smoker and non-drinker refer to the people who had never smoked or never drunk, respectively.

Laboratory Methods

All sputum samples were adopted from patients conforming to the conditions by suspected site. Then these samples were sent to the TB Reference Laboratory of SPCH for further detection. Samples were cultured on Löwenstein-Jensen (LJ) culture medium, and then growing colonies were sent for further identification and DST. Para-nitro benzoic acid (PNB) and Thiophene-2-carboxylic acid hydrazide (TCH) medium tubes were used for identification of the species *M. tuberculosis*. The susceptibility to four first-line drugs (rifampicin, isoniazid, streptomycin, and ethambutol) was tested by the proportional method on Löwenstein-Jensen (LJ) culture medium according to the WHO guidelines.[11] The concentration of drugs were as follows: 0.2 µg/mL (isoniazid, INH), 40 µg/mL (rifampin, RFP), 10 µg/mL (streptomycin, SM), 2 µg/mL (ethambutol, EMB). [12]

Quality Control

Quality assessment and data extraction were complicated by two professional investigators respectively. Superior TB National Reference laboratory in SPCH implemented the external quality assessment regularly for all laboratories in our study.

Data Inclusion And Definitions

TB patients with a positive *M. tuberculosis* culture were included, DST results, demographic information, and clinical information of the patients were available .

Drug-resistant tuberculosis (DR-TB) include acquired and primary drug resistance according to whether having a history of previous treatment.[13]

The elderly primary TB refers to a patient ≥ 60 years of age with primary TB.

Drug-resistant tuberculosis (DR-TB): Resistance to any drugs.[14]

Mono-resistance (MR): Resistance to one first-line anti-TB drug only.[15]

Polydrug resistance (PDR): Resistance to more than one first-line anti-TB drug, other than both isoniazid and rifampicin.[15]

Multidrug resistance (MDR): Resistance to at least both isoniazid and rifampicin.[15]

Rifampicin resistance (RR): Resistance to rifampicin detected using phenotypic or genotypic.[15]

Statistical Analysis

Chi-square test for trends and linear regression in line charts and stacked bar charts were used to analyze the changes and temporal trend in quantity and proportions of the different resistance patterns over time. Odds ratios (ORs) and 95% CIs for the comparisons of specific characteristics between the non elderly (< 60 years) and the elderly (≥ 60 years) were acquired by Pearson Chi-square test. $P < 0.05$ was considered to be significant statistically. All analyses were implemented by using SPSS software (version 20.0).

Results

Patients' Characteristics

We collected 12661 primary TB case-patients, and analyzed the demographic and clinical information of them from 2004 to 2019 in Shandong, China. 4368 primary TB case-patients were the elderly (≥ 60 years), which accounted for 34.50% of the total primary TB case-patients collected. There were 8183 primary TB case-patients were the non elderly (< 60 years), which accounted for 64.63% of the total primary TB case-patients collected. The elderly primary TB case-patients were more likely than the non elderly primary TB case-patients to be male (OR:2.045, 95%CI:1.850–2.280), to have habits of smoking (OR:1.447, 95%CI:1.300–1.611) and drinking (OR:1.144, 95%CI:1.019–1.284), and to have COPD (OR:1.320, 95%CI:7.457–17.183) and diabetes (OR:1.399, 95%CI:1.186–1.651). The non elderly TB case-patients were more likely than the elderly TB case-patients to have cavitory pulmonary disease (OR:0.815, 95%CI:0.751–0.884). We also found that the elderly DR-TB case-patients were more likely than the non elderly DR-TB case patients to be male (OR:2.048, 95%CI:1.575–2.663), to have habits of smoking (OR:1.511, 95%CI:1.169–1.954) to have COPD (OR:23.883, 95%CI:7.193–79.305) and diabetes (OR:1.658, 95%CI:1.144–2.402) (Table 1).

Table 1
Sociodemographic and clinical characteristics of elderly and non elderly primary TB patients

characteristic		Age<60 years,no.(%)n = 8183					characteristic		Age ≥ 60 years
		Total n = 8183	DR-TB n = 1600	Susceptible TB n = 6583	OR(95% CI)	P value			Total n = 4368
Sex(N = 8181/N = 1600/N = 6581)	Female	1823(22.28)	314(19.63)	1509(22.93)	1.218(1.063–1.396)	0.004	Sex(n = 4367/n = 751/n = 3616)	Female	535(12.25)
	Male	6358(77.72)	1286(80.38)	5072(77.07)			Male	3832(87.75)	
Cavity(n = 7126/n = 1397/n = 5729)	No	4224(59.28)	792(56.69)	3432(59.91)	1.141(1.014–1.285)	0.028	Cavity(n = 3778/n = 657/n = 3121)	No	2422(64.11)
	Yes	2902(40.72)	605(43.31)	2297(40.09)			Yes	1356(35.89)	
Smoking(n = 4801/n = 922/n = 3879)	No	3722(77.53)	719(77.98)	3003(77.42)	0.968(0.814–1.151)	0.711	Smoking(n = 2680/n = 438/n = 2242)	No	1888(70.45)
	Yes	1079(22.47)	203(22.02)	876(22.58)			Yes	792(29.55)	
Drinking(n = 4761/n = 917/n = 3844)	No	3809(80.00)	752(82.01)	3057(79.53)	0.852(0.708–1.026)	0.092	Drinking(n = 2667/n = 438/n = 1886)	No	2074(77.77)
	Yes	952(20.00)	165(17.99)	787(20.47)			Yes	593(22.23)	
Type(n = 8183/n = 1600/n = 6583)	Extrapulmonary TB	23(0.28)	4(0.25)	19(0.29)	1.115(0.392–3.400)	0.794	Type(n = 4368/n = 750/n = 3618)	Extrapulmonary TB	16(0.37)
	Pulmonary TB	8160(99.72)	1596(99.65)	6564(99.71)			Pulmonary TB	4352(99.63)	
COPD(n = 6033/n = 1199/n = 4834)	No	6007(99.57)	1196(99.75)	4811(99.52)	0.350(0.082–1.486)	0.155	COPD(n = 3340/n = 460/n = 2880)	No	3184(95.33)
	Yes	26(0.43)	3(0.25)	23(0.48)			Yes	156(4.67)	
diabetes(n = 6033/n = 1199/n = 4834)	No	5683(94.20)	1128(94.08)	4555(94.23)	1.028(0.786–1.344)	0.842	diabetes(n = 3340/n = 563/n = 2779)	No	3075(92.07)
	Yes	350(5.80)	71(5.92)	279(5.77)			Yes	265(7.93)	

Drug-resistance Patterns

The elderly patients with primary DR-TB were 751, which accounted for 17.19% among the total primary TB-case-patients collected. Among 4368 the elderly primary TB patients, the highest number and proportion of resistance were SM 469 (10.74%), followed by INH 446 (10.21%), RFP 136 (3.11%), EMB 56 (1.28%) respectively; the number and proportion of MR-TB including INH, RFP, EMB, SM were 197 (4.51%), 23 (0.53%), 13 (0.30%) and 250 (5.72%), respectively. MDR TB were 100 (2.29%) among the elderly TB patients. There were four main types of primary MDR-TB, for example, MDR1 (INH + RFP), MDR2 (INH + RFP + EMB), MDR3 (INH + RFP + EMB + SM), and MDR4 (INH + RFP + SM), which accounted for 0.80% (35), 0.05% (2), 0.60% (26), 0.76% (33) respectively. There were five main types of primary PDR-TB, for example, PDR1 (INH + EMB), PDR2 (INH + SM), PDR3 (RFP + EMB), PDR4 (RFP + SM), PDR5 (INH + EMB + SM), PDR6 (RFP + EMB + SM), which accounted for 0.11% (5), 3.16% (138), 0.05% (2), 0.23% (10), 0.14% (6) and 0.02% (1) respectively. The elderly primary TB cases had lower rate of DR-TB (17.19% vs 19.55% $P < 0.05$), MDR-TB (2.29% vs 3.72% $P < 0.001$) than the non elderly. The proportion of resistance to RFP or SM was lower among the elderly than the non elderly ($P < 0.001$). The proportion of resistance only to RFP, SM was lower among the elderly than the non elderly ($P < 0.05$). The proportion of resistance only to INH, EMB was higher among the elderly than the non elderly ($P < 0.05$). (Table 2)

Table 2
Primary drug resistance profiles of mycobacterium tuberculosis between elderly people and non elderly people,Shandong,China,2004–2019*

Drug resistance	Age < 60 years,no.(%)n = 8183	Age ≥ 60 years,no.(%)n = 4368	P value
DR-TB(Total)	1600(19.55)	751(17.19)	0.001
Any resistance to first-line drugs			
INH	873(10.67)	446(10.21)	0.426
RFP	415(5.07)	136(3.11)	<0.000
EMB	131(1.60)	56(1.28)	0.16
SM	1143(13.97)	469(10.74)	<0.000
MR-TB(Total)	962(11.76)	488(11.17)	0.330
INH	286(3.50)	197(4.51)	0.005
RFP	72(0.88)	23(0.53)	0.031
EMB	9(0.11)	13(0.30)	0.022
SM	588(7.19)	250(5.72)	0.002
Others	7(0.09)	5(0.11)	0.619
MDR-TB(Total)	304(3.72)	100(2.29)	<0.000
MDR1:INH + RFP	55(0.67)	35(0.80)	0.415
MDR2:INH + RFP + EMB	11(0.13)	2(0.05)	0.161
MDR3:INH + RFP + EMB + SM	69(0.84)	26(0.60)	0.127
MDR4:INH + RFP + SM	153(1.87)	33(0.76)	<0.000
Others	16(0.20)	4(0.09)	0.174
PDR-TB(Total)	343(4.19)	163(3.73)	0.212
PDR1:INH + EMB	9(0.11)	5(0.11)	0.943
PDR2: INH + SM	272(3.32)	138(3.16)	0.621
PDR3:INH + EMB + SM	11(0.13)	6(0.14)	0.966
PDR4:RFP + EMB	5(0.06)	2(0.05)	0.729
PDR5:RFP + SM	36(0.44)	10(0.23)	0.067
PDR6:RFP + EMB + SM	4(0.05)	1(0.02)	0.497
Others	6(0.07)	1(0.02)	0.254

Trends Over Time

The elderly DR-TB patients were divided into several different subgroups featured by drug resistance (MR-TB/MDR-TB/PDR-TB, INH/RFP/SM/EMB-resistant), sex (male or female), drinking history (yes/no/unknown), smoking history (yes/no/unknown), cavity (yes/no/unknown), the change of the number and proportions of each subgroups among the total elderly DR-TB patients collected from 2004–2019 were demonstrated by Fig. 1 (a,b,c,d,e) and Fig. 2. Among the total elderly DR-TB patients, the percentage of male varied from 85.19–89.06% ($R^2 = 0.0901$; χ^2 test for trends: $\chi^2 = 3.941$, $p < 0.05$), the percentage of cavity varied from 7.41–46.88% ($R^2 = 0.6069$; χ^2 test for trends: $\chi^2 = 97.545$, $p < 0.001$), the percentage of RFP-resistant varied from 3.70–21.88% ($R^2 = 0.0531$; χ^2 test for trends: $\chi^2 = 5.502$, $p < 0.05$), the percentage of SM -resistant varied from 37.04–62.50% ($R^2 = 0.1574$; χ^2 test for trends: $\chi^2 = 24.756$, $p < 0.001$), the proportion of these subgroups including cavity, RFP-resistant and SM-resistant increased significantly from 2004 to 2019. In addition, the proportion of these two subgroups including non-cavity and INH-resistant decreased significantly from 2004 to 2019. The percentage of female varied from 14.81–10.94% ($R^2 = 0.0901$; χ^2 test for trends: $\chi^2 = 3.941$, $p < 0.05$), The percentage of non-cavity varied from 92.59–32.81% ($R^2 = 0.6551$; χ^2 test for trends: $\chi^2 = 208.201$, $p < 0.001$), INH-resistant varied from 66.67–57.81% ($R^2 = 0.2437$; χ^2 test for trends: $\chi^2 = 25.532$, $p < 0.001$).

Table 4
Changes in proportions of different primary drug-resistant Mycobacterium Tuberculosis subgroups among the elderly, Shandong Province, China, 2004–2019*

Subgroups	X2	P Value	R2	X-coefficient	SE
MR-TB(%)	1.793	0.181	0.0241	-0.003437	0.67614
MDR-TB(%)	1.179	0.278	0.0098	0.002233	0.1324
PDR-TB(%)	0.486	0.486	0.0057	0.001366	0.18946
Male(%)	3.941	0.047	0.0901	-0.00307	0.9315
Female(%)	3.941	0.047	0.0901	0.00307	0.0685
Cavity(%)	97.545	< 0.000	0.6069	0.024115	0.076289
Non-cavity(%)	208.201	< 0.000	0.6551	-0.038137	0.94479
Smoking(%)	101.315	< 0.000	0.5459	0.019259	-0.016761
Non-smoking(%)	390.327	< 0.000	0.7902	0.051071	-0.087337
Drinking(%)	58.02	< 0.000	0.4013	0.013079	-0.002038
Non-drinking(%)	461.412	< 0.000	0.8027	0.056592	-0.099645
INH(%)	25.532	< 0.000	0.2437	-0.013242	0.74462
RFP(%)	5.502	0.019	0.0531	0.005063	0.1506
EMB(%)	0.722	0.395	0.0236	0.001139	0.057315
SM(%)	24.756	< 0.000	0.1574	0.013045	0.51201
*EMB, ethambutol; INH, isoniazid; RIF, rifampin; SM, streptomycin; TB, tuberculosis. INH (%), RFP (%),EMB (%), and SM (%) refer to the proportion of primary INH/RFP/EMB/SM resistant TB among total primary DR TB cases, respectively. MR-TB, mono-resistant tuberculosis; MDR-TB, multi-resistant tuberculosis; PDR-TB, polydrug resistant tuberculosis. EMB, ethambutol; INH, isoniazid; RFP, rifampin; SM, streptomycin.					

Total And Annual Drug Resistance Rate

Total and annual drug resistance rates of the elderly in different subgroups are shown in Table 3. The drug resistance rates among these subgroups including MDR-TB, PDR-TB, cavity, RFP-resistant increased by160.00%,18.18%, 255.00%, 231.82%, and changed from 1.10–2.86%, from 2.2–2.60%, from 2.2–7.81%, from 1.1–3.65% respectively. On the contrary, the drug resistance rates among non cavity, INH-resistant, EMB-resistant, SM-rentsista reduced by 80.09%, 51.26%, 52.73%, 5.19%, and changed from 27.47% to 5.47%, from 19.78–9.64%, from 2.2–1.04%,from 10.99–10.42% respectively.

Table 3
The temporal change trend of primary drug resistance rate among the elderly TB cases in Shandong, China, 2004–2019*

characteristic	drug resistance rate(%)															
	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
DR-TB(Total)	29.67	20.24	20.31	14.5	19.73	10.94	10	19.08	16.72	15.57	15.77	17.11	17.26	17.87	15.70	16.1
Type																
MR-TB(Total)	26.37	14.88	13.79	7.85	11.66	7.03	5	12.5	7.62	10.78	9.32	12.83	10.68	10.66	11.43	11.1
MDR-TB(Total)	1.10	1.79	3.07	2.11	1.35	1.56	5	1.97	4.11	2.1	2.15	0.8	3.29	2.82	1.57	2.8
PDR-TB(Total)	2.2	3.57	3.45	4.53	6.73	2.34	0	4.28	4.99	2.69	4.3	3.48	3.29	4.39	2.69	2.6
Sex																
Male	25.27	19.05	18.39	12.99	18.39	10.934	10	17.43	15.25	13.77	13.62	13.9	15.89	15.99	13.68	14.1
Female	4.4	1.19	1.92	1.51	1.35	0	0	1.64	1.47	1.8	2.15	3.21	1.37	1.88	2.02	1.8
Cavity																
Yes	2.2	2.98	6.9	2.72	4.93	1.56	0	3.29	4.99	5.09	6.45	5.62	7.67	7.84	6.95	7.8
No	27.47	16.67	12.64	10.57	13	9.38	10	15.46	10.85	8.98	6.45	7.49	4.93	8.15	5.61	5.4
Smoking																
Yes					1.35	0.78	0	4.93	4.99	4.79	4.66	3.21	3.56	5.02	3.14	2.8
No					2.24	3.91	0	10.86	7.04	8.98	8.6	9.89	9.32	9.72	10.99	9.9
Drinking																
Yes					0.9	0.78	80	0	2.93	2.69	4.66	2.41	2.47	2.82	2.69	1.9
No					2.69	3.91	0	10.53	8.8	11.08	8.6	10.7	10.41	11.6	11.44	10.1
First-line drugs																
INH	19.78	14.29	12.26	9.37	13.45	7.81	10	11.51	12.61	8.38	9.32	8.02	9.32	9.09	8.30	9.6
RFP	1.1	1.79	3.45	2.72	3.14	2.34	5	3.29	4.99	2.69	2.51	1.87	4.93	2.82	2.69	3.6
EMB	2.2	1.19	1.15	1.21	1.35	0	0	2.3	1.76	0.6	1.79	8.02	1.64	1.57	0.90	1.6
SM	10.99	9.52	12.26	10.57	9.87	4.69	5	9.54	10.56	10.18	11.47	10.96	12.05	14.73	9.87	10.1

Discussion

This retrospective cohort study collected 12661 primary TB case-patients in Shandong, the second largest province in China, from 2004 to 2019, to evaluate the epidemiological characteristics and trend among the elderly DR-TB. We have some findings in this study. Among the elderly, the proportions in these subgroups including MDR-TB, PDR-TB, RFP-resistance and cavitory DR-TB increased significantly. The pattern of DR-TB shifted into male,cavity and RFP, SM-resistant groups. Male,smoking,drinking, COPD and diabetes subgroups.subgroups should get more attention.

According to the WHO report, TB prevalence increased with age in Asia and some African countries (e.g. Ghana, Malawi,Rwanda, the United Republic of Tanzania and Zimbabwe), the peak of prevalence in some Africa countries (e.g. Ethiopia, Gambia, Namibia, Nigeria, Sudan, Uganda and Zambia) were among those people aged 35–54 years.[15] And there is a estimated that the elderly population will come up to 400 million by 2030.² The prevalence of tuberculosis in aged 65 years and older was more than twice as high than that in younger adults.[16] Elderly patients have been repeatedly reported to have a lower treatment completion rate and are less health awaeness than younger patients .That means the diagnosis and treatment in elderly TB is very difficult for us. [17],[18] So the TB in the elderly should be appreciated. Meanwhile we found that the elderly (≥ 60 years) primary TB patients accounted for about one third(4368/12661, 34.50%)of the total new TB cases.

Besides, we found that the elderly with TB were more likely to be male, to have habits of smoking or drinking, and to develop complications such as COPD or diabetes than the non-elderly .We found that there was no statistical significance between elderly DR-TB cases and elderly susceptible TB cases in our statistical data. But we found that elderly DR-TB cases are more likely to be male and to like smoking than non elderly DR-TB cases. Some surveys showed a systematically higher burden of TB disease among men, with M:F (Male/Female) ratios ranging from 1.2 (in Ethiopia) to 4.9 (in Viet Nam). The M:F ratios were generally higher in Asia than in Africa, that was in the range 2–4.[2] In 2017 ,TB cases in all EU/EAA (European Union/East Asian Area) member States tended to be male. In Poland, men was the biggest in older age groups with TB.[19] This phenomenon may be associated with Social behavior factors and biological sex-related factors, such as sex steroid hormones, the genetic makeup of the sex chromosomes, and sex-specific metabolic features.[20] Risk factors are also very important in the control of tuberculosis. Diabetes, alcohol use, and smoking all accounted for about a quarter of tuberculosis deaths and

DALYs (disability-adjusted life years)around the world in 2015.[7] These factors may increase the risk of TB by impairing the immune system of human.[21]-[23] Smoking made it easy to develop TB which is related to ciliary dysfunction, to a reduced immune response, and to defects in the immune response of macrophages, with or without a decrease in the CD4 count.[24] Some evidence suggested that drinking was linked to tuberculosis treatment compliance and may lead to subsequent acquired drug resistance.besides it might be related to the sequelae of AUD (Alcohol Use Disorders), [21],[25] Diabetes leded the susceptibility to tuberculosis to increase by a few mechanisms, including hyperglycemia and cellular insulinopenia, which have indirect effects on macrophage and lymphocyte function.[26] The study pointed out that factors impaired the innate defence mechanisms in the airways in COPD might increase the risk of TB infection or become activeTB.[27] Besides the study suggested that immunity declined and susceptibility to chronic disease increased with aging.[28] Taking some measures to prevent these risk factors may make cascade effect on the control of TB and DR-TB in the elderly.

The results of the National Prevalence Survey showed China has 5.7% of new and 25.6% of previously treated cases of MDR-TB.[29] In addition, the DR-TB and MDR-TB were accounted for 18.10% and 2.89% respectively among the elderly with TB in our study. Meanwhile, we found that the annual drug resistant rate of MDR-TB, PDR-TB,RFP-resistance and cavitary DR-TB increased significantly in our study. The increment of MDR-TB were also be found in previous studies in Beijing(from 2005 to 2008)[30], in Korea[31], in Taiwan[32] et al. And in Zhejiang province the drug resistant rate of MDR-TB decreasedvery slowly. [33] China has the world's largest number of patients with MDR -TB. Inadequate treatment in both the public health system and the hospital system may induced the MDR-TB.The treatment of MDR-TB/RR-TB is difficult, complicated and costly. [9],[34] All of these alarm us that the MDR-TB plays a key role in the burden of DR-TB disease. We found that the elderly had a higher resistantce rate only to INH or EMB and a lower resistance rate to any one of INH, RFP, EMB, and SM compared to that in non elderly. These could be found in TaiWan [35]-[38], in United Kindom [39]. And we also found that the drug resistant patterns changed into male, cavitary TB, RFP-resistant and SM-resistant among the elderly. Although we found that the drug resistant rates of different subgroups(MR-TB, male, cavity, smoking, drinking, INH-resistant, RFP-resistant, EMB-resistant, SM-resistant) declined and became very low during 2008–2010.We speculated that may be related to the policies China carried out before those years and the delayed action.[40]-[42]Some previous studies suggested that the cavity of tuberculosis could lead to an increased possibility of DR-TB during treatment.[43] the prevalence of DR-TB was significantly higher among males illuminated in some study.[44]-[47] It had been noticed that cavities were more common in DR-TB cases than in susceptible TB cases, and this phenomenon may be caused by limited drug penetration into cavities, the suitable environment provided by cavities for bacili, patients' immunity et. al.[45]-[51] Elderly patients were more probably to get RR-TB than the younger patients which was stated in some surveis.[45],[47] These may be the reasons that DR-TB pattern changed The change of DR-TB pattern will bring us a huge challenge to control the DR-TB in the elderly.

There were several advantages in our study. Firstly, the study were conducted in Shandong province, the second largest province in China ,from 2004 to 2019. All DST data were involved in our study. The research time span is large and the scope is wide So that our findings are more likely to be generalized throughout the country. Secondly, we screened out the elderly with TB,and divided the elderly with TB and DR-TB into different subgroups according to sex, smoking history, drinking history, cavity, COPD, diabetes and so on.

Our study also had some limitations. Firstly, DST were not regularly executed among all TB patients, TB surveillance stations had differences in screen density and medical conditions, which might induce selection bias in our data. Secondly, there were some unavoidable bias induced by different technical levels and experimental conditions in TB surveillance. Lastly, the statistical data on smoking and drinking from 2004 to 2007 is missing in our study, thus we could not analyze the subgroups among the elderly with DR-TB including smoking, drinking et. al very well .

Conclusion

The study presented the epidemiological characteristics and trend of primary DR-TB among the elderly in Shandong, China, from 2004–2019. We found that the proportion of MDR-TB, PDR-TB and RFP-resistance and the rate of cavitary DR-TB among the elderly increased significantly, drug resistance patterns among the elderly modified from female, non-cavity and INH-resistant to male, cavity and RFP, SM-resistant. The elderly primary TB case-patients were more common in male, having history of smoking or drinking, having COPD or diabetes. We should pay more attention to these subgroups including male, smoking, drinking, COPD and diabetes subgroups. groups to prevent DR-TB in the elderly. Besides, support of government, improvement of medical, enhancement of public awareness are also very important. Older adults play very important roles in nowadays society in China, understanding the epidemiological characteristics and trend of primary DR-TB among the elderly will make the control of DR-TB more easier.

Abbreviations

TB
tuberculosis; DR-TB:drug-resistant tuberculosis;WHO:world health organization; COPD:chronic obstructive pulmonary disease; SDG:Sustainable Development Goal; RR-TB:rifampin-resistant tuberculosis; MR-TB:mono-resistant tuberculosis; MDR-TB:multi-resistant tuberculosis; PDR-TB:polydrug resistant tuberculosis; XDR-TB:extensive drug resistant TB; ORs:odds ratios; CI:confidence interval; EMB:ethambutol; INH:isoniazid; RFP:rifampin; SM:streptomycin; M:Male; F:Female; EU:European Union; EAA:East Asian Area; DALYs:Disability-adjusted life years; AUD:alcohol use disorder.

Declarations

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Availability of data and materials

Data can be available through contact with the corresponding author.

Authors' contributions

H.C.L.conceived and designed the study. H.C.L.and Q.Q.A.directed its implementation including the data analysis and writing of the paper. Q.Q.A analyzed the data; Y.L., Q.Y.Z., J.Y.L, T.T.X, S.J.L, S.Q.L, N.N.T., Y.F.L.and C.B.Y. contributed materials/analytic tools; Q.Q.A ,W.M.S. and H.C.L. wrote and revised the manuscript. All authors reviewed and approved the manuscript.

Ethics approval and consent to participate

The protocols applied in this study were approved by the Ethics Committee of Shandong Provincial Hospital, affiliated with Shandong University (SPH) and and the Ethic Committee of Shandong Provincial Chest Hospital (SPCH), China. Before analysis, patient records were anonymized and deidentified.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

Figure 1

Trends for the quantity and proportions of different subgroups among total the elderly primary DR-TB cases, Shandong, China, 2004–2019* Figure a, Trends for MR-TB, MDR-TB, PDR-TB among the elderly with primary TB; Figure b, Trends for the elderly primary DR-TB cases of different sex (male or female); Figure c, Trends for primary DR-TB cases with or without cavity; Figure d, Trends for primary DR-TB cases with or without smoking history; Figure e, Trends for primary DR-TB cases with or without drinking history; The proportions of each subgroups were calculated as follows: (the quantity of each subgroups/ the quantity of total the elderly primary DR-TB subgroups in the same year)*100%. The χ^2 and linear regression results are shown in Table 4. TB, tuberculosis; DR-TB, drug-resistant tuberculosis; MR-TB, mono-resistant tuberculosis; MDR-TB, multi-resistant tuberculosis; PDR-TB, polydrug resistant tuberculosis. EMB, ethambutol; INH, isoniazid; RFP, rifampin; SM, streptomycin

Figure 2

Overall first-line drug resistance for INH, RIF, EMB, and SM among the elderly cases of primary drug-resistant tuberculosis in Shandong, China, 2004–2019. The proportions of INH-, RIF-, EMB-, and SM-resistance were calculated as follows: (the quantity of each subgroups/ the quantity of total the elderly primary DR-TB subgroups in the same year)*100% ;The χ^2 and linear regression results are shown in Table 4. EMB, ethambutol; INH, isoniazid; RIF, rifampin; SM, streptomycin.