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Clinical spectrum and outcomes of geriatric tuberculosis emergencies in North India

Nadim Rahman¹, Rakesh Yadav², Sunil Sethi², Atul Saroch¹, Ashish Behera¹, Ashish Bhalla¹, Mandeep Garg³, Ashok Kumar Pannu^{1*}

¹Department of Internal Medicine, Postgraduate Institute of Medical Education and Research, Nehru Hospital, Chandigarh, India, ²Department of Radiodiagnosis, Postgraduate Institute of Medical Education and Research, Nehru Hospital, Chandigarh, India, ³Department of Medical Microbiology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

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ORCID:

NR: 0000-0003-4666-3806
RY: 0000-0003-1677-5989
SS: 0000-0002-8421-3593
AS: 0000-0001-9723-6500
AB: 0000-0002-1750-2352
AB: 0000-0001-5210-1012
MG: 0000-0002-2780-8101
AKP: 0000-0002-4476-3478

Address for correspondence:

Dr. Ashok Kumar Pannu,
4th Floor, F Block,
Department of Internal
Medicine, Postgraduate
Institute of Medical
Education and Research,
Nehru Hospital, Sector 12,
Chandigarh - 160 012,
India.
E-mail: gawaribacchi@gmail.com

Abstract:

OBJECTIVES: Despite the acute and life-threatening repercussions that tuberculosis (TB) may have on the burgeoning older population in endemic countries like India, the spectrum of geriatric TB emergencies is not adequately understood.

METHODS: We performed a prospective observational study at the emergency department of an academic hospital in north India between January 2019 and June 2020, investigating the clinical and laboratory features and outcomes of active TB in older patients aged 60 years and above.

RESULTS: Out of 71 geriatric TB emergencies, central nervous system disease predominated ($n = 41$, 57.7%), followed by pulmonary ($n = 16$, 22.5%), pleural TB ($n = 8$, 11.3%), and multisite involvement ($n = 6$, 8.4%). Nearly 71.8% were male, and 77.4% belonged to low socioeconomic status (lower-middle or lower class). Usual predisposing factors were tobacco smoking (38.0%), chronic alcohol use (27.0%), and diabetes mellitus (23.9%). Atypical features were more frequent with extrapulmonary TB. Only 28.2% were microbiologically confirmed cases, and rifampicin resistance was seen in only one case. The mortality rate was considerably high (24.0%), highest with pulmonary TB (37.0%).

CONCLUSION: Older patients with TB emergencies have atypical presentations, diagnostic difficulties, and high mortality.

Keywords:

Cartridge-based nucleic acid amplification test, diagnosis, emergency, geriatrics, mortality, older, spectrum, tuberculosis, Xpert

Introduction

Tuberculosis (TB) is a significant health concern in low- and middle-income countries (LMIC), and India carries highest burden with almost one-fourth of global cases.^[1] Older people are at higher risk for TB.^[2,3] By the year 2021, an anticipated 103 million Indian population will be

aged 60 years or above.^[4] The growing life expectancy would increase the relative contribution of older patients to the total TB cases. Data from the national family health survey 2015–2016 found that the prevalence of TB in India was highest (0.88%) among the age group of > 60 years, compared to the overall prevalence of 0.32%.^[5]

Age-related altered immunity (immunosenescence), characterized by attenuated T-helper cell function and impaired tumor necrosis factor secretion,

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Box-ED section

What is already known on the study topic?

Older people are at higher risk for tuberculosis (TB). The growing life expectancy in low- and middle-income countries would increase the relative contribution of older patients to the total TB cases.

What is the conflict on the issue? Has it importance for readers?

The spectrum of geriatric TB emergencies is not adequately understood.

Pulmonary TB is predominantly considered an outpatient disease and is thought to have a better prognosis than central nervous system (CNS) disease.

How is this study structured?

This was a single-center, prospective, observational study conducted with 71 patients.

What does this study tell us?

The extrapulmonary disease may have an atypical presentation in older patients admitted in a medical emergency. CNS disease is the most common form, but pulmonary tuberculosis has the worst prognosis.

makes older persons more susceptible to reactivation of latent TB or new infection. Other well-recognized predisposing factors such as diabetes mellitus, tobacco smoking, and poor nutritional and socioeconomic status are more prevalent in older people than the young.^[2,6,7] Geriatric TB also poses unique challenges on diagnostic and therapeutic fronts. The diagnosis may be delayed because of atypical presentation (lack of fever response and absence of cough) or symptomatology confused with age-related conditions (easy fatigability, decreased appetite, or weight loss).^[2,7,8] On a therapeutic front, poor compliance, inadequate response, adverse effects, drug interactions due to polypharmacy, and unfavorable outcomes are more frequent in the aged population.^[9,10]

Despite the acute and life-threatening repercussions that TB may have on the older population, the spectrum of geriatric TB emergencies is not adequately understood. This prospective study was designed to document the clinical and laboratory features and outcomes of active TB in older patients admitted in a medical emergency.

Methods

Study design

During 18 months (from January 2019 to June 2020), we studied prospectively all patients admitted to the medical emergency in an academic hospital of India, which covers a large population of north India.

Patients

Patients aged 60 years and older admitted in the emergency with a diagnosis of TB were included in

the study. The diagnosis was made according to the national TB guidelines [Figure 1].^[11,12] Patients who had fever and/or cough for > 2-week duration with no identified cause were evaluated as presumptive pulmonary TB. Similarly, extrapulmonary TB was suspected based on organ-specific clinical features with fever or other constitutional symptoms in the absence of an alternative etiology. Smear microscopic examination, mycobacterial culture, and molecular testing were performed to establish a microbiological diagnosis. However, when microbiological investigations could not be performed or were unhelpful, clinical diagnosis was established based on the constellation of characteristic radioimaging, pathological examination, or fluid analysis and along with negative evaluation for alternate diagnoses.^[11,12] Patients admitted with sequelae of the previous TB without evidence of active disease or anti-TB therapy-related complications were excluded from the study. Study cases underwent a comprehensive history taking, physical examination, and relevant investigations and received management according to standard guidelines.^[11,12] The patients were initially admitted to an emergency observation unit and subsequently shifted to a high dependency unit or a step-down unit according to the bed's availability. Socioeconomic

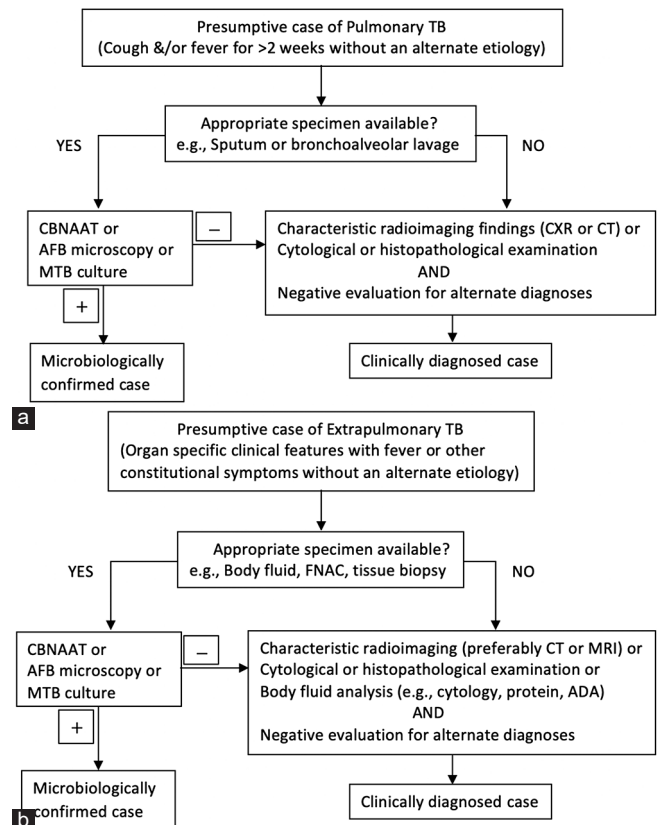


Figure 1: Diagnostic algorithm of (a) Pulmonary TB and (b) Extrapulmonary TB. CBNAAT: Cartridge-based nucleic acid amplification test, AFB: Acid-fast bacilli, MTB: *Mycobacterium tuberculosis*, CXR: Chest X-ray, CT: Computed tomography, MRI: Magnetic resonance imaging, FNAC: Fine-needle aspiration cytology, ADA: Adenosine deaminase, TB: Tuberculosis

status was categorized into five classes based on the modified Kuppaswamy scale, i.e., upper (Class I), upper-middle (II), lower-middle (III), upper-lower (IV), and lower (V).^[13]

Standard protocol approvals and patient consent

(Name: Institutional Ethics Committee, PGIMER, Chandigarh, Date of the ethical approval: 09/08/2019, Number of ethical approval: INT/IEC/2019/001528).

Laboratory methods

Smear microscopy for acid-fast bacilli (AFB) was performed using the Ziehl-Neelsen staining technique. An appropriate specimen was stained using carbol fuchsin and methylene blue stain and was examined under a microscope. The culture of *Mycobacterium tuberculosis* (*Mtb*) was done using an automated liquid culture system mycobacterial growth indicator tube, which uses a fluorescent compound sensitive to the presence of oxygen dissolved in the liquid medium to detect active growth of *Mtb*. The culture was read every week for 8 weeks before declaring it as negative.

Rapid molecular diagnostics with a fully automated real-time nucleic acid amplification test or Xpert MTB/RIF assay (Xpert) were used to detect TB and rifampicin resistance in sputum and other extrapulmonary specimens. Line probe assay was used to identify isoniazid and rifampicin resistance in AFB smear-positive sample or culture positive for *Mtb*.

Different body fluids, such as cerebrospinal fluid (CSF), pleural fluid, ascitic fluid, and pericardial fluid, were analyzed for cytology (total cell counts with differential) and biochemical analysis including glucose, protein, and adenosine deaminase (ADA) levels. ADA assay was carried out using a spectrophotometry method based on the Giusti-Galanti method of enzymatic analysis. For cytological or histopathological examination, an appropriate specimen was obtained by fine-needle aspiration or biopsy from nodules in the lung or other organs, enlarged lymph nodes, or bone marrow, when required.

A chest radiograph (chest X-ray [CXR]) was done in all patients. It remained a primary tool for the detection of pulmonary TB. Computed tomography (CT) was used whenever there is doubt in CXR or for extrapulmonary TB. Brain imaging, preferably magnetic resonance imaging (MRI), was performed in all cases of central nervous system (CNS) TB.

All patients had blood investigations including complete blood count (hemoglobin, leukocyte count, and platelets), biochemistry panel (serum electrolytes, blood urea, creatinine, and bilirubin), and human

immunodeficiency virus (HIV) testing (commercial enzyme-linked immunosorbent assay kit containing antigens from both HIV-1 and HIV-2; Diagnocure, India). For tuberculin skin testing (TST), 0.1 ml of tuberculin purified protein derivative was injected intradermally and observed for 72 h for any reaction.

Statistical analysis

For data analysis, we used Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA, version 25.0 for Mac). Discrete variables were described as frequency (*n*) and percentage (%). Continuous variables were summarized using mean with standard deviation, or median with interquartile range, according to the normalcy of data.

Results

Demographic characteristics

Seventy-eight older patients were enrolled with a presumptive diagnosis of TB in the medical emergency. However, we excluded seven patients because of insufficient evidence or a possibility of alternate diagnosis and yielded a final sample size of 71 (51 males and 20 females). The mean age was 66.7 ± 6.2 years, ranging from 60 to 87 years. The study population was contributed by adjoining geographic areas of northern India including Punjab (42.3%), Haryana (28.2%), Uttar Pradesh (11.3%), Chandigarh (9.9%), and Himachal Pradesh (8.5%).

Clinical presentation and baseline parameters

CNS disease was the most common clinical presentation ($n = 41$, 57.7%), followed by pulmonary ($n = 16$, 22.5%) and pleural TB ($n = 8$, 11.3%). Six patients had clinical features of more than one site involvement [Table 1]. Presenting symptoms were according to the site of involvement. Overall, fever was present in 55 (77.5%) cases. CNS TB typically had altered mental status (100%), meningeal signs (61%), headache (36%), and seizure (20%). Pulmonary TB presented with cough (100%), shortness of breath (81%), expectoration (68%), and hemoptysis (42%). Fever (100%), dyspnea (100%), cough (75%), and chest pain (62%) were common symptoms of pleural TB. The median systolic and diastolic blood pressures were 111.0 ± 27.0 mmHg and 74.0 ± 13.5 mmHg, and 16.9% of patients had hypotension (systolic blood pressure < 90 mmHg). Tachycardia (>100 beats/min) was common (35.2%), and the mean pulse rate was 97.7 ± 13.9 /min.

Overall, regarding addiction behaviors, 27 (38.0%) had a history of tobacco smoking, and 19 (27.0%) had excessive alcohol use. Predisposing medical comorbidities in the study population were diabetes mellitus ($n = 16$), immunosuppressive therapy ($n = 3$), HIV ($n = 2$),

Table 1: Clinical presentation, diagnosis, and outcomes of geriatric tuberculosis emergencies (n=71)

Types of tuberculosis	Total, n (%)	Microbiological diagnosis, n (%)	Died, n (%)	Hospital stay (days), median (range)
CNS	41 (57.7)	7 (17.1)	10 (24.4)	4 (1–38)
Pulmonary	16 (22.5)	9 (56.2)	5 (31.3)	2 (1–7)
Pleural	8 (11.3)	1 (12.5)	0	2 (1–4)
Pulmonary and CNS	3 (4.2)	2 (66.7)	2 (66.7)	1 (1–4)
CNS and pleural	1 (1.4)	0	0	3
Pleural and pericardial	1 (1.4)	1 (100)	0	3
Gastrointestinal and pleural	1 (1.4)	0	0	11
Total	71	20 (28.0)	17 (23.9)	3 (1–38)

CNS: Central nervous system

malignancy ($n = 1$), past history of TB ($n = 1$), and both diabetes and past history of TB ($n = 1$) [Table 2].

Diagnostic evaluation

Among 71 older patients, 20 (28.2%) had microbiologically confirmed TB, and 51 (72.8%) were clinically diagnosed cases [Table 1]. Xpert was positive in seven out of 12 sputum examinations, six in 45 CSF, two in 10 pleural fluid, and one pericardial fluid analysis. Rifampicin resistance was detected only in one (the patient with pleural and pericardial TB). Only two cases had *Mtb* isolation on culture.

All patients with CNS disease ($n = 45$) underwent lumbar puncture for CSF analysis. It typically showed lymphocytic pleocytosis with median total cells of 50 per μL (range: 0–3200) and median lymphocytes of 70% (range: 0–100). CSF protein was invariably elevated (median: 195 mg/dL; range: 51–612). Nearly 89% had low CSF glucose or hypoglycorrhachia, i.e., CSF: blood glucose ratio < 0.6 (median: 0.3; range: 0.0–0.8). The median level of ADA was 6 U/L (range: 2–35). Seven cases were microbiologically confirmed with Xpert ($n = 6/45$) and *Mtb* culture (1/43). CSF smear microscopy did not find AFB in any case. CT head was performed in 43 patients, and 17 underwent an MRI brain. Hydrocephalus was the most common finding ($n = 13$), with noncommunicating type in six cases. Other neuroimaging features were vasculitis brain infarcts ($n = 11$), meningeal enhancement ($n = 8$) (including basilar meningitis and diffuse pachymeningitis, each contributed one case), ring-enhancing lesions ($n = 4$), abscess ($n = 1$), and spinal involvement of TB ($n = 4$) [Figure 2].

Among 19 cases of pulmonary TB, 14 had a sputum examination. Xpert was detected in 7/12, AFB in 7/14, and *Mtb* culture in 1/14. All patients had a CXR ($n = 19$), and about half of them had a subsequent CT chest ($n = 9$). Multifocal involvement of both lungs ($n = 11$) was the most common pattern, followed by upper lobe disease predominance ($n = 4$). The parenchymal lesions were consolidation ($n = 12$), cavitation ($n = 6$), and miliary nodules ($n = 1$) [Figure 2]. CT bronchial angiography

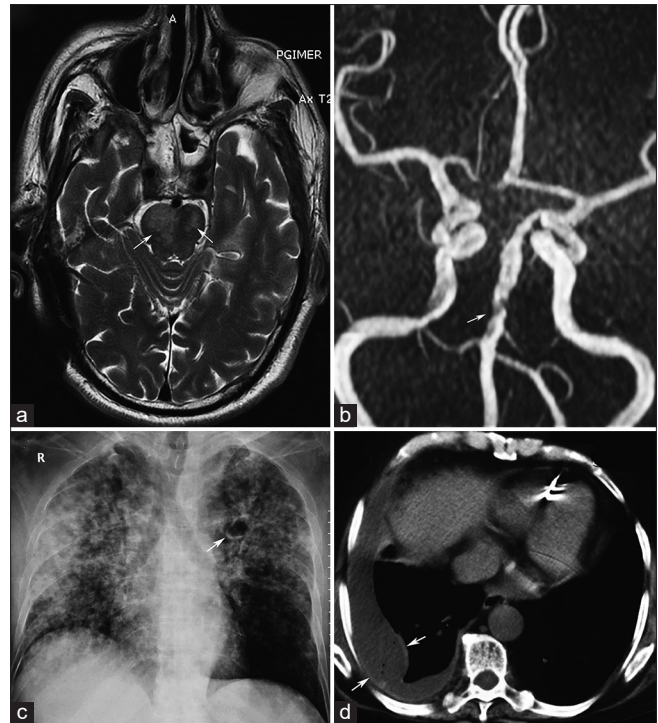


Figure 2: Radioimaging. (a and b) CNS TB: Magnetic resonance imaging brain (T2-weighted fluid-attenuated inversion recovery) showing acute infarct in both halves of the pons and pontomedullary junction (a, arrows) with filling defects in the mid basilar artery (b, arrow) related to TB meningovascularitis. (c) Pulmonary TB: Chest radiograph showing extensive multifocal opacities in both lungs and cavitation in the left upper lobe (arrow). (d) Pleural TB: Computed tomography chest showing right-sided loculated pleural effusion with split pleura sign (suggesting infectious etiology) (arrow). TB: Tuberculosis, CNS: Central nervous system

detected Rasmussen's aneurysm in two patients with hemoptysis.

Thoracentesis was performed in all cases of pleural TB and demonstrated a lymphocyte-rich exudative type of effusion ($n = 11$). The median value of protein was 4.7 g/dL (range: 2.3–6.0), and the median glucose level was 50 mg/dl (range: 24–123). Median total leukocytes were 280 per μL (range: 50–4800) with median lymphocyte of 78% (range: 10–100). ADA was elevated in all patients (median: 68 U/L; range: 43–114). Xpert was detected in 2/10 patients. None had positive microscopy or culture. The patient with pleural and pericardial

Table 2: Baseline characteristics of older patients with active tuberculosis (n=71)

Parameter(s)	Value(s)
Age (years), median (range)	65 (60–87)
Male gender, n (%)	51 (72.0)
Medical comorbidities, n (%)	
Diabetes mellitus	17 (24.0)
Immunosuppressive therapy	3 (4.0)
Previous episode of tuberculosis	2 (3.0)
Human immunodeficiency virus	2 (3.0)
Addiction behaviors, n (%)	
Ever smoking (current or reformed)	11 (15.5)
Alcohol use disorder	3 (4.2)
Both smoking and alcohol use	16 (22.5)
Socioeconomic status (modified Kuppuswamy's scale), n (%)	
Upper class (I)	3 (4.2)
Upper-middle class (II)	13 (18.3)
Lower-middle class (III)	25 (35.2)
Upper-lower class (IV)	27 (38.0)
Lower class (V)	3 (4.2)
Duration of illness (days), median (range)	30 (4–270)
Acute presentation (<14 days), n (%)	17 (24.0)
History of fever, n (%)	55 (77.5)
Systolic blood pressure (mmHg), mean±SD	111.0±27.0
Diastolic blood pressure (mmHg), mean±SD	74.0±13.5
Mean arterial pressure (mmHg), mean±SD	87.0±16.3
Pulse rate (/min), mean±SD	98.0±13.8
Respiratory rate (/min), mean±SD	22.0±3.9
Requirement of endotracheal intubation at presentation, n (%)	6 (9.0)
Hemoglobin (g/dL), mean±SD	10.7±2.0
Total leukocyte count (/μL), median (range)	11,700 (3400–133,200)
Platelet count (/μL), mean±SD	234,000±140,000
Sodium (mEq/L), mean±SD	134.0±6.6
Potassium (mEq/L), mean±SD	3.7±0.8
Blood urea (mg/dL), median (range)	46 (13–177)
Creatinine (mg/dL), median (range)	0.8 (0.2–5.8)
Bilirubin (mg/dL), median (range)	0.8 (0.2–9.4)
Positive tuberculin skin test (n=26), n (%)	2 (8.0)

SD: Standard deviation

involvement also underwent pericardiocentesis, which showed seventy leukocytes per μL with 70% lymphocytes and elevated protein (3.8 g/dL) and ADA (72 U/L). Xpert was positive in both pleural and pericardial fluid with rifampicin resistance. Ascitic fluid analysis in the case with gastrointestinal TB revealed 6000 leukocytes per μL (lymphocytes, 80%), an increased protein of 4.5 g/dL, an elevated ADA of 90 U/L, and negative results for Xpert and AFB.

Outcome

The in-hospital mortality from TB emergencies in older patients was 24.0%, highest in the patients with pulmonary involvement (37.0%), followed by CNS TB (27.0%). The median length of stay in hospital stay was 3 days (range, 1–38), longest for CNS TB [Table 1].

Discussion

Although the literature on TB in older populations always discusses atypical presentations and poor outcomes, the spectrum of geriatric TB-related emergencies, in particular, is only rarely addressed. The convergence of the aging and TB epidemics may place a significant strain on emergency services in LMIC. In this study of 71 patients, we have noted that CNS disease was the most frequent emergency presentation of geriatric TB, followed by pulmonary and pleural TB. Earlier studies demonstrated that the overall prevalence of extrapulmonary disease was relatively low, with pleural involvement as the predominant form in aged people.^[7,14] Data from the London TB register, which consisted of 29% of older patients of Indian origin, also showed that pulmonary TB was more likely to be diagnosed in a medical emergency than extrapulmonary TB.^[15]

Like most previous studies on TB in older people, a male predominance was seen in our cohort.^[16,17] The biological basis of the gender difference is mostly unknown; however, sometimes attributed to social factors such as women's reduced access to health care and men's smoking habits in LMIC.^[7] More than half of the males were current or reformed smokers in the study. Greater smoking exposure was found to be associated with increased prevalence and severity of TB in India.^[18] Chronic alcohol use was prevalent in our patients, a significant contributor to the global TB burden.^[19] Poverty is a well-recognized risk for TB. The majority of our patients belonged to low socioeconomic status (lower-middle or lower class). Diabetes mellitus was present in one-fourth of study patients and remained the leading predisposing condition for TB. TB is also not an uncommon infection in Indian diabetic patients, resulting in emergency hospitalization.^[20]

Unusual presentation is always a concern for any infection in old age. About one-fourth cases admitted with an acute illness of < 2 weeks, and at least one out of five patients had an absence of fever response. Nearly all patients of CNS TB and pleural TB had altered sensorium and dyspnea, respectively, but meningismus and tuberculous pleurisy were present in less than two-third. However, pulmonary TB demonstrated typical features, supporting the results of a meta-analysis of 12 studies.^[14] Clinical presentation of a disseminated infection was not uncommon in our patients.

The diagnostic yield of the microbiological testing was low and relied mainly on Xpert. Xpert produced results more rapidly and provided valid information on rifampicin susceptibility, albeit with a lower sensitivity. The use of the next-generation NAAT (Xpert MTB/RIF Ultra) might yield a higher detection rate in older patients. Microscopy and culture identified only a few cases in this series, and TST was frequently negative. Neuroimaging in CNS TB revealed that hydrocephalus and infarct were more usual than RELs and basilar meningitis. Pulmonary TB often had bilateral multilobar involvement, and the predominant radiologic pattern was consolidation. A lower prevalence of upper lobe predominance and cavitary lung lesions has been well reported in geriatric TB.^[16,21-23]

TB remains a particularly severe condition in older patients. This study demonstrated considerable mortality with both pulmonary and CNS infections.

Limitations

Our study's main limitations are single-center data with a relatively small sample and the absence of a control group of younger patients for comparison. We also had a low percentage of laboratory-proven diagnosis, which

might be because of the problems obtaining adequate quantity and good quality specimens from the older patients in the busy medical emergency.

Conclusion

Geriatric TB is a growing public health concern and would rise to the forefront in India's coming years. Emergency physicians must remain vigilant about the possibility that TB, particularly extrapulmonary, may underlie atypical presentation in older patients. Emergency hospitalization for CNS disease is most common, followed by pulmonary and pleural TB. Laboratory-confirmed cases contribute less and rely mainly on Xpert. Mortality remains considerably high, except in pleural TB. The geriatric population of LMIC may require better diagnostic tools and active surveillance for TB.

Author's contributions statement

NR patient management, collected patient data, drafted the manuscript. RY patient management, collected patient data. SS patient management, revised the manuscript. AS patient management, revised the manuscript. AB patient management, revised the manuscript. MG patient management, revised the manuscript. AKP conceived the idea, patient management, drafted and revised the manuscript.

Ethical approval

Ethical approval obtained. Name: Institutional Ethics Committee, PGIMER, Chandigarh, Date of the ethical approval: 09/08/2019, Number of ethical approval: INT/IEC/2019/001528). A written informed consent form was obtained from all study participants.

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None.

Conflicts of interest

None Declared.

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