

Citation: Murali S, Krishnamoorthy Y, Knudsen S, Roy G, Ellner J, Horsburgh CR, et al. (2021) Comparison of profile and treatment outcomes between elderly and non-elderly tuberculosis patients in Puducherry and Tamil Nadu, South India. PLoS ONE 16(8): e0256773. https://doi.org/ 10.1371/journal.pone.0256773

Editor: Frederick Quinn, The University of Georgia, UNITED STATES

Received: March 31, 2021

Accepted: August 13, 2021

Published: August 27, 2021

Copyright: © 2021 Murali et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability Statement: All the relevant data are within the manuscript and its Supporting Information files.

Funding: This work was supported by in whole or in part with extramural grant of Federal funds from the Government of India's (GOI) Department of Biotechnology (DBT), the United States National Institutes of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID), Office of AIDS Research (OAR), and distributed in part by **RESEARCH ARTICLE**

Comparison of profile and treatment outcomes between elderly and non-elderly tuberculosis patients in Puducherry and Tamil Nadu, South India

Sharan Murali^{1®}, Yuvaraj Krishnamoorthy^{1®}, Selby Knudsen², Gautam Roy¹, Jerrold Ellner³, Charles Robert Horsburgh⁴, Natasha Hochberg², Padmini Salgame⁵, Senbagavalli Prakash Babu¹, Sonali Sarkar¹

1 Department of Preventive & Social Medicine, JIPMER, Puducherry, India, 2 Section of Infectious Diseases, Boston University School of Medicine, Boston, MA, United States of America, 3 Department of Medicine, Rutgers University, Newark, NJ, United States of America, 4 School of Public Health, Epidemiology & Biostatistics, Boston University, Boston, MA, United States of America, 5 Department of Immunology, Rutgers University, Newark, NJ, United States of America

These authors contributed equally to this work.

* yuvi.1130@gmail.com

Abstract

The rising geriatric population and the increased susceptibility of this age group to tuberculosis (TB), the deadliest single infectious agent, is bothersome for India. This study tried to explore the demographic and treatment outcome differences between the elderly (aged 60 years and above) and non-elderly TB (<60 years) patients from South India. This study was part of a large ongoing cohort study under the RePORT India consortium. Newly diagnosed TB patients recruited into the cohort between 2014 and 2018 were included in this study. Pretested and standardized questionnaire and tools were used to collect data and were stored securely for the entire cohort. Required demographic, anthropometric and treatment related variables were extracted from this database and analyzed using Stata version 14.0. Prevalence of elderly TB was summarized as percentage with 95% confidence interval (CI). Generalized linear modelling was attempted to find the factors associated with elderly TB. A total of 1,259 eligible TB patients were included into this present study. Mean (SD) of the participants in the elderly and non-elderly group was 65.8 (6.2) and 40.2 (12.0) respectively. Prevalence of elderly TB was 15.6% (95%CI: 13.6%-17.6%) with nearly 71% belonging to 60-69 age category. Male sex, OBC caste, poor education, unemployment, marriage, alcohol consumption and unable to work as per Karnofsky score were found to be significantly associated with an increased prevalence of elderly TB. Unfavorable outcomes (12% vs 6.5%, p value: 0.018), including death (9.3% vs 3.4%, p value: 0.001) were significantly higher among the elderly group when compared to their non-elderly counterparts. The current TB programme should have strategies to maintain follow up with due attention to adverse effects, social support and outcomes. Additional research should focus on predictors for unfavorable outcomes among the elderly TB group and explore ways to handle the

CRDF Global. The contents of this publication are solely the responsibility of the authors and do not represent the official views of the DBT, the NIH, or CRDF Global. Any mention of trade names, commercial projects, or organizations does not imply endorsement by any of the sponsoring organizations. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. There was no additional external funding received for this study.

Competing interests: The authors have declared that no competing interests exist.

same. Rendering adequate social support from the health system side and family side would be a good start.

Introduction

With nearly 10 million new cases reported in 2019, tuberculosis (TB) is the single infectious agent causing maximum morbidity and mortality globally [1]. India stands prominent in the TB map of the world by contributing to almost one-fourth of the global TB burden [2]. A significant focus of the Global End TB strategy is on reducing the mortality, morbidity, and catastrophic cost due to TB, but progress to the targets has been plodding and is worrisome [1].

The Government of India defines the population over the age of 60 years as elderly [3]. The elderly population in India is on the rise due to the increasing life expectancy and declining fertility rates [4]. The elderly age group is more susceptible to TB disease due to various reasons. Comorbidities, immunosuppressive drugs, malnutrition, chronic alcohol use, and underlying malignant conditions predispose the elderly to TB [5, 6]. The increased notification of TB in older persons (aged 65 years and above) in 2016 globally confirms this [7]. Many countries are now reporting a disproportionate increase in elderly TB compared to the rise in the elderly population [8–10]. Age and nutrition-related factors have also been shown to negatively impact treatment outcomes among elderly TB [11–13]. These could further aggravate the situation by establishing the elderly TB case as a potential source of infection in the community [14–16].

The ever increasing elderly population of India is projected to cross 12.6% of the total population by 2026 [17]. While the overall disease prevalence is high among the 15–30 age group in the country, the South Indian states, including the Union Territory (UT) of Puducherry is showing a higher elderly prevalence. The India TB report has reported this vast disparity in age distribution among the incident cases of TB in the country 2020 [18]. Identifying TB disease in this high-risk population by using an active screening approach is technically and economically not feasible for a low-middle income country (LMIC) like India. But at the same time, failure in identifying and engaging this mounting burden of elderly TB could be a significant challenge to the ongoing efforts by the National TB Elimination Programme (NTEP) in achieving the ambitious end TB targets of the country by 2025 [19].

Evidence-based elderly health-focused treatment protocols and adequate follow-up of elderly TB is the need of the hour for India [20, 21]. A thorough understanding of the epidemiological features and adverse treatment outcomes among elderly TB patients can help address this emerging threat. Although several studies have been conducted worldwide describing the elderly TB population, the evidence on profile and outcomes between elderly and non-elderly TB patients in India is scarce. Hence, we undertook this study to compare the profile and treatment outcomes between elderly and non-elderly TB patients in South India.

Methods

Study setting and study population

This study was a part of a large-scale ongoing cohort study under Regional Prospective Observational Research for Tuberculosis (RePORT)-India Consortium [22]. It is conducted by Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER) in collaboration with Boston University Medical Campus and Rutgers University. It has two prospective observational cohorts: (1) active pulmonary TB cases and (2) their household contacts. Participants with sputum positive for TB were included in this study as Active Pulmonary TB case.

The study encompassed three districts from South India: Puducherry from the UT of Puducherry and two districts from Tamil Nadu adjacent to Puducherry: Villupuram and Cuddalore. Total number of TB cases reported in Puducherry during 2018 was 3489 with only 23 cases reported from the private sector as per the latest report [2]. In Cuddalore and Villupuram, total TB cases reported nearly 3000 cases with 90% reported from public sector alone [2]. Enrollment started in May 2014 in Puducherry, August 2014 in Cuddalore, and November 2015 in Villupuram. The details of the study protocol have been reported hitherto [23–26].

One TB unit (TU) in Puducherry (population \approx 9.5 million) and two TUs each in Villupuram (population \approx 3.5 million) and Cuddalore (population \approx 2.6 million) were selected to recruit study participants. One TU in Puducherry caters to a population of about 950,000 and TUs selected in Villupuram and Cuddalore serve a population of about 500,000 per TU. The TB program is decentralized to the sub-district level. Service delivery in the selected districts at this level is operationalized through the Designated Microscopy Centers (DMCs) and the Peripheral Health Institutions (PHIs) like Primary Health Centers (PHC) and Subcenters with TUs as the nodal point. Diagnosis and treatment for TB are provided free of cost at the TUs. Individuals diagnosed with TB at the DMC are referred to their nearby PHC for initiation of treatment. Screening for comorbidities like Type II Diabetes, HIV, etc., is also done here. Sociodemographic details, their clinical course, medication adherence, and comorbidity profile are maintained at the PHC level and followed up using treatment cards. The same gets updated into the RePORT system. RePORT system does not provide any intervention to TB patients.

All newly diagnosed sputum smear-positive TB patients (at least 1+ acid-fast bacilli [AFB]) more than or equal to six years of age from the selected districts during the study duration 2014 to 2018 were included in this study. We excluded patients with a previous history of TB disease or treatment, drug resistant TB, and patients currently on TB treatment for more than or equal to seven days from the analysis.

Study procedure

A pretested semi-structured questionnaire was used to capture the sociodemographic characteristics such as age, sex, education (classified as no formal education/primary/secondary/ higher), occupation, religion, caste, and marital status. Karnofsky score was used to assess functional impairment [27]. History of current tobacco smoking and alcohol use were selfreported by the participants. Height and weight were measured for calculating the body mass index (BMI).

A majority of the interviews were conducted in the clinic, though some were in the participants' homes. Filled questionnaires were scanned and transferred to Boston University using the Verity Tele Form Information Capture System software V10.8 (Sunnyvale, CA, USA). It was read into a Microsoft Access (Seattle, WA, USA) database. Errors in the data entry process were reviewed and duly corrected by the on-site team in India. After the baseline assessment, compliance with TB medications and sputum smear examination was done at the end of the intensive phase (2 months after treatment initiation) and the continuation phase (6 months after treatment initiation). At the end of the continuation phase, the treatment outcome was recorded and updated into the same database from the treatment cards.

Study definitions

TB diagnosis. Diagnosis of active TB was made using sputum smear examination—positive for MTB with at least 1+ AFB.

Hazardous alcohol user. A participant was classified as a hazardous alcohol user if they have reported drinking alcohol for about 2 to 3 times/week and had \geq 3 drinks on a typical day; or 2 to 4 times/month and had \geq 6 drinks in one sitting at the least monthly.22 No differentiation was made between males and females.

BMI classification. BMI was categorized as underweight (<18.5 kg/m2), normal (18.5–22.9 kg/m2), overweight (23–24.9 kg/m2) and obese (\geq 25 kg/m2) based on Asian classification [28].

Karnofsky score. Patients with score between 80 and 100 were able to carry on normal activity and work without requiring any special care; score between 50 and 70 indicated participants were unable to work but able to live at home and carry out personal needs with varying requirement of assistance; score between 0 and 40 were considered unable to care for self and requires hospital or institutional care [29].

Elderly TB. Participants diagnosed with TB and aged ≥ 60 years were considered as elderly TB patients [3].

Compliance to TB medication. Patients who never skipped medications were considered to have good compliance to TB treatment. This data was retrieved from the treatment cards of the patients.

TB treatment outcomes [22]. At the end of continuation phase (six months after treatment initiation), outcomes were assessed.

Bacteriological cure. Participant completing the drug therapy and has a documented negative culture results at the last month or end of the treatment and at least one previous occasion

Treatment completed. Participant who has taken at least 90% of the total doses recommended under the NTEP treatment guidelines

Favorable treatment outcome. Participants satisfying the criteria of treatment completed and/or bacteriological cure were classified as having favorable treatment outcome

Bacteriological failure. Participant having positive sputum culture at the last month of treatment and the result was not found to be false positive.

Clinical failure. Participant who has completed at least four months of treatment regimen, but still have persistent signs and symptoms, progression of disease or recurrence of symptoms and/or signs of TB found to be because of TB and not because of any other underlying causes.

Emerging resistance. Participant who had a change in baseline drug sensitivity before the drug sensitive bacteriological failure can be determined (i.e., after baseline visit, but before 5 months of treatment).

Treatment not completed. Participants who interrupt or drop out of the treatment regimen for two or more months consecutively, but continues to be in the study follow-up

Lost to follow-up. Participants who stopped having their follow-up visits after at least one month of treatment initiation

Death. Participant who have died of any cause after enrollment into the study and before the study completion

Unfavorable treatment outcome. Participants satisfying any of the following criteria: death, bacteriological/clinical failure, emerging resistance, clinical relapse were classified as having unfavorable treatment outcome

Statistical analysis

Data were extracted from the RePORT India consortium project database for the JIPMER site and analyzed using Stata v.14.2 software. The demographic and treatment variables for the entire cohort was summarized first. Continuous variables such as age was summarized as mean and standard deviation (SD). Categorical variables were summarized as proportions. Prevalence of elderly TB was summarized as percentage with 95% confidence interval (CI). We used generalized linear model (GLM) applying Poisson regression with robust error variance and a log-link to find the factors associated with elderly TB. We have applied this model to obtain the prevalence ratio (PR), which is more interpretable and easy to communicate with the clinicians than odds ratio (OR) [30]. In addition, OR tends to inflate the association if the prevelance of outcome is more than 5%. Hence, Poisson regression model with robust error variance is a suitable alternative to the traditional logistic regression analysis [30]. Sex, education, occupation, marital status, religion, caste, Karnofsky score, BMI, comorbidity, smoking and alcohol use were considered as covariates. Factors with p value less than 0.2 in the univariable analysis were considered for multivariable analysis using forward model building. Unadjusted and adjusted PR were obtained from univariable and multivariable analysis. Variables with p value less than 0.05 in the final model were considered as statistically significant. Difference in compliance to medications and TB treatment outcomes at the end of follow-up between elderly and non-elderly TB patients was assessed using Chi-square test and p value less than 0.05 was considered statistically significant.

Ethical considerations

Informed written consent or assent in addition to parents' consent (in case of participant <18 years) was obtained from all participants enrolled in the study. The study protocol was approved by the Institute Ethics Committee and Scientific Advisory Committee of JIPMER, and the Institutional Review Boards at Boston University Medical Campus and Rutgers-New Jersey Medical School.

Results

Sociodemographic, behavioral and anthropometric characteristics

A total of 1,259 eligible TB patients were included during the study period. Sociodemographic, behavioral and anthropometric characteristics of the study participants are described in Table 1. The mean (SD) age of the study participants was 43.7 (14.6) years, with mean (SD) in non-elderly group was 40.2 (12) years and in elderly group was 65.8 (6.2) years. Majority (985; 78.2%) of the participants were males and 944 (75.2%) were employed; about 204 (16%) participants did not have any formal education; majority (1119 participants; 89.2%) were Hindus; about 909 participants (72.3%) were currently married; about 335 participants (27%) belonged to Scheduled Caste (SC) /Scheduled Tribe (ST) category. Majority (765 participants; 61.2%) were underweight; about 741 participants (58.9%) were alcohol users and 311 participants (24%) were smokers. Performance status assessed by Karnofsky score showed that only 364 participants (29%) were able to carry on normal activity and to work without the requirement of special care.

Comparison of sociodemographic, behavioral and anthropometric profile between elderly and non-elderly TB patients

Of the total participants, 197 (15.6%; 95%CI: 13.6%-17.6%) had elderly TB. Out of these 197 elderly TB patients, 152 (77%) belonged to the 60–69 age category. Among the rest, 41 (21%) belonged to 70–79 and 4 participants (2%) were aged 80 years and above. Table 1 documents the comparison of sociodemographic, behavioral and anthropometric profile between elderly and non-elderly TB patients. In unadjusted analysis, there was significant difference between elderly and non-elderly TB patients in terms of education (p<0.001), marital status (p<0.001), occupation (p<0.001), caste (p = 0.03), presence of diabetes mellitus as comorbidity (p = 0.03),

	Characteristic	Total	Elderly TB	Unadjusted PR (95% CI)	P value	Adjusted PR (95% CI)	P valu	
		n (%)	n (%)					
1	Sex							
	Male	985 (78.2)	164 (83.2)	1.4 (0.95-2.01)	0.06	3.4 (2.07-5.61)	<0.00	
	Female	274 (21.8)	33 (16.8)	(ref)	-	(ref)	-	
2	BMI Category* (N = 1250)							
	Underweight (<18.50)	765 (61.2)	109 (55.3)	0.8 (0.57-1.05)	0.07	0.8 (0.57-1.17)	0.28	
	Normal (18.50–22.99)	365 (29.2)	67 (34.0)	(ref)	-	(ref)	-	
	Overweight (23.00–24.99)	65 (5.2)	8 (4.1)	0.7 (0.32-1.40)	0.24	0.7 (0.33-1.44)	0.32	
	Obesity (≥ 25.00)	55 (4.4)	13 (6.6)	1.3 (0.71-2.33)	0.35	1.0 (0.55-1.88)	0.95	
3	Religion (N = 1255)							
	Hindu	1119 (89.2)	178 (0.8)	(ref)	-	Not included in model		
	Christian	82 (6.5)	9 (4.6)	0.7 (0.35-1.35)	0.24			
	Islam	54 (4.3)	9 (4.6)	1.0 (0.54-2.05)	0.88			
4	Caste (N = 1239)							
	SC/ST	335 (27.0)	39 (20.2)	(ref)	-	(ref)		
	OBC	904 (73.0)	154 (79.8)	1.5 (1.02-2.07)	0.03	1.6 (1.08-2.32)	0.01	
5	Educational Status (N = 1254)							
	No formal education	204 (16.3)	59 (30.1)	7.6 (3.79–15.42)	<0.001	5.2 (2.46-11.02)	<0.00	
	Primary	287 (22.9)	59 (30.1)	5.4 (2.69–10.96)	<0.001	3.7 (1.78-7.71)	<0.00	
	Secondary	525 (41.9)	69 (35.2)	3.4 (1.73-6.96)	<0.001	2.5 (1.21-5.12)	0.01	
	Higher	238 (19.0)	9 (4.6)	(ref)	-	(ref)	-	
6	Employment status (N = 1258)	. ,						
	Unemployed	114 (9.1)	47 (23.9)	3.0 (2.16-4.21)	<0.001	2.4 (1.69-3.54)	<0.00	
	Employed	944 (75.2)	129 (65.5)	(ref)	-	(ref)		
	Others	198 (15.7)	21 (10.7)	0.8 (0.48–1.23)	0.25	1.3 (0.77–2.18)	0.33	
7	Marital status (N = 1257)							
	Currently married	909 (72.3)	147 (74.6)	5.0 (2.37-10.80)	<0.001	3.2 (1.34–7.57)	0.00	
	Never married	219 (17.4)	7 (3.6)	(ref)	-	(ref)		
	Widowed/Divorced/Separated	129 (10.3)	43 (21.8)	10.4 (4.69–23.18)	<0.001	6.9 (2.78–17.3)	<0.00	
8	Comorbidity							
A	Diabetes (N = 1186)							
A	Absent	791 (66.7)	112 (59.3)	(ref)	-			
	Present	395 (33.3)	77 (40.7)	1.4 (1.03–1.83)	0.03	1.2 (0.83-1.68)	0.35	
B	HIV (N = 1259)							
	Absent	1056 (99.4)	197 (100.0)		Not included	l in model		
	Present	6 (0.5)	0 (0)	-				
С	Others** (N = 1259)	- ()						
	Absent	1226 (97.4)	195 (99.0)	(ref)	-			
	Present	33 (2.6)	2 (1.0)	0.4 (0.09–1.53)	0.19	0.6 (0.16–2.67)	0.56	
9	Habits (N = 1257)	55 (2.0)	2 (1.0)	0.1(0.0) 1.00)	0.17	0.0 (0.10 2.07)	0.50	
A	Smoker [#]	311 (24.7)	50 (25.4)	1.0 (0.75–1.42)	0.82	Not included in model		
B	Alcohol user [#]	741 (58.9)	99 (50.2)	0.7 (0.53-0.93)	0.02	0.4 (0.29–0.58) <0.00		
10	Karnofsky [#] (N = 1257)	, 11 (30.7)	,, (30.2)	0.7 (0.00 0.00)	0.01	0.1 (0.2) 0.30)		
10	Able to carry normal activity and work	364 (29.0)	47 (23.9)	(ref)	-	(ref)		

Table 1. Profile of the study participants across the 2 groups—elderly & non-elderly (N = 1259).

(Continued)

Table 1. (Continued)

Characteristic	Total	Elderly TB	Unadjusted PR (95% CI)	P value	Adjusted PR (95% CI)	P value
Unable to work, able to live at home	893 (71.0)	150 (76.1)	1.3 (0.94–1.82)	0.09	1.4 (1.01-2.02)	0.04

(1) Total and elderly TB are summarized as frequency with proportions.

(2) Keeping elderly TB as outcome, unadjusted (Unadjusted PR) & adjusted prevalence (Adjusted PR) ratios with its Confidence Intervals (95% CI) was calculated using MEGLM modelling using a poisson family and log link. (N = 1259).

(3) Religion and Current tobacco use were not included into the model as the p value was more than 0.20

Self-reported by the participants |

*Asia Pacific guidelines for obesity

**Other Co- morbidity include: Asthma (2), Urinary Calculus (11) & Hepatitis (20)

https://doi.org/10.1371/journal.pone.0256773.t001

and alcohol use (p = 0.01). Apart from these variables, sex, BMI category, Karnofsky score, presence of other comorbidities in the patient were also included in the final multivariable model as these variables had p value less than 0.2.

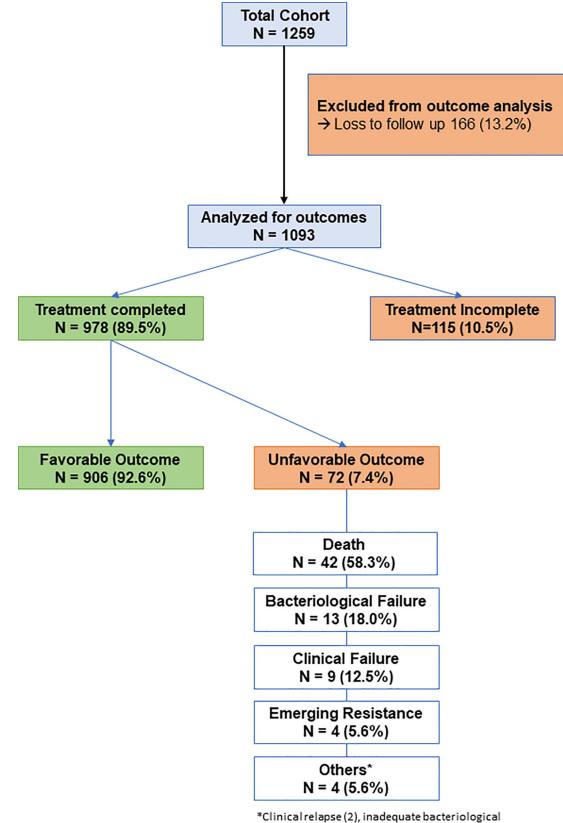
The adjusted analysis was performed with the above-mentioned variables and the final model had 1,157 participants owing to missing data with respect to one or more of the covariates. Male sex was significantly associated with elderly TB (aPR = 3.4; 95% CI: 2.07–5.61; p<0.001), after adjusting for potential confounders. Patients with no formal education had 5.2 times higher prevalence of being in elderly TB group compared to those having higher educational qualification (aPR = 5.2; 95%CI: 2.46–11.02; p<0.001) and this association was statistically significant. Unemployed TB patients had 2.4 times more chance of being in the elderly TB group compared to those employed TB patients (aPR = 2.4; 95%CI: 1.69–3.54; p<0.001). OBC caste was also significantly associated with elderly TB (aPR = 1.6; 95%CI: 1.08–2.32; p = 0.01). Patients who are unable to work with varying assistance needed were 1.40 times more likely to be in elderly TB group compared to those who were able to work without any special care required (aPR = 1.40; 95%CI: 1.01–2.02; p = 0.04). Alcohol drinkers were significantly associated with non-elderly TB (aPR = 0.40; 95%CI: 0.29–0.58; p<0.001) (Table 1).

Comparison of compliance and outcomes between elderly and non-elderly TB patients

Fig 1 explains the flow of participants through the study.

Compliance data was available for only 988 patients at the end of intensive phase and 819 patients at the end of continuation phase. From the treatment initiation till the end of intensive phase, 145 out of 988 patients (14.7%) had poor compliance to medications, and 83 out of 819 patients (10.1%) had poor compliance between End of intensive and End of continuation phase. Overall, during the six months follow-up period, 209 out of 819 patients (25.5%; 95%CI: 22.5%-28.5%) had poor compliance to medications. Poor compliance was higher among non-elderly TB patients compared to elderly TB patients (26.3% vs 21.1%). However, this difference was not statistically significant (p = 0.21). Sputum conversion at the end of two months was achieved among 84.6% of the study participants. Sputum conversion was found to be better among the non-elderly TB patients (85.0%) compared to elderly TB patients (82.0%), but this difference was not statistically significant (p = 0.40) (Fig 2).

From among the 1,259 participants in the original cohort, at the end of 6 months, 166 (13.2%) participants were lost to follow up with almost equal proportion in both elderly (14.7%) and non-elderly group (12.9%) (p value: 0.488). About 115 (9.4%) did not fully complete their treatment with almost equal proportion, i.e., 9.4% of elderly and the same of non-elderly TB maintained an incomplete treatment status (p value: 0.988).



documentation at baseless for age <14 years (2)

Fig 1. Summary of flow of participants into various stages during the follow up of the study.

https://doi.org/10.1371/journal.pone.0256773.g001

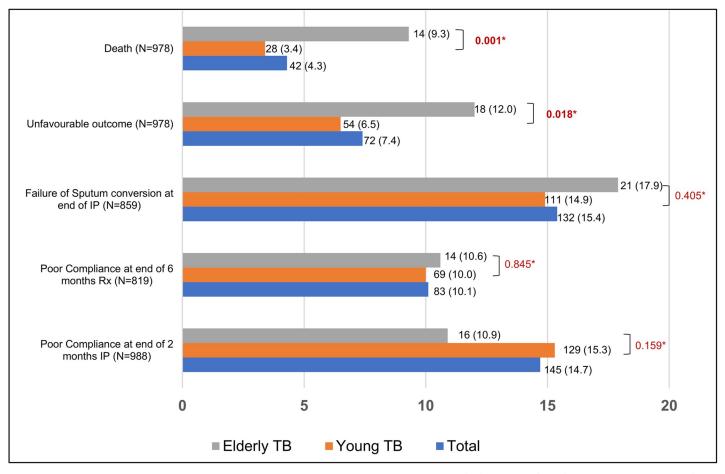


Fig 2. Comparing selected poor outcomes across the two study groups, elderly and non-elderly TB. (1) The denominator for each outcome is written in parenthesis with the axis title. (2) Frequency (proportion) of the outcome in the study group–non-elderly or elderly TB is given as value labels. *p values of comparison of outcome between the two groups, obtained by Chi-Square test.

https://doi.org/10.1371/journal.pone.0256773.g002

Forty-two (4.3%) participants were reported dead at the end of 6 months follow up. A higher proportion of elderly TB patients (9.3%) were marked dead than the non-elderly participants (3.4%) and this difference was found to be statistically significant (p value = 0.001). Treatment failure (bacteriological or clinical) was found among 2.2% of study participants with outcome data available. Overall prevalence of unfavorable outcomes among the study participants was 7.4% (95%CI: 5.7%-9.0%). Unfavorable outcomes were more common among elderly TB patients (12%) compared to non-elderly TB patients (6.5%), and this difference was found to be statistically significant (p = 0.018) (Fig 2).

Discussion

TB in the elderly population has emerged as an important public health issue globally. The outcome in this group is crucial in the control of disease and success of the National TB Elimination Program [31]. The higher proportion of elderly TB in the present cohort (15%) could be explained by the higher elderly population in Tamil Nadu (10%) and Pondicherry (10%) as per the India Census 2011 data [32]. Elderly TB patients were more likely to be males, have no formal education, unemployed, requiring assistance and less alcohol users compared to the non-elderly TB patients, the difference being statistically significant. Compliance to medications

was better among the elderly TB patients, while the treatment outcomes at the end of intensive and continuation phase were better among non-elderly TB patients and this difference was statistically significant.

The proportion of elderly TB observed in our study (14.9%) is similar to that observed in previous studies conducted in India such as Karnataka (18.7%) [33], Tamil Nadu (14%) [34] and Punjab (12.3%) [35] and other countries such as Nigeria [36], Uganda [8], Taiwan [9] and United States [10]. However, this might be expected to increase over time given the increasing life expectancy in India. The existing TB control program is silent about any specific policies/ programs/schemes for elderly patients with TB. This policy or program gaps is of concern given expected rising problem of TB in the elderly. Hence, this group should be given special attention and have targeted intervention to improve the success of the TB control program.

We found that elderly males have higher rate of TB compared to females in South India. This finding is in line with the epidemiological trend of TB in India (males are more affected than females) [37, 38]. Previous studies conducted in India and other LMIC countries have also reported that elderly males have higher rate of TB than females [33–36]. Possible reasons for this pattern could be better healthcare service accessibility and higher rate of social interaction among males [39, 40]. We also found that elderly patients were more likely to be unemployed than non-elderly TB. This might be attributable to poor health seeking behavior among these individuals, as the costs involved in seeking health care might be unaffordable for the unemployed individuals, leading to delayed diagnosis of the condition [41]. We also identified OBC caste as a significant determinant of TB among elderly patients, which indicates the social and economic differences existing across the region. This might limit the treatment seeking behavior leading to delayed diagnosis as TB among elderly patients. Regular screening for active case finding of TB, increased awareness about the importance of early testing and mobile clinics could help in early case identification. This can be substantiated by the better adherence despite their lower Karnofsky scores.

Sputum smear conversion at the end of intensive phase is an early indicator for successful TB treatment outcome [42]. Though compliance to medication was better among the elderly patients, sputum conversion at end of intensive phase was lower among elderly patients compared to non-elderly patients. Though not statistically significant, a similar finding was reported in previous studies conducted in India where the sputum conversion was lower among the TB patients in elderly age group [33–35]. Possible reasons for this lower conversion rate could be due to the high bacillary load among the elderly patients leading to delayed clearance and sputum conversion, reported in some studies [43]. Another reason could be the higher rate of adverse reactions, drug interactions, and comorbidities leading to dosage reduction and poor absorption of anti-tubercular drugs among the elderly [44].

The rate of unsuccessful treatment outcomes such as bacteriological or clinical failure, death were more among elderly compared to non-elderly TB patients. However, certain undesirable outcomes such as lost to follow-up and treatment incomplete status, though the most commonly found among the total study participants, it was not significantly different between elderly and non-elderly group. This finding was in line with the previous studies conducted around the world (high- and low-income countries alike like Hong Kong, Taiwan, Uganda, Nigeria, United States) and also past evidences in India [8–10, 33–35, 45–50]. Reason for such unsuccessful outcomes could be the higher rate of comorbidities and advanced/severe form of disease among elderly [51, 52]. Hence, elderly patients should be provided extra care and attention to reduce the extent of unsuccessful outcomes. Target groups among elderly patients at risk of unsuccessful outcomes can be identified and close monitoring of such patients can be done. However, there is still a major policy gap exist in the current TB control program. Future TB surveys should have a specific focus on the elderly age group, while the national TB

programs should consider performing active case finding among the elderly population and include them in their preventive strategies.

In India, elderly population provides the careers for the societies, leaders and mentors for the communities, and also play a major role in educating and motivating the young generation throughout the country [53]. However, it is common for the elderly to be stressed by various factors like the loss of spouse, high income insecurity and compulsion to work, poor nutrition, rising incidence of non-communicable diseases including mental illnesses [32]. High incidence of poor outcomes among the elderly TB patients complicates this situation further [54]. Support from the family or social support systems during these crucial times are necessary for improving the general quality of life. Understanding and quantifying the level of support necessitated by the elderly TB patients would be a novel addition to the model and can be taken up in future studies. However, caring for the rising numbers of elderly with TB might prove to be difficult in the resource constrained regions. Still, the care and attention for elderly TB should be improved as much as the attention provided currently to the burden of childhood TB patients (\leq 14 years). Health systems must confront these challenges of the aging population and provide integrated services required for addressing the health needs of the elderly. Treatment regimens should also be framed specific to the elderly population just like the childhood TB patients. For this purpose, further research should emphasize on the inclusion of elderly in the development of newer TB drugs and assessing the effectiveness of existing drugs and regimens [53]. Our study has several strengths. Firstly, our study adds to the limited evidence available on comparison of sociodemographic, behavioral, anthropometric profile, compliance and treatment outcomes between non-elderly and elderly TB patients. Longitudinal analysis of compliance and treatment outcomes data will help in causal inference between the exposure and outcomes. We also have comprehensively covered majority of the newly diagnosed TB patients receiving care at DOTS centers during the study period. High sample size, response rate, quality assurance of data through double data entry & validation are added advantages of the study. We also used validated questionnaires such as AUDIT-C, Karnofsky score for the assessment of behavioral and mobility profile of patients. All these factors together enable valuable comparisons with other TB cohorts across India and other similar settings.

Still, our study has certain limitations. TB patients included in our study were from three selected districts in South India which might limit the generalizability of the study findings. In addition, only the patients diagnosed in public healthcare facilities were included. Hence, the sample may not be representative of patients diagnosed in private health sector. In spite of these limitations, our study has several programmatic implications. First, we provided baseline comparison of profile between non-elderly and elderly people with large-scale representation of TB patients. We also identified specific target groups-male sex, underweight, OBC, non-formal education, unemployment, widowed, divorced individuals etc—requiring additional attention and focused interventions. Policy makers and program managers can make use of this information to develop appropriate interventions aimed at increasing successful management of TB among this vulnerable population.

Conclusion

With a prevalence of 16%, TB among elderly patients stands out as an urgent and important concern that needs to be handled for effective control of the ongoing TB pandemic. Nonelderly TB patients were poorly compliant than the older ones, but the outcomes were statistically unfavorable in the latter. TB among elderly patients causes more deaths and other unfavourable outcomes. The need for more focused attention to this group of TB patients is more relevant considering our strive to achieve the ambitious targets of End TB in India by 2025.

Supporting information

S1 File. Data collection form. (PDF)S1 Dataset. Elderly TB-full dataset. (DTA)

Acknowledgments

The authors would like to acknowledge the work done by the field and office staff of the Indo-US TB project under the Department of Preventive & Social Medicine, JIPMER. The authors would like to extend heartfelt gratitude to each of the participant from the study sites.

Author Contributions

Conceptualization: Sharan Murali, Yuvaraj Krishnamoorthy.

- **Data curation:** Gautam Roy, Jerrold Ellner, Charles Robert Horsburgh, Padmini Salgame, Senbagavalli Prakash Babu, Sonali Sarkar.
- Formal analysis: Sharan Murali, Yuvaraj Krishnamoorthy, Charles Robert Horsburgh, Senbagavalli Prakash Babu.
- **Funding acquisition:** Selby Knudsen, Gautam Roy, Jerrold Ellner, Charles Robert Horsburgh, Natasha Hochberg, Padmini Salgame, Senbagavalli Prakash Babu, Sonali Sarkar.
- Investigation: Selby Knudsen, Natasha Hochberg, Padmini Salgame, Senbagavalli Prakash Babu.
- Methodology: Sharan Murali, Jerrold Ellner, Natasha Hochberg, Padmini Salgame, Sonali Sarkar.
- Project administration: Selby Knudsen, Gautam Roy, Jerrold Ellner, Charles Robert Horsburgh, Senbagavalli Prakash Babu, Sonali Sarkar.
- **Resources:** Selby Knudsen, Gautam Roy, Jerrold Ellner, Charles Robert Horsburgh, Natasha Hochberg, Senbagavalli Prakash Babu.
- Software: Sharan Murali, Yuvaraj Krishnamoorthy, Senbagavalli Prakash Babu.
- Supervision: Selby Knudsen, Gautam Roy, Jerrold Ellner, Charles Robert Horsburgh, Natasha Hochberg, Padmini Salgame, Sonali Sarkar.
- Validation: Yuvaraj Krishnamoorthy, Selby Knudsen, Jerrold Ellner, Charles Robert Horsburgh, Padmini Salgame, Sonali Sarkar.
- Writing original draft: Sharan Murali, Yuvaraj Krishnamoorthy.
- Writing review & editing: Sharan Murali, Yuvaraj Krishnamoorthy, Selby Knudsen, Gautam Roy, Jerrold Ellner, Charles Robert Horsburgh, Natasha Hochberg, Padmini Salgame, Senbagavalli Prakash Babu, Sonali Sarkar.

References

- World Health Organization. Global tuberculosis report 2020. Geneva: World Health Organization; 2020 (https://apps.who.int/iris/bitstream/handle/10665/336069/9789240013131-eng.pdf, accessed 29 May 2021).
- 2. Ministry of Health and Family Welfare. Central TB division. India TB Report. 2019. Available from: https://www.tbcindia.gov.in/WriteReadData/India%20TB%20Report%202019.pdf
- Ministry of Statistics and Programme Implementation. Elderly in India. 2016. Available from: http://mospi.nic.in/sites/default/files/publication_reports/ElderlyinIndia_2016.pdf
- World Health Organization. World Report on Ageing & Health 2015: World Health Organization; 2015 (https://apps.who.int/iris/bitstream/handle/10665/186463/9789240694%20811_eng.pdf?sequence=1, Accessed on 4 July 2020)
- Stead WW. The pathogenesis of pulmonary tuberculosis among older persons. Am Rev Respir Dis. 1965; 91:811–822. https://doi.org/10.1164/arrd.1965.91.6.811 PMID: 14294702
- Schaaf HS, Collins A, Bekker A, Davies PD. Tuberculosis at extremes of age. Respirol. 2010; 15 (5):747–763 https://doi.org/10.1111/j.1440-1843.2010.01784.x PMID: 20546192
- World Health Organization. Global tuberculosis report 2017. Available from: <u>https://www.who.int/tb/</u> publications/2017/en/. Accessed 8 Aug 2019.
- Kirirabwa NS, Kimuli D, DeJene S, Nanziri C, Birabwa E, Okello DA, et al. Response to anti-tuberculosis treatment by people over age 60 in Kampala, Uganda. Plos One. 2018; 13(12):e0208390. https://doi. org/10.1371/journal.pone.0208390 PMID: 30566486
- Yew WW, Yoshiyama T, Leung CC, Chan DP. Epidemiological, clinical and mechanistic perspectives of tuberculosis in older people. Respirol. 2018; 23(6):567–75. <u>https://doi.org/10.1111/resp.13303</u> PMID: 29607596
- Hochberg NS, Horsburgh CR Jr. Prevention of tuberculosis in older adults in the United States: obstacles and opportunities. Clin Infect Dis. 2013; 56(9):1240–7. https://doi.org/10.1093/cid/cit027 PMID: 23362286
- Salvado´ M, Garcia-Vidal C, Va´zquez P, Riera M, Rodrı´guez-Carballeira M, et al. Mortality of tuberculosis in very old people. J Am Geriatr Soc. 2010; 58:18–22. <u>https://doi.org/10.1111/j.1532-5415.2009</u>. 02619.x PMID: 20122037
- 12. Davies PD. Tuberculosis in the elderly: epidemiology and optimal management. Drugs Aging. 1996; 8:436–444. https://doi.org/10.2165/00002512-199608060-00005 PMID: 8736627
- 13. Leung KK, Tang LY, Chie WC Lue BH, Lee LT. Mortality trends of elderly people in Taiwan from 1974 to 1994. Age Ageing. 1999; 28:199–203.
- Pratt RH, Winston CA, Kammerer JS, Armstrong LR. Tuberculosis in older adults in the United States, 1993–2008. J Am Geriatr Soc. 2011; 59:851–857 <u>https://doi.org/10.1111/j.1532-5415.2011.03369.x</u> PMID: 21517786
- 15. Wang CS, Chen HC, Yang CJ, Wang WY, Chong IW, et al. The impact of age on the demographic, clinical, radiographic characteristics and treatment outcomes of pulmonary tuberculosis patients in Taiwan. Infection. 2008; 236:335–340. https://doi.org/10.1007/s15010-008-7199-8 PMID: 18629436
- Ijaz K, Dillaha JA, Yang Z, Cave MD, Bates JH. Unrecognized tuberculosis in a nursing home causing death with spread of tuberculosis to the community. J Am Geriatr Soc. 2002; 50:1213–1218. <u>https://doi.org/10.1046/j.1532-5415.2002.50307.x PMID: 12133015</u>
- Government of India. Elderly in India: 2016. New Delhi: Central statistics Office, Ministry of Statistics & Programme Implementation, Government of India; 2016. Available from: http://mospi.nic.in/sites/ default/files/publication_reports/ElderlyinIndia_2016.pdf
- 18. Ministry of Health and Family Welfare. Central TB division. India TB Report. 2020. (Available from: https://tbcindia.gov.in/showfile.php?lid=3538, Accessed on 4 July, 2020)
- Ministry of Health and Family Welfare. Central TB division. National Strategic Plan for TB elimination 2017–2025. Available from: https://tbcindia.gov.in/WriteReadData/NSP%20Draft%2020.02.2017% 201.pdf
- Golub JE, Mohan CI, Comstock GW, Chaisson RE. Active case finding of tuberculosis: historical perspective and future prospects. Int J Tuberc Lung Dis. 2005; 9(11):1183–203. PMID: 16333924
- Lönnroth K, Castro KG, Chakaya JM, Chauhan LS, Floyd K, Glaziou P, et al. Tuberculosis control and elimination 2010–50: cure, care, and social development. Lancet. 2010; 375(9728):1814–29 <u>https://</u> doi.org/10.1016/S0140-6736(10)60483-7 PMID: 20488524
- Hamilton CD, Swaminathan S, Christopher DJ, et al. Report international: advancing tuberculosis biomarker research through global collaboration. Clin Infect Dis 2015; 61:S155–9. <u>https://doi.org/10.1093/ cid/civ611 PMID: 26409277</u>

- Hochberg NS, Sarkar S, Horsburgh CR, et al. Comorbidities in pulmonary tuberculosis cases in Puducherry and Tamil Nadu, India: opportunities for intervention. PLoS One. 2017; 12:e0183195 https://doi. org/10.1371/journal.pone.0183195 PMID: 28832615
- Leong S, Zhao Y, Joseph NM, et al. Existing blood transcriptional classifiers accurately discriminate active tuberculosis from latent infection in individuals from South India. Tuberculosis. 2017; 2018:41– 51.
- Hoyt KJ, Sarkar S, White L, et al. Effect of malnutrition on radiographic findings and mycobacterial burden in pulmonary tuberculosis. PLoS One. 2019; 14:e0214011–11 <u>https://doi.org/10.1371/journal.pone.0214011</u> PMID: 30917170
- 26. Van Ness SE, Chandra A, Sarkar S, et al. Predictors of delayed care seeking for tuberculosis in southern India: an observational study. BMC Infect Dis. 2017; 17:1–9 <u>https://doi.org/10.1186/s12879-016-</u> 2122-x PMID: 28049444
- The Clinical Evaluation of Chemotherapeutic Agents in Cancer–ScienceOpen [Internet]. [cited 2020 Sep 16]. Available from: <u>https://www.scienceopen.com/document?vid=b6149047-7b97-4b0b-bfef-995cb93d5174</u>
- World Health Organization. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet. 2004; 363:157–63. https://doi.org/10.1016/S0140-6736(03) 15268-3 PMID: 14726171
- Karnofsky Performance Status. [Internet]. Available: <u>https://www.cancer.gov/publications/dictionaries/</u> cancer-terms?cdrid=44156
- Barros AJ, Hirakata VN. Alternatives for logistic regression in cross-sectional studies: an empirical comparison of models that directly estimate the prevalence ratio. BMC Med Res Methodol. 2003; 3:1–3. https://doi.org/10.1186/1471-2288-3-1 PMID: 12515580
- 31. Sood R. The problem of geriatric tuberculosis. J Acad Clin Med. 2000; 5: 156–162.
- 32. United Nations Population Fund 2017. 'Caring for Our Elders: Early Responses'—India Ageing Report-2017. UNFPA, New Delhi, India
- Nehal, Tiwari S, Kothandapani SK, Khena, Usha. Tuberculosis in elderly: The Indian perspective. Int J Adv Med 2018; 5:983–7
- Ananthakrishnan R, Kumar K, Ganesh M, Kumar AMV, Krishnan N, et al. The Profile and Treatment Outcomes of the Older (Aged 60 Years and Above) Tuberculosis Patients in Tamilnadu, South India. PLoS ONE. 2013; 8(7): e67288 https://doi.org/10.1371/journal.pone.0067288 PMID: 23861755
- Joshi JL, Devi S, Mohan V, Kaur RP, Kaur R. Clinico-radiological variability of pulmonary tuberculosis in young patients as compared to elder patients prior to RNTCP and after 18 years RNTCP. Int J Res Med Sci 2018; 6:2116–26
- Oshi DC, Oshi SN, Alobu I, Ukwaja KN. Profile and Treatment Outcomes of Tuberculosis in the Elderly in Southeastern Nigeria, 2011–2012. PLoS ONE. 2014; 9(11): e111910. <u>https://doi.org/10.1371/</u> journal.pone.0111910 PMID: 25369001
- Subramani R. Rapid decline in prevalence of pulmonary tuberculosis after DOTS implementation in a rural area of South India. Int J Tuberc Lung Dis. 2008; 12: 916–20. PMID: 18647451
- Gopi PG, Subramani R, Radhakrishna S, Kolappan C, Sadacharam K, et al. A baseline survey of the prevalence of tuberculosis in a community in south India at the commencement of a DOTS programme. Int J Tuberc Lung Dis. 2003; 7: 1154–62 PMID: 14677890
- Neyrolles O, Quintana-Murci L. Sexual Inequality in Tuberculosis. PLoS Med 2009; 6: e1000199. https://doi.org/10.1371/journal.pmed.1000199 PMID: 20027210
- Ukwaja KN, Alobu I, Nweke CO, Onyenwe EC. Healthcare-seeking behavior, treatment delays and its determinants among pulmonary tuberculosis patients in rural Nigeria: A cross-sectional study. BMC Health Serv Res. 2013; 13:25. https://doi.org/10.1186/1472-6963-13-25 PMID: 23327613
- Storla DG, Yimer S, Bjune GA. A systematic review of delay in the diagnosis and treatment of tuberculosis. BMC Public Health. 2008; 8:15 https://doi.org/10.1186/1471-2458-8-15 PMID: 18194573
- Zhao FZ, Levy MH, Wen S. Sputum microscopy results at two and three months predict outcome of tuberculosis treatment. Int J Tuberc Lung Dis 1997; 1(6):570–572 PMID: 9487456
- **43.** Davies PD. Tuberculosis in the elderly: epidemiology and optimal management. Drugs Aging. 1996; 8: 436–444. https://doi.org/10.2165/00002512-199608060-00005 PMID: 8736627
- Arora VK, Singla N, Sarin R. Profile of geriatric patients under DOTS in revised national tuberculosis control programme. Indian J Chest Dis Allied Sci. 2003; 45: 231–235. PMID: 12962456
- 45. Leung CC, Yew WW, Chan CK, Chau CH, Tam CM, et al. tuberculosis in older people: a retrospective and comparative study from Hong Kong. J Am Geriatr Soc. 2002; 50: 1219–1226. <u>https://doi.org/10. 1046/j.1532-5415.2002.50308.x PMID: 12133016</u>

- 46. Pratt RH, Winston CA, Kammerer JS, Armstrong LR. Tuberculosis in older adults in the United States, 1993–2008. J Am Geriatr Soc. 2011; 59:851–857 <u>https://doi.org/10.1111/j.1532-5415.2011.03369.x</u> PMID: 21517786
- **47.** Wang CS, Chen HC, Yang CJ, Wang WY, Chong IW, et al. The impact of age on the demographic, clinical, radiographic characteristics and treatment outcomes of pulmonary tuberculosis patients in Taiwan. Infection. 2008; 236: 335–340. https://doi.org/10.1007/s15010-008-7199-8 PMID: 18629436
- Ijaz K, Dillaha JA, Yang Z, Cave MD, Bates JH. Unrecognized tuberculosis in a nursing home causing death with spread of tuberculosis to the community. J Am Geriatr Soc. 2002; 50:1213–1218. <u>https://doi.org/10.1046/j.1532-5415.2002.50307.x PMID: 12133015</u>
- 49. Patra S, Lukhmana S, Tayler Smith K, Kannan AT, Satyanarayana S, et al. Profile and treatment outcomes of elderly patients with tuberculosis in Delhi, India: implications for their management. Trans R Soc Trop Med Hyg. 2013; 107: 763–768. https://doi.org/10.1093/trstmh/trt094 PMID: 24189479
- Hauer B, Brodhun B, Altmann D, Fiebig L, Loddenkemper R, et al. Tuberculosis in the elderly in Germany. Eur Respir J. 2011; 38:467–470 https://doi.org/10.1183/09031936.00199910 PMID: 21804163
- Toure' NO, Dia Kane Y, Diatta A, Ba Diop S, Niang A, et al. tuberculosis in elderly persons. Rev Mal Respir. 2010; 27:1062–1068 https://doi.org/10.1016/j.rmr.2010.04.017 PMID: 21111277
- Balakrishnan S, Vijayan S, Nair S, Subramoniapillai J, Mrithyunjayan S, et al. High Diabetes Prevalence among Tuberculosis Cases in Kerala, India. PloS One. 2012; 7:e46502 <u>https://doi.org/10.1371/journal.pone.0046502</u> PMID: 23077512
- 53. Negin J, Abimbola S, Marais BJ. Tuberculosis among older adults-time to take notice. Int J Infect Dis. 2015 Mar 1; 32:135–7. https://doi.org/10.1016/j.ijid.2014.11.018 PMID: 25809769
- 54. Dey S, Nambiar D, Lakshmi JK, Sheikh K, Reddy KS. Health of the elderly in India: challenges of access and affordability. In Aging in Asia: Findings from new and emerging data initiatives 2012. National Academies Press (US).