

# Are all tuberculosis deaths correctly attributed due to tuberculosis? Analysis of causes of death (COD) using verbal autopsy: A cross-sectional study in Puducherry

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## ABSTRACT

**Background:** State Task Force National Tuberculosis Elimination Programme (STF-NTEP) wanted to ascertain the cause of death of tuberculosis (TB) patients was due to TB. Hence, this study was done to determine the cause of death among TB patients using verbal autopsy. **Material and Method:** The community-based cross-sectional study was conducted among the closest caregivers of the reported TB death cases using a verbal autopsy questionnaire. A list of TB deaths was extracted from Puducherry's State Tuberculosis Office (STO). The VA questionnaires were reviewed by two trained faculties and experts independently who were also asked to code the cause of death according to the International Classification of Diseases – 10<sup>th</sup> Revision. Data were analysed using the SPSS software receiver operator curve (ROC) curve and Cohen's kappa statistics with 95% confidence interval (CI) were applied to compare agreement between the raters. **Results:** Out of 307 TB deaths, 143 were contacted and the remaining were migrated, missing or not available. Among them 34.9% of the declared TB deaths are not due to TB. Cohen's kappa = 0.4; 95% CI: (0.858-0.985) showed moderate agreement between the raters. Experts' review was used as a reference standard to compare rater agreements. The Predictive accuracy of Rater 2 (area under the curve [AUC] –0.953; *P* value <0.001) was slightly higher than Rater 1 (AUC –0.942; *P* value <0.001). **Conclusion:** The findings of the study have clearly indicated that 34.9% of the declared TB deaths are not due to TB.

**Keywords:** AUC, COD, kappa, ROC, TB deaths, verbal autopsy

## Background

India follows the routine surveillance and reporting guidelines recommended by the World Health Organization (WHO) and considers any death that occurs during TB treatment as a TB-related death.<sup>[1]</sup> Most of the deaths are not medically certified by the doctor in developing countries, thus the cause of death (COD) is incomplete. Death audit is essential to have an epidemiological and programmatic understanding of the distribution and determinants of TB mortality so that we can

identify the crucial gaps and take remedial measures to avert all preventable TB deaths in our state.<sup>[2]</sup> In settings with no or poorly documented vital registration and medical certification of the COD, a verbal autopsy (VA) can be an essential public health tool for obtaining a reasonable estimation of the causal structure of mortality. VA uses systematic retrospective inquiry of family members about the symptoms and signs of illness before death to help determine the putative medical COD.<sup>[1-3]</sup> VA can be used as a tool to ascertain the COD by interviewing the close caregiver.<sup>[2,4,5]</sup> VA is a method 'based on the assumption that most causes of deaths have distinct symptoms complexes which can be recognized, remembered and reported by the lay respondents and possible to classify deaths, based on the reported information, into useful categories of causes of deaths'.<sup>[6,7]</sup> The mortality due to pulmonary tuberculosis (PTB) in India is

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32/lakh and the target to reduce further to 3/lakh by 2025.<sup>[8]</sup> In Puducherry, the death among the microbiologically confirmed TB patients is 4% and 10% among new and previously treated patients.<sup>[9]</sup> In the quarterly review meeting during ascertaining the TB deaths as a treatment outcome, it was stated by the state treatment supervisors that the reported TB death was not directly related to TB, it was due to comorbid conditions. There is a lack of reliable information on the cause of TB deaths among registered TB patients.<sup>[3]</sup> With this background, this study was done to determine the COD among PTB patients using VA and to ascertain if these deaths are due to TB.

### Case definition

A TB death is any death occurring to a patient who is diagnosed with TB and who has been on treatment for TB, or who has interrupted treatment not longer than one month ago, regardless of the COD.<sup>[3]</sup>

## Materials and Methods

### Study area and settings

The present community-based cross-sectional study using the VA questionnaire was conducted by the Department of Community Medicine, Sri Manakula Vinayagar Medical College and Hospital, Puducherry, which is an active member in the STF-NTEP (State Task Force-National Tuberculosis Elimination Programme) mechanism. The study was carried out in the urban and rural localities of

Puducherry district which comes under the state tuberculosis unit (TU) of Puducherry union territory. The study area is spread over a radius of 25 km. The chest clinic as well as state TU situated in the heart of the city and functions as a core of the NTEP covering the urban and the rural population of Puducherry district.

### Study participants and sampling technique

The study participants included family proxies of deceased patients including spouses, parents, adult children, siblings or relatives who were providing care to the deceased person. The closest caregivers of the adult death (18 years and above) of all cases enlisted as dead due to TB during the study period were the potential participants, preferably females (wife/sister/daughter/daughter-in-law) who are full-time in the house aware of all the events. Purposive sampling was applied.

### Sample size

All the TB case with outcomes as death from 1<sup>st</sup> January 2020 till 31<sup>st</sup> December 2021 was included in the study as follows. Based on the data reported from the STO Office, Puducherry, the number of TB deaths in the year 2018 and 2021 was found to be 306. We were able to collect data from 143 caregivers.

### Technical information

After obtaining approvals from the institutional ethical committee and Operational Research Committee State Task Force and

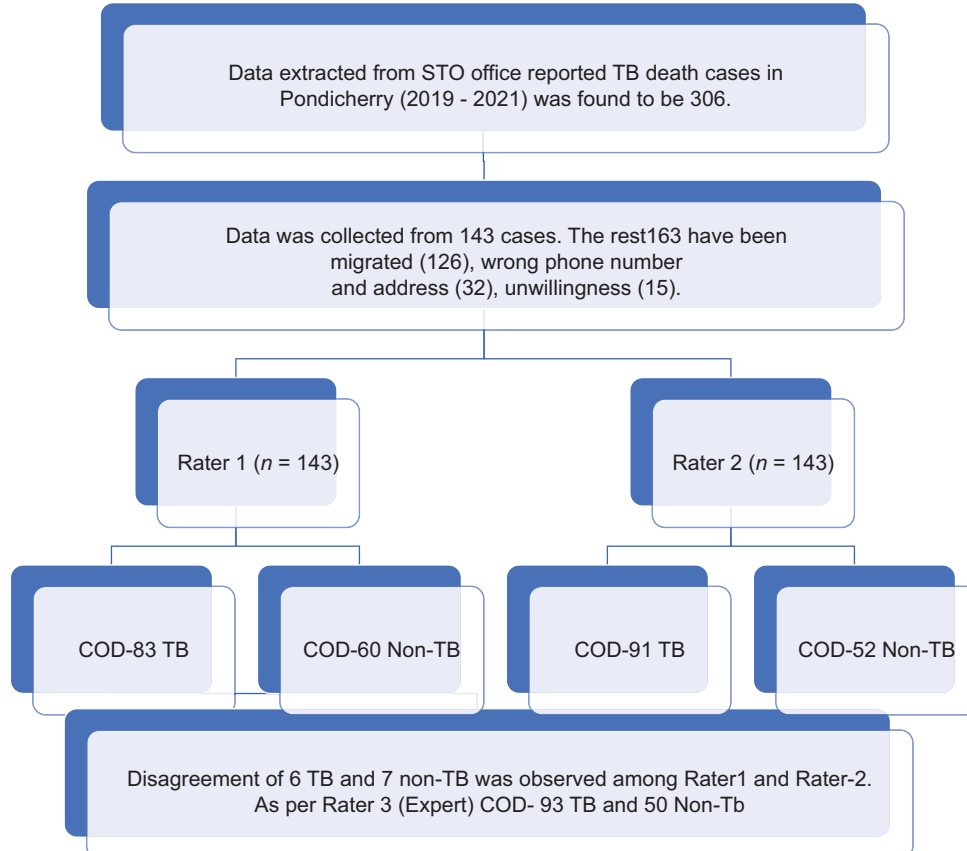


Figure 1: Flow of the study

Office of STO of Puducherry, the data were collected for one year.

### Data collection tool

VA questionnaire developed by Gajalakshmi *et al.* was used for data collection.<sup>[9,10]</sup> It is a validated questionnaire which composed of information regarding behavioural, demographic, socioeconomic, and comorbid factors; specific symptoms; and chronology of events preceding death, the condition that initiated the series of events between normal health and death.

Data collection was done in two stages: the proportion of the death of all registered TB patients between 2020 and 2021 was included. The information on age, sex, residence, date of diagnosis, treatment outcome, and so on between the period January 2020 and 2021 were extracted from the records. Since the data are already in electronic format, data extraction sheets/proforma were not required. The list was segregated PHC-wise in Puducherry.

As a part of intern's orientation programme in the skill-based training component, the compulsory rotatory residential internship, also called as medical interns, is routinely provided hands-on training to ascertain the COD. In addition, they are also provided sensitization programme to identify various signs and symptoms of diseases, the technique of administering VA questionnaire.<sup>[11]</sup> The training was conducted for a period of seven days which includes mock interview, hands-on training on writing VA and ascertaining the most probable COD. A recall period of three years was used as adult death regarded as a significant event as compared to child death.<sup>[12]</sup> Five per cent of verbal autopsies were rechecked to ensure the validity of data. The address and the contact phone number were collected from STO office. Home visits were done with the help of TB health visitors of the respective PHC. After obtaining the informed consent, the closest caregivers of the adult death (18 years and above) of a TB case was identified and interviewed. The first part of the questionnaire comprised information regarding socio-demographic details of the deceased person such as age at death, sex, residence, type of housing, type of family, education, caste, occupation, place of death, respondents of deceased, history of chronic illness, source of treatment, default history if any and environmental details and sequence of events. The most probable COD was found using VA questionnaire.<sup>[9-11]</sup> If the house was locked or the potential participants were not available for three consecutive visits, they were excluded from the study.

### COD: Physician review-based assignment

The VA questionnaires were reviewed by two trained faculties independently to code the COD according to the International Classification of Diseases (ICD) – 10<sup>th</sup> Revision.<sup>[13]</sup> The trained medical intern based on the history and sequence of events found the single-most probable COD using ICD-10 and later the same was reviewed by two independent physicians to increase the internal validity of the study. The raters' agreement

was compared with expert from forensic medicine department who are involved in conducting regular training programme on VA. Receiver operating characteristic (ROC) curve, probability, sensitivity, specificity and Cohen's kappa statistics with 95% confidence interval (CI)<sup>[4,6]</sup> were applied to compare agreement between the raters and expert which increases the integrity of the study [Figure 1].

### Ethics issues

Institutional Research and Ethics Committee clearance was obtained [EC no.: 15/2018]. Ethical principles such as respect for the persons, beneficence, justice and ensuring confidentiality was adhered to throughout the study. Informed written consent was obtained from all participants.

## Results

Table 1 shows among the TB death patients, almost 64.4% were male. It was found that 97.3% were Puducherry residents

**Table 1: Sociodemographic table**

Variables	Frequency (%)
Sex	
Male	92 (64.4)
Female	51 (35.6)
Ration card	
Puducherry	139 (97.3)
Tamil Nadu	4 (2.7)
Occupation	
Unemployed/Housework	33 (23.1)
Service/Business	31 (21.7)
Skilled worker (sutar/mistary)	18 (22.6)
Unskilled worker	18 (22.6)
Education	
No formal education	9 (6.3)
Primary	30 (21)
Secondary	39 (27.3)
Higher secondary	21 (14.6)
Diploma/Graduate	44 (30.8)
Type of house	
Kutcha	22 (15.4)
Semi-pukka	30 (21)
Pukka	91 (63.7)
Place of death	
Hospital	52 (36.4)
Home	91 (63.6)
Addictions	
Smoking	16 (10.5)
Alcohol	54 (37.8)
Comorbidities	Yes
Hypertension	35 (25.2)
Heart disease	8 (0.7)
Stroke	3 (2.1)
Diabetes	54 (37.7)
Asthma	13 (9.1)
HIV/AIDS	1 (0.6)
Cancer	5 (3.5)

as they had Puducherry ration card, whereas 84% were born in Puducherry. Considering their occupation status 42% were skilled workers, 4.9% were farmers. Among them, 19.6% were graduates and 6.3% were illiterate. A total of 15.4% lived in kutch house. Considering the place of death, 63.6% of them died at home. It was found that 10.5% TB death patients were smokers and 37.8% were alcoholics as per the history of the relative. Among TB death patient 37.7% were found to be diabetic. It was found that 0.6% had HIV coinfection and 3.5% had underlying cancer problems.

From **Table 2**, it was found that among 143 dead patients, 50 had died due to non-TB causes. It was found 37.7% were diabetic.

Figure 2 and Table 3 illustrate the predictive accuracy of Rater 2 (area under the curve [AUC] = 0.953; *P* value < 0.001) which was slightly higher than Rater 1 (AUC = 0.942; *P* value < 0.001) for identifying deaths due to TB in VA. Specificity, positive predictive value and negative predictive value of Rater 2 were also slightly better than Rater 1, whereas sensitivity is the same for both the raters. The level of agreement between the raters and experts in assigning TB as COD was found to be moderate (Cohen's kappa = 0.4; 95% CI: [0.858–0.985]).

### Discussion

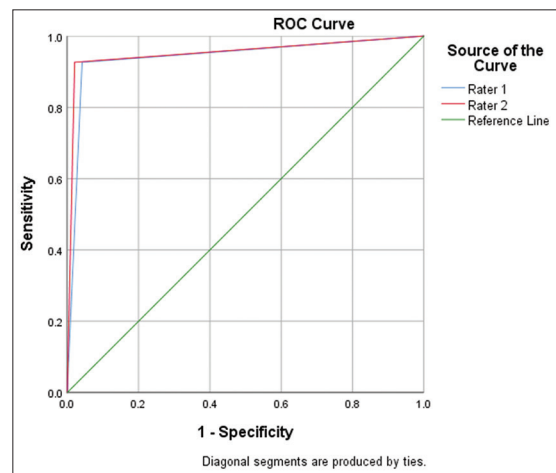
After complete evaluation, it was found that 65.1% of deaths were due to TB and its complications in Puducherry. The rest 34.9% deaths were due to non-TB causes due to age-related

factors, comorbid conditions, addiction factors and so on. Similar findings were reported in a study conducted in Kerala,<sup>[14]</sup> regarding COD it was found that out of 87 deaths, 36 were non-communicable disease-related deaths which included myocardial infarction, stroke, cancers and others. They have had a past history of TB and a full course of treatment were completed. This community-based death review, that is, VA provides a unique opportunity to include the family's perspective.<sup>[7,11,12]</sup> It allows medical and non-medical factors to be explored in an analysis of events leading up to a TB death and thus provides a more comprehensive picture of the determinants of TB mortality.<sup>[15-18]</sup> There may be a certain amount of recall bias due to the tragic outcome and amount of time that may have passed between the events and the interview. There may be difficulty in finding the deceased family in the community, often because death results in them moving away. Social cultural limitations in discussing the death of a relative in some cultures.<sup>[2,3]</sup>

In the present study, the level of agreement between the raters and experts in assigning TB as COD was found to be moderate (Cohen's kappa = 0.4; 95% CI: [0.858–0.985]). Experts review was used as a reference standard to compare raters' agreement. Similar findings were noted in studies conducted by Bisrat *et al.*<sup>[4]</sup> The level of agreement between physician review and inter-VA model to identify TB-related mortality was moderate (kappa = 0.59%, CI: 0.57–0.61) and according to Tadesse *et al.*<sup>[6]</sup> that is, moderate agreement between inter-VA model and the physician in assigning TB as COD (kappa = 0.5%; 95% CI: 0.40 - 0.60). By using kappa and ROC curve approach to validate the rater's interpretation we were able to minimize observers' bias. Over a period of time, other comorbid conditions and synergistic effects would have been the reason for the death. In the present, it was found that 63.6% of them died at home which is again a point of concern. Our investigation primarily looked at determining the medical COD. By following established protocols, we made an effort to avoid making mistakes, but it is still the possibility of information

**Table 2: TB death classified as per ICD 10 classification**

ICD-10 classification	n (%)
A15 – Respiratory tuberculosis, bacteriologically and histologically confirmed	71
A16 – Respiratory tuberculosis, not confirmed bacteriologically or histologically	8
A17 – Tuberculosis of nervous system	2
A17.8 – Other Tuberculosis of nervous system	1
A18 – Tuberculosis of other organs	3
A18.3 – Tuberculosis of intestines, peritonium and mesenteric glands	4
A19 – Miliary tuberculosis	1
A19.9 – Miliary tuberculosis, unspecified	2
B90 – Sequelae of tuberculosis	1
Total number of deaths due to TB	93/143
Total number of deaths due to non-TB reasons	50/143
A41.9 – Septic shock	2
I46 – Cardiac arrest	13
K70–77: Alcoholic liver disease – other disease of liver	4
J10 – Influenza due to other identified influenza virus	3
T51: Toxic effect of Alcohol	4
J17 – Pneumonia in disease classified elsewhere	2
J15 – Bacterial pneumonia not elsewhere classified	2
E10–14 – Diabetes mellitus	2
I64: Stroke, not specified as haemorrhage or infarct	2
J81: Pulmonary oedema	2
Other causes	14



**Figure 2:** The receiver operating curves (ROC) of Rater 1 and Rater 2. The area under the curve follows the left-hand border and then the top border of the ROC space indicating an acceptable level of accuracy



**Table 3: The corresponding area under the curve (AUC) for predicting deaths due to tuberculosis in verbal autopsy**

	Area under the curve	P	Sensitivity (95% CI)	Specificity (95% CI)	Positive Predictive Value (95% CI)	Negative Predictive value (95% CI)
Rater 1	0.942	<0.001	92.63% (85.41–96.99%)	95.83% (85.75–99.49%)	97.78% (92.20–99.73%)	86.79% (74.66–94.52%)
Rater 2	0.953	<0.001	92.63% (85.41–96.99%)	97.92% (88.93–99.95%)	98.88% (93.90–99.97%)	87.04% (75.10–94.63%)

bias as some of the participants would have not disclosed a few information-like addictions.

As per NTEP, TB death audit is essential to have an epidemiological and programmatic understanding of the distribution and determinants of TB mortality so that we can identify the crucial gaps and take remedial measures to avert all preventable TB deaths in our state. In-depth audits should be carried out for all the deaths occurring amongst all types of TB patients irrespective of initiation of treatment.<sup>[1-3]</sup> VA is one of the tool, community-based TB death review (CBTBDR), that is, VA should be completed within 21 days of the death of a TB patient. The community-based review actually provides the family's perspectives on factors which may have contributed to the death of the TB patient.<sup>[1-3]</sup>

Among the TB death patients, almost 64.4% were male; among them, 34.8% were alcoholics, 10.5% were smokers, 5.6% had COVID-19 infection and 37.7% were diabetic. As we all know, addictions and diabetes are the major risk factors<sup>[19]</sup> as it suppresses the immune system. Similar findings were reported in a study conducted by Gajalakshmi *et al.*<sup>[20]</sup> in Tamil Nadu where it was found that smoking increases the incidence of clinical TB. Hence, an intensified case-finding approach<sup>[18]</sup> has been imparted to address the risk of acquiring TB in NCD patients to screen them at the earliest (NTEP).<sup>[18]</sup> We were not able to evaluate all the declared TB death cases because of the geographic location of Pondicherry borders with Tamil Nadu which was the major limitation of the study; there is a high influx of patients from Tamil Nadu for seeking health care by providing temporary address.<sup>[21]</sup> This would have been the reason for the non-traceable of cases due to migration, wrong phone numbers and so on. A smaller sample size of the study leads to an underestimation of sensitivity and specificity value. The findings of the study have found that 34.9% of the declared TB deaths are not due to TB; hence, CBTBDR has to be done by the programme within 21 days to confirm the cause.

## Conclusion

In the present study, it was found that 65.1% of deaths were due to TB and its complications in Puducherry. In order to track India's progress towards its goal of reducing the number of TB deaths by 95% by 2035, our findings will encourage to record and investigate all potential TB-related deaths in the community.

## Acknowledgement

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## Conflicts of interest

There are no conflicts of interest.

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