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Cardiac dysfunction in active pulmonary tuberculosis: Mysterious facts of TB's pandora

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ABSTRACT

Introduction: Cardiac dysfunction in pulmonary tuberculosis is relatively more common and underestimated due to lack of suspicion. We have studied prevalence of cardiac dysfunction in pulmonary tuberculosis with special emphasis on echocardiography, serum cortisol and its correlation in cases with unstable cardiorespiratory parameters.

Methods: Prospective, observational, complete workup, and one year follow up study conducted during January 2016 to December 2020 included 800 cases of active pulmonary tuberculosis with specified inclusion criteria of disproportionate tachycardia, tachypnea with or without hypoxia and shock. Cases with known risk factor for cardiac disease and taking cardiac medicines, and cases with pericardial effusion were excluded from study. All study cases were undergone protocolized analysis such as chest radiograph, pulse oximetry, ECG, sputum examination, cardiac enzymes (CPK-MB, NT-Pro-BNP, and cardiac troponins), serum cortisol, and echocardiography at entry point, at two and six months of treatment with anti-tuberculosis medicines as per NTEP. Statistical analysis was carried out by Chi-square test.

Observations and analysis: In a study of 800 pulmonary tuberculosis cases, 56.00% (448/800) cases were males, and 44.00% (352/800) cases were females. Cases with BMI<18 was 41.62% (333/800) and BMI>18 was 58.37% (467/800). Radiological patterns as unilateral disease in 33.62% (269/800) & bilateral disease in 66.37% (531/800). Hemoglobin less than 10 gm% were documented in 85.12% (681/800) and above 10 gm% were in 14.87% (119/800) cases. Serum albumin less than 3.5 gm% and more than 3.5 gm% were observed in 48.12% (385/800) and 51.12% (415/800) cases respectively. Hypoxia was documented 26.12% (209/800) cases and normal oxygen saturation in 73.87% (591/800) cases. cases with normal and abnormal serum cortisol were 61.37% (491/800) & 38.62% (309/800) respectively. Sputum examination for AFB observed in 30.00% (240/800) and gene Xpert MTB/RIF documented in 51.37% (411/800) cases respectively. Bronchoscopy guided techniques were used in 149 cases and BAL smear AFB in 44.96% (67/149) cases, gene Xpert MTB/RIF in 97.31% (145/149) cases and MGIT culture in four cases (positive in 100% cases subjected to MGIT culture). We have observed global hypokinesia is predominant cardiac dysfunction documented in 82.21% (171/208) cases, followed by left heart systolic dysfunction in 16.34% (34/208) cases and left heart diastolic dysfunction in 75% (156/208) cases. Right heart dysfunction as dilated right atrium and right ventricle documented in 52.88% (110/208) cases and pulmonary hypertension in 40.38% (84/208) cases. Covariates such as age, gender, hemoglobin, BMI, serum cortisol, serum albumin, oxygen saturation and radiological involvement has significant association with cardiac dysfunction. ($p<0.00001$) Response to treatment with antituberculosis medicines and steroids has documented as improved in 77.40% cases (161/208) cases, persistent in 13.46% (28/2028) cases and progressive in 9.13% (19/208) cases. Final outcome of cardiac dysfunction in Pulmonary tuberculosis cases has significant association with serum cortisol level ($p<0.00086$).

Conclusion: Cardiac dysfunction is active pulmonary tuberculosis needs prompt workup in presence of disproportionate tachypnea, tachycardia with or without hypoxia and shock. Echocardiography is basic tool to evaluate these cases and global hypokinesis is most common abnormality. Serum cortisol abnormality documented in fair number of cases and very well correlated with left ventricular dysfunction abnormalities. Steroids with antituberculosis treatment backup is mainstay protocol during management of these cases. Cardiac dysfunction is reversible in majority of cases and proportionate number shown complete improvement in cardiac dysfunction.

Keywords: pulmonary tuberculosis, cardiac dysfunction, echocardiography, serum cortisol, BAL, gene Xpert MTB/RIF

INTRODUCTION

Pulmonary tuberculosis is most common respiratory infection in India, caused by *mycobacterium tuberculosis bacillus*. Pulmonary tuberculosis has significant health burden across the globe in terms of mortality and morbidity. Tuberculosis is in list of top ten causes of mortality from infectious disease especially in low- and middle-income countries and come ahead to malaria and HIV-AIDS in these countries [1]. Although WHO has declared tuberculosis as a 'global public health emergency' 25 years before and many measures are undergoing for three decades still it remains poorly controlled. India, China, Indonesia, South Africa and Nigeria rank first to fifth respectively in terms of the incidence, mortality, and morbidity [2]. According to an estimate by the

WHO, severity of tuberculosis increased globally and resulted in increase in one billion newly infected cases and predicted for 200 million people will get sick and 70 million will die from TB if timely measures not undertaken such as active case detection and universal availability of ATT [3].

Tuberculosis can affect every organ of body except hairs and nails. Primary target organ of involvement in tuberculosis is lung and more than 80% reported cases are pulmonary tuberculosis cases [4]. Extrapulmonary tuberculosis commonly involves lump node sand pleura and central nervous system, and cardiovascular systems were not very common. Cardiovascular involvement usually associated with pulmonary disease. Isolated cardiopulmonary tuberculosis without evident pulmonary disease has been documented in 1% and 2% of all tuberculosis cases in immunocompetent persons [5]. Cardiovascular involvement in tuberculosis has documented poor outcome due to delayed diagnosis. Pericardial tuberculosis has reported mortality up to 40% and is marker of advanced involvement due to tuberculosis process [6]. The “neglected tropical diseases and other infectious diseases involving the heart” (the NET-heart project) has started in last decade to target cardiovascular involvement in tuberculosis. In this project various aspects have been involved such as factors associated with delay in cardiovascular involvement, predictors of poor outcome, increase awareness about cardiovascular tuberculosis and therapeutic options available to treat include medical and surgical options. Vison of this project is to decrease mortality and morbidity of cardiovascular tuberculosis in developing countries [7, 8].

Tuberculosis of adrenal gland is not uncommon. Primarily tuberculosis can involve adrenal glands causing Addison’s disease [9]. Adrenal suppression equally documented in advanced pulmonary tuberculosis due to lymphatic dissemination of pulmonary tuberculosis to adrenal gland unilaterally or bilaterally. Adrenal suppression during treatment of anti-tuberculosis treatment in rifampicin containing regimen in advanced pulmonary tuberculosis cases especially in those case with hypoalbuminemia and cachexia has been reported called as pseudo adrenal insufficiency. Case with adrenal insufficiency usually present with cardiovascular symptoms such as hypotension, arrhythmias, and congestive heart failure [10-14]. Pathophysiology resulting into cardia dysfunction secondary to adrenal insufficiency would be left ventricular myocardial suppression, poor glycogen reserves, hemoconcentration, low blood volume, and reduced coronary blood flow, and disturbances in electrolyte levels [10-14].

Cardiac dysfunction is pulmonary tuberculosis has been reported in cases and case series. Very few literatures are available for cardiac dysfunction in pulmonary tuberculosis in large number of cases with specified inclusion criteria. In present study we have documented prevalence of cardiac dysfunction in pulmonary tuberculosis in unstable cardiorespiratory parameters, risk factors associated, and outcomes in these cases after treatment completion.

METHODS

Data Source

Prospective, observational, complete workup and one year follow up study conducted during January 2016 to December 2020 in Chest Diseases Department in Venkatesh Chest Hospital & MIMSR Medical College Latur included pulmonary tuberculosis cases with specified inclusion criteria after institutional review board and ethical committee approval.

Inclusion Criteria

1. All cases between 18-85 age with respiratory symptoms as cough, sputum production, fever, weight loss, anorexia, and shortness of breath lasted for more than 3 months, and smear microscopy or nucleic acid amplification test documented acid-fast bacilli or MTB genome.
2. Cases with disproportionate tachycardia and tachypnea with or without shock and hypoxia were key entry point criteria in this study.

Exclusion Criteria

1. All those not willing to participate, age <18 years, pregnant and lactating mothers.
2. Tuberculosis patients with HIV co-infection, patients receiving chemotherapeutic drugs, radiotherapy and immunosuppressive therapy were also excluded.
3. Patients with other comorbid illnesses such as diabetes mellitus, ischemic heart disease, hypertension, cardiomyopathy, and stroke were excluded.
4. Cases with exudative tuberculous pleural effusion were excluded. Sputum negative and clinical pulmonary tuberculosis cases also excluded as our study protocol.
5. Cases on treatment and not willing to perform routine echocardiography and during follow-up or cases died during course of treatment were excluded.
6. Cases with stable cardiorespiratory parameters or cases without tachycardia and tachypnea with or without hypoxia were excluded.

Case Definition Used in Present Study

Case definitions were formulated by teaching faculties of tertiary care hospitals involved in present study.

1. **Pulmonary tuberculosis:** ‘Patients with constitutional symptoms (cough with or without sputum, fever, anorexia, weight loss with or without shortness of breath lasted for four to 12 weeks) and lung parenchymal abnormality in chest X-ray and sputum/induced sputum/BAL smear microscopy documented acid fast bacilli and or gene Xpert MTB/RIF documented MTB genome.
2. **Disproportionate tachycardia:** Pulmonary tuberculosis cases with resting heart rate above 100 per minute or heart rate above 130 per minute with minimal exertion without causing hypoxia or oxygen saturation less than 90% or more than 5% fall from resting saturation.
3. **Tachypnea:** Pulmonary tuberculosis cases with resting respiratory rate above 20 breaths per minute or respiratory rate above 40 per minute with minimal exertion without causing hypoxia or oxygen saturation less than 90% or more than 5% fall from resting saturation.
4. **Hypoxia:** Pulmonary tuberculosis cases with resting oxygen saturation less than 90% at room air and falls to more than 5% with minimal exertion and will take more

than five minutes to return to normal or more than 90%.

5. **Shock:** Pulmonary tuberculosis cases with resting blood pressure systolic less than 90 mmhg and diastolic less than 60 mmhg with other causes of shock excluded

All study cases were undergone following assessment before enrolling in the study:

1. Patient information recorded as age, gender, weight, height, and BMI in all cases. Clinical details as heart rate, respiratory rate, blood pressure, oxygen saturation, exertional parameters and respiratory system examination in all cases.
2. Chest X-ray (posteroanterior view) performed in all cases. Routine hematological investigations as hemoglobin, serum proteins, cardiac enzymes (CPK creatine kinase-MB & cardiac troponins-troponin T) cardiac function marker NT-pro-BNP, CRP (C-reactive protein) titer, liver and kidney functions, HIV 1 and II antibody, and blood sugar level in all cases.
3. Serum cortisol was measured in blood sample collected in early morning (empty stomach or without any food for six-eight hours) during 5.00 am to 8.00 am. Fever, stress was common in tuberculosis which may alter cortisol level, but other comorbid illnesses and exogenous steroid exposure were excluded.
4. Sputum smear microscopy for acid fast bacilli and gene Xpert/MTB Rif done in all cases. sputum induction techniques were used in cases with unable to produce sputum. In cases with unable to produce sputum, fiberoptic video-bronchoscopy guided BAL samples were sent for smear and gene Xpert/MTB Rif.
5. All cases with positive smear or nucleic acid amplification test (gene Xpert MTB/RIF) were included.
6. Cases with negative results or clinical tuberculosis were excluded. NT-pro-BNP was done in all cases along with cardiac enzymes cardiac enzymes (CPK creatine kinase-MB & cardiac troponins-troponin T).
7. We have utilized NT-pro-BNP level along with clinical criteria and echocardiography during assessment of cardiac dysfunction.
8. All cases were undergone echocardiography analysis as a study protocol. Echocardiography was performed by cardiologist at our center. Echocardiographic abnormalities were categorized as right and left heart dysfunction.
9. Echocardiography analysis was done by Interventional cardiologist and main findings were global hypokinesia, LVSD (left ventricular systolic dysfunction), LVDD (left ventricular diastolic dysfunction), pulmonary hypertension, dilated RA (right atrium), and RV (right ventricle).
10. We have used global longitudinal strain (GLS) parameter during echocardiography to document early signs of LV (left ventricular) dysfunction. We have documented added value of this methodology in assessing to response to therapy. This methodology helped us to assess the improvement LV function after treatment and after completion of treatment.
11. During echocardiography, left ventricular diastolic dysfunction was graded as (1) normal; (2) mild diastolic dysfunction called when abnormal relaxation without increased LV end-diastolic filling pressure; (3) moderate or “pseudo normal” diastolic dysfunction called when abnormal relaxation with increased LV end-diastolic filling pressure; or (4) severe diastolic dysfunction called when advanced reduction in compliance (i.e., markedly increased stiffness) with restrictive filling.
12. We have done correlation of symptoms with diastolic dysfunctions and documented that majority of cases were having moderate cardiac dysfunction.
13. Serum cortisol correlation with type of left ventricular cardiac dysfunction was documented.
14. Cardiologist was also involved in workup of pericardial effusion to excluded exudative pericardial effusion and procedure coronary angiography in selected cases with persistent cardiac dysfunction after completion of treatment.
15. All cases were offered ATT with steroids for six weeks in cases with cardia dysfunction as omnacortil two mg/kg in tapering doses irrespective of serum cortisol level.
16. Cases with abnormal serum cortisol level were reassessed for cortisol level after six weeks of treatment with oral steroids to assess recurrence of adrenal insufficiency.
17. Echocardiographic response to cardiac dysfunction recovery were documented and categorized as improved, progressive and persistent done at completion of treatment.
18. Case with persistent and progressive cardiac dysfunction after completion of treatment were subjected to computerized and conventional coronary angiography as per their willingness and affordability
19. Radiological response to treatment in pulmonary involvement were documented in chest radiograph after completion of ATT.
20. All cases with cardiac dysfunction were offered steroids with Antituberculosis treatment as per NTEP (national tuberculosis elimination program) regimen (**Figure 1**-flow of the study).

Study Design Methodology

Figure 1 shows the study design methodology.

Statistical Analysis

The statistical analysis was done using single proportion test (Chi test) in R-3.4 software. Significant values of $\chi 2$ were seen from the probability table for different degrees of freedom required. A value of p was considered significant if it was below 0.05 and highly significant in case it was less than 0.001.

RESULTS

Covariates

In a study of 800 pulmonary tuberculosis cases, 56.00% (448/800) cases were males, and 44.00% (352/800) cases were females, with age between 18-85 years and <50 age group were 55.12% (441/800) and >55 age group were 44.87% (359/800). Cases with BMI<18 was 41.62% (333/800) and BMI>18 was 58.37% (467/800). Radiological patterns as unilateral disease in

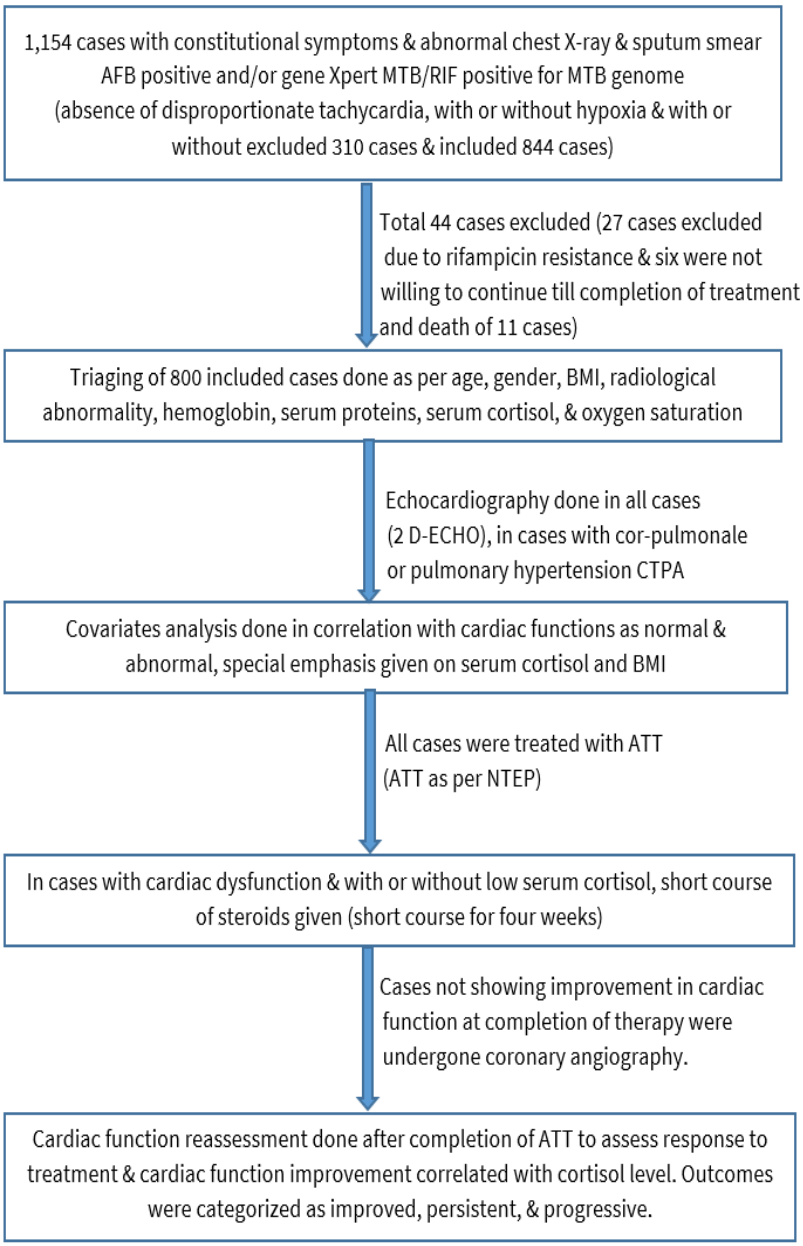

Figure 1. Flow of the study (Source: S Patil, Venkatesh Chest Hospital and critical care center Latur)

33.62% (269/800) and bilateral disease in 66.37% (531/800). Hemoglobin less than 10 gm% were documented in 85.12% (681/800) and above 10 gm% were in 14.87% (119/800) cases. Serum albumin less than 3.5 gm% and more than 3.5 gm% were observed in 48.12% (385/800) and 51.12% (415/800) cases respectively. Hypoxia was documented 26.12% (209/800) cases and normal oxygen saturation in 73.87% (591/800) cases. cases with normal and abnormal serum cortisol were 61.37% (491/800) & 38.62% (309/800) respectively (**Table 1**).

Diagnostic methods and techniques used in study cases with positive results as sputum examination for AFB observed in 30.00% (240/800) and gene Xpert MTB/RIF documented in 51.37% (411/800) cases, respectively (**Table 2**).

Bronchoscopy guided techniques were used in 149 cases and BAL smear AFB in 44.96% (67/149) cases, gene Xpert MTB/RIF in 97.31% (145/149) cases and MGIT culture in four cases (positive in 100% cases subjected to MGIT culture).

Table 1. Other variables studies in this study associated with cardiac dysfunction

	TPTBP (n=800)	%
Age <50 years	441	55.12
Age >50 years	359	44.87
Males	448	56.00
Females	352	44.00
BMI <18	333	41.62
BMI >18	467	58.37
Chest X-ray unilateral diseases	269	33.62
Chest X-ray bilateral disease	531	66.37
Albumin <3.5 gm%	385	48.12
Albumin >3.5 gm%	415	51.87
Hemoglobin <10 gm%	681	85.12
Hemoglobin >10 gm%	119	14.87
Normal cortisol level	491	61.37
Abnormal cortisol level	309	38.62
PTB with hypoxemia	209	26.12
PTB without hypoxemia	591	73.87

Note. TPTBP: Total pulmonary TB patients

Table 2. Diagnostic methods used during course of pulmonary tuberculosis (n=800)

	Positivity	%
Sputum AFB	240	30.00
Sputum CBNAAT or gene Xpert MTB/RIF	411	51.37
Bronchoscopy guided techniques in 149 cases of total 800 cases		
BAL AFB (67/149)	67	44.96
BAL CBNAAT or BAL gene Xpert MTB/RIF (145/149)	145	97.31
BAL MTB in MGIT culture (four undiagnosed samples sent for culture)	4	100.00

Table 3. Echocardiographic patterns of cardiac abnormality in study cases

	PTCWCD (n=208)	%
Global hypokinesia	171	82.21
LVSD	34	16.34
LVDD	156	75.00
PAH	84	40.38
Dilated RA & RV	110	52.88

Note. PTCWCD: Pulmonary tuberculosis cases with cardiac dysfunction

Table 4. Association of variables with cardiac dysfunction in pulmonary tuberculosis study cases

	Cardiac dysfunction present (n=208)	Cardiac dysfunction absent (n=592)	Chi test & p-value
Age <50 years (n=441)	78	363	$\chi2$=34.3407
Age >50 years (n=359)	130	229	p<0.00001
Males (n=448)	50	398	$\chi2$=114.78
Females (n=352)	158	194	p<0.00001
BMI <18 (n=333)	168	165	$\chi2$=177.24
BMI >18 (n=467)	40	427	p<0.00001
Chest Xray unilateral diseases(n=269)	107	162	$\chi2$=38.90
Chest Xray bilateral disease (n=531)	101	430	p<0.00001
Albumin <3.5 gm% (n=385)	156	229	$\chi2$=79.87
Albumin >3.5 gm% (n=415)	52	363	p<0.00001
Hemoglobin <10 gm% (n=681)	156	525	$\chi2$=21.68
Hemoglobin >10 gm% (n=119)	52	67	p<0.00001
Normal cortisol level (n=491)	31	460	$\chi2$=253.41
Abnormal cortisol level (n=309)	177	132	p<0.00001
PTB with hypoxia (n=209)	141	68	$\chi2$=249.89
PTB without hypoxia (n=591)	67	524	p<0.00001
Cardiac enzymes raised (CPK-MB/trop-T)	198	46	$\chi2$=542.14
Cardiac enzymes normal (CPK-MB/trop-T)	20	546	p<0.00001
CRP titer raised	202	165	$\chi2$=297.22
CRP titer normal	6	427	p<0.00001

Core Observations

We have observed global hypokinesia is predominant cardiac dysfunction documented in 82.21% (171/208) cases, followed by left heart systolic dysfunction in 16.34% (34/208) cases & left heart diastolic dysfunction in 75% (156/208) cases. Right heart dysfunction as dilated right atrium and right ventricle documented in 52.88% (110/208) cases & pulmonary hypertension in 40.38% (84/208) cases (**Table 3**).

Covariates such as age, gender, hemoglobin, BMI, serum cortisol, serum albumin, oxygen saturation, and radiological involvement has significant association with cardiac dysfunction (p<0.00001) (**Table 4**).

Table 5. Profile of cardiac dysfunction at the completion of anti-tuberculosis treatment (n=208)

	Cardiac dysfunction (n=208)	%
Improved	161	77.40
Persistent	28	13.46
Progressed	19	9.13

Table 6. Association of final cardiac outcomes in treated cases with serum cortisol level (n=208)

	Normal cortisol level (n=31)	Abnormal cortisol level (n=177)	Chi test & p-value
Improved (n=161)	22	139	$\chi2$=14.11
Persistent (n=28)	1	27	p<0.00086
Progressed (n=19)	8	11	

Response to treatment with antituberculosis medicines and steroids has documented as improved in 77.40% cases (161/208) cases, persistent in 13.46% (28/2028) cases & progressive in 9.13% (19/208) cases (**Table 5**).

Final outcome of cardiac dysfunction in pulmonary tuberculosis cases has significant association with serum cortisol level (p<0.00086) (**Table 6**). Coronary angiography was done in 28 patients after completion of ATT course (19 cases with progressed cardiac dysfunction and nine cases with persistent cardiac dysfunction, and 19 cases were not willing for coronary angiography) and documented insignificant coronary artery disease in majority of cases and only two cases were documented double vessel coronary artery disease with less than 50% occlusion.

DISCUSSION

Cardiac Dysfunction Assessment by Echocardiography in Pulmonary Tuberculosis Cases with Specified Inclusion Criteria

In 800 cases with active pulmonary TB with unstable cardiorespiratory parameters with specified inclusion criteria, cardiac dysfunction was documented in 26% (208/800) cases. Echocardiography documented global hypokinesia as predominant cardiac dysfunction documented in 82.21% (171/208) cases. Proportionality higher number of cases were having raised cardiac enzymes which indicates underlying myocarditis as pathological cause for cardiac dysfunction. Interestingly, a very few cases were documented abnormal myocardial echogenicity in echocardiography which indicates cardiac dysfunction without structural disease. Myocardial involvement due to tuberculosis rare and reported in case reports in available literature. Tuberculous myocarditis usually results from lymphohematogenous dissemination either from pulmonary focus or mediastinal lymph nodes. Direct spread from pericardial tuberculosis is another possibility of myocardial involvement [15, 16]. Tuberculous myocarditis usually shown involvement of left ventricle then right ventricle and biventricular disease in decreasing frequency. Interestingly, one study conducted to observe myocardial involvement in cardiovascular tuberculosis by analyzing myocardial biopsy. They have reported 70% of case with cardiovascular tuberculosis have biventricular disease, 22%

cases left ventricular disease and 8% cases with right ventricle involvement [17].

Myocardial involvement due tuberculosis process has documented in ECG, echocardiography and abnormal cardiac enzymes. In tuberculous myocarditis, typical ECG findings were sinus tachycardia with aberrant rhythms as ventricular strain patterns documented in our study. Echocardiographic abnormalities in myocardial involvement noted as localized or global wll motion abnormalities reported by cardiologist as 'global or regional hypokinesia'. Pulmonary hypertension and cor-pulmonale, i.e., right heart abnormalities secondary to advanced pulmonary tuberculosis with hypoxia on pulse oximetry were also documented during echocardiography.

Cardiac enzymes analysis during tuberculous myocarditis were shown increased cardiac enzyme such as NT-pr-BNP, CPK MB and cardiac troponins levels. Proportionate number of cases were shown all three cardiac enzymes were raised, while few cases were shown only NT-pro-BNP raised. We further analyzed abnormalities in cardiac enzymes and echocardiographic cardiac function abnormalities and documented that significantly raised isolated NT-pro-BNP were raised cases with left ventricular dysfunction in comparison with right heart dysfunction and all three enzymes were raised in cases with global hypokinesia on echocardiography.

Myocarditis is often difficult to diagnose, and no single test will give confirm diagnosis in tuberculous myocarditis. Endomyocardial biopsy is specific test and current gold standard. Negative endomyocardial biopsy does not rule out Tuberculous myocarditis [18, 19]. Cardiac MR (CMR) is underutilized in comparison with echocardiography due to cost constraint and lack of availability in resource limited countries as in our study. CMR is considered as most reliable test in documenting myocardial involvement in comparison with echocardiography [20]. CMR also has several advantages over echocardiography identifying, characterizing, and assessing whole cardiac abnormalities including a high contrast resolution, an unlimited field of view, the ability to conduct multiplanar imaging and tissue characterization, multiparametric imaging, strain imaging, and a high degree of contrast variability [19, 21-23]. Echocardiography has many limitations as mentioned in advantages of CMR. Poor acoustic window, improper pericardial thickness evaluation, lack of multiplanar evaluation, absence of contrast evaluation in three dimensional pericardial, myocardial and endocardial structural and characterization of cardiac tissue is under evaluated during echocardiography [24, 25]. Echocardiography is the first and preferred test to evaluate cardiac evaluation over CMR similarly to our study.

Mycobacterium tuberculosis may affect coronary arteries and coronary atherosclerotic lesions documented during coronary angiography as isolated findings or with myocarditis. It was observed sudden cardiac deaths (SCD) in cases with myocardial tuberculosis in apparently asymptomatic young patients [16]. The researchers have reported aberrant ventricular rhythms and tachyarrhythmias as probable cause for SCD secondary to ventricular septal involvement along with myocardial necrosis [26, 27]. Cardiovascular tuberculosis has been associated with SCD in absence of direct myocardial or coronary arteries involvement and mechanism resulting in to SCD require further research [28].

Adrenal Suppression or Abnormal Adrenal Functions Without Adrenal Involvement in Cases with Pulmonary Tuberculosis with Cardiac Dysfunction

In present study, adrenal suppression and abnormal adrenal functions has documented significant association with cardiac dysfunction. In autopsy series performed in early 19th century in 403 cases with Addison disease with adrenal involvement due to tuberculosis in 69.7% of cases [9]. Globally tuberculosis is leading cause of Addison's disease and since last five decades it is commonly reported in developing countries due to declined trends of tuberculosis in developed countries [29-31]. Adrenal suppression is independent of structural adrenal abnormalities due to tuberculous pathology. Cases with normal adrenal glands during imaging workup as in ultrasound or MRI have shown significant adrenal suppression or abnormalities as in our study.

We have observed myocarditis and dilated cardiomyopathy in study cases with abnormal cortisol as compared to normal cortisol ($p<0.00001$). Cardiac dysfunction abnormalities documented in adrenal suppression cases were global hypokinesia and left ventricular diastolic dysfunction. Very few literatures are available mentioning adrenal functions tests measurements in active pulmonary tuberculosis cases. Isolated adrenal tuberculosis in absence of pulmonary involvement is rare and these cases usually present with hypotension usually resulted hematogenous dissemination of form early pulmonary focus which has been resolved or undetected on routine imaging [9]. Autopsy series performed for Addison's disease and suspected cardiovascular tuberculosis including large number of cases have reported 6% adrenal involvement in cases with active pulmonary tuberculosis and one fourth of cases were having isolated adrenal involvement without lung parenchymal disease.[32] Published case series have reported isolated adrenal tuberculosis in 3% cases [9, 33]. Studies of adrenal tuberculosis have documented dissemination most commonly from pulmonary focus and second most common is genitourinary tuberculosis [34].

Cardiovascular autonomic nervous system is largely affected in pulmonary tuberculosis especially in presence of hypoxia as manifested with tachycardia and shock as a result of sympathetic augmentation. Autonomic dysfunction usually resulted from adrenal suppression and presenting clinically with syncope, fatigability, anorexia, cachexia and reported to have postural hypotension and cardio-respiratory arrest [35]. Studies have documented concurrent pulmonary tuberculosis with adrenal insufficiency in 6% cases after evaluation with serum cortisol in cases with sputum positive pulmonary tuberculosis cases [36]. The researchers have documented subclinical adrenal insufficiency in proportionate number of pulmonary tuberculosis without obvious adrenal gland pathology or enlargement. They have also mentioned that only few cases were shown adrenal gland enlargement in spite of serum cortisol abnormality [37]. Numerous authors have reported subclinical adrenal insufficiency in more than half cases with active pulmonary tuberculosis without structural adrenal change [38-45].

Inflammatory Marker's Role in Cardiac Dysfunction in Absence of Structural Heart Disease

Majority of study cases with cardiac dysfunction were associated with inflammatory surge due to systemic inflammatory response due to mycobacterium tuberculosis

which has been documented with raised CRP titer. We have documented this was the rationale to add steroid replacement in addition to anti-tuberculosis treatment as per NTEP irrespective of serum cortisol level in all cases with cardiac dysfunction. Steroids (omnacrotil) were given in dose two mg/kg in tapering dosage over duration for six weeks with ATT which was continued for 6 months as per NTEP. In correlation with our observations and our protocol with concurrent use of steroids with ATT in management of these cases, European society of cardiology recommended use of immunosuppressive or immunomodulatory therapies in cases with ejection fraction less than 40% [46]. Duration and dosage of steroid use along with ATT has not mentioned in any guidelines or available in published literature especially in those case with cardiac dysfunction without structural myocardial or pericardial heart disease. We have postulated that inflammatory surge as reported with raised titer of CRP would be leading event in myocardial suppression and global hypokinesia in absence of structural heart disease. Numerous authors in their case studies have reported cardia dysfunction in absence of direct cardia involvement and they postulated various mechanisms for some including our observations documented in present study [47, 48].

Risk Factors Associated with Cardiac Dysfunction (Covariates Analysis and Association with Cardiac Dysfunction)

In present study, age>50 years, female gender, hemoglobin <10.0 gm%, hypoalbuminemia, bilateral advanced pulmonary disease, oxygen saturation <90% were associated with cardiac dysfunction. Cases with hypoxia were documented additional right heart dysfunction and pulmonary hypertension along with left heart dysfunction. Cases with advanced pulmonary disease were having other two associated risk factors as advanced age and hypoalbuminemia. Various authors have mentioned similar plausible mechanism leading to cardiac dysfunction in advanced active pulmonary tuberculosis [27, 49-53].

Cases showing female gender predisposition and cardiac dysfunction were having other predominant associated risk factor is anemia. As per through covariates evaluation including all these risk factors and its association with cardiac dysfunction, there are two plausible mechanisms resulting into cardiac dysfunction in these cases. First mechanism would be inflammatory surge measured by universal marker of inflammation CRP and second is concurrent clinical or subclinical adrenal suppression as measured by serum cortisol level resulting into cardiac dysfunction. Similarly, in [27, 50-55], the researchers have mentioned similar observations.

Outcomes of Cardiac Functions in Study Cases in Correlation with Adrenal Functions

Response to treatment with antituberculosis medicines and steroids has documented as improved in 77.40% cases (161/208) cases, persistent in 13.46% (28/2028) cases and progressive in 9.13% (19/208) cases. Final outcome of cardiac dysfunction in Pulmonary tuberculosis cases has significant association with serum cortisol level. As per available literature, this is first study targeting cardiac dysfunction in absence of structural heart disease, correlation with serum cortisol level, and final outcome and its correlation with serum cortisol.

We have excluded pericardial TB, cases with structural heart disease and coronary vascular heart disease initially at entry point and we have followed all these cases for any possibility of similar diagnosis after completion of treatment. In present study, coronary angiography was done in 28 patients after completion of ATT course (19 cases with progressed cardiac dysfunction and nine cases with persistent cardiac dysfunction, and 19 cases were not willing for coronary angiography) and documented insignificant coronary artery disease in majority of cases and only two cases were documented double vessel coronary artery disease with less than 50% occlusion. Similar to our observation's, the researchers in [54-56] have documented cardiac dysfunction in advanced pulmonary tuberculosis cases absence of structural cardiac disease. As we observed only few cases were having coronary artery disease in case with active pulmonary tuberculosis, the researchers in [57-59] have documented coronary artery disease and stroke in significant number of cases. Systematic review by author mentioned that there was no correlation between active pulmonary tuberculosis and new onset hypertension [60].

Limitations of Present Study

First limitation is advanced investigation were not routinely utilized during study for diagnose of cardiac dysfunction in advanced pulmonary tuberculosis cases with specified inclusion criteria. CT coronary angiography is preferred in few cases and conventional CAG done in few cases to analyze direct coronary artery involvement. cost factor is the major issue while doing these investigations. Coronary angiography was performed in selected cases with persistent cardiac dysfunction, and we are unable draw conclusion regarding coronary arterial disease in rest of the cases with cardiac dysfunction. Second limitation is study done in selected class of pulmonary TB cases with specified inclusion criteria and this study does not represent cardiac dysfunction in cases with stable cardiorespiratory parameters. Third limitation is myocardial biopsy not done in any case also cardiac MRI is not used for myocardial pathology. We have utilized 2-D-echo for cardiac dysfunction analysis performed by cardiologist. Fourth limitation is adrenal involvement assessed by 4 D sonography in all cases irrespective of serum cortisol level. Although MRI is best test to document adrenal involvement, performed in 12 cases only. Fifth limitation is cases expired during study were excluded due to non-willingness of relatives for post-mortem analysis of cardiac and adrenal pathology and these cases remains unevaluated histopathological workup for tuberculosis.

Issues Needs Further Global Research

1. What are possible mechanisms or pathophysiological process for cardiac dysfunction in pulmonary tuberculosis in absence of direct myocardial involvement or structural heart disease?
2. Is there direct correlation with systemic inflammatory surge (evidenced by raised CRP titer) and cardiac dysfunction in pulmonary tuberculosis cases?
3. Are these direct and indirect pathophysiological mechanisms evolved during tuberculosis pathology resulting into cardiac dysfunction?
4. Are we underestimating cardiac dysfunction in advanced tuberculosis cases due to scarcity of invasive myocardial sampling techniques? Myocardial biopsy is

best way to documented myocardial involvement due to tuberculosis process, but underutilized due to lack of trainings.

5. Cardiac dysfunction resulted in pulmonary tuberculosis by indirect myocardial involvement either due to inflammatory surge or adrenal suppression. Adrenal suppression in pulmonary tuberculosis cases especially in advanced stage is underestimated and should be sought actively in cases with cardiac dysfunction.
6. Is real choice of addition of steroids with ATT backup is key step in controlling cardiac dysfunction by means of curtailing inflammatory surge and aiding adrenal support? This concept is really a though provoking and needs further research.
7. Advanced pulmonary tuberculosis cases with tachycardia and shock usually have myocardial suppression and cardiac pump failure visualized during echocardiography as global hypokinesia.
8. Very few literatures are available regarding cardiac dysfunction without direct cardiac involvement and is considered in presence of specified features as mentioned in inclusion criteria of present study. This is unique component of study.

CONCLUSIONS

Cardiac dysfunction is active pulmonary tuberculosis needs prompt workup in presence of disproportionate tachypnea, tachycardia with or without hypoxia and shock. Cases with advanced pulmonary tuberculosis, malnutrition and cachexia, geriatric cases, female gender, albumin <3.5 gm% and hemoglobin <10.0gm% mandates thorough evaluation to rule out cardiac dysfunction.

Echocardiography is basic bedside cost effective, noninvasive tool to evaluate cardiac dysfunction in these cases with specified inclusion criteria. Proportionate number of cases were having global hypokinesia as predominant cardiac dysfunction abnormality. Hypoxia is determining factor for Echocardiography abnormality as right heart dysfunction and proportionate number of left heart dysfunction were without hypoxia.

Serum cortisol abnormality documented in fair number of cases and very well correlated with left ventricular dysfunction abnormalities. These cases have shown excellent clinical and echocardiographic cardiac function improvement after treatment with steroids under cover of antituberculosis treatment regimen. Thus, abnormal serum cortisol is predictor of cardiac dysfunction and also timely management of adrenal suppression has recovered cardiac function to normal.

Cardiac dysfunction is reversible in majority of cases and proportionate number shown complete improvement in cardiac dysfunction. Favoring markers for near complete improvement were male gender and abnormal cortisol level. Never hesitate to give steroids even in advanced cases with ATT backup, which will significantly impact final outcome in both, TB and cardiac dysfunction.

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