Prevalence, clinical presentation and outcome of tuberculosis in patients with chronic kidney disease at a tertiary care hospital in Nepal

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Abstract

Background: Tuberculosis (TB) is a serious public health threat in low- and middle-income countries like Nepal. Chronic kidney disease (CKD) patients are at higher risk of developing new infection as well as reactivation of TB. We aimed to determine the prevalence, clinical presentations, and outcome of TB in patients with CKD in Nepal.

Methods: A hospital-based cross-sectional study was performed at Tribhuvan University Teaching Hospital (TUTH), a tertiary level referral centre in Kathmandu, Nepal. We included patients older than 16 years with the diagnosis of CKD stage 3, 4, 5, and 5D (CKD 5 on maintenance dialysis); renal transplant recipients and patients living with HIV/AIDS were excluded. Tuberculosis was diagnosed based on clinical, radiological and laboratory findings. Prior written informed consent was obtained. Approval was obtained from Institutional review Board of Institute of Medicine. Data entry and statistical analysis were performed using SPSS v21.

Results: A total of 401 patients with CKD were included in the study (mean age, 50.92 ±17.98 years; 64.8% male). The prevalence of TB in CKD patients was found to be 13.7% (55), out of which 49 were newly diagnosed cases. Most common clinical presentations of TB in CKD were anorexia (85.7%), fever (83.7%), weight loss (51%), and cough (49%). Thirty eight patients (69.1 %) had extrapulmonary TB (EPTB), 12 (21.8%) had pulmonary TB, 3 (5.5%) had disseminated TB and 2 (3.6%) had miliary TB. Only 4.1% cases were sputum smear positive. Pleural effusion (34.2%) was the most common EPTB. At 2 months of starting anti-tubercular therapy, 29 patients out of the 49 newly cases of TB (59.2%) had responded to therapy. Mortality at 2 months was 28.6% (14 died amongst 49 patients). Four out of 49 patients (8.2%) didn’t improve, and 2 (4%) patients were lost to follow up.

Conclusion: Prevalence and mortality of TB was higher in cohort of CKD. Special attention must be given to these people for timely diagnosis and treatment as the presentation is different and diagnosis can be missed.

Background

Chronic kidney disease (CKD) is a global health problem with estimate that it affects 8-16% of world's population.\textsuperscript{1, 2} It is a major public health problem in Nepal. It is estimated that the prevalence
of CKD is around 10.6% in urban areas of Nepal.\(^3\) Tuberculosis (TB) is the second most frequent cause of death from infectious disease worldwide and its control was one of the millennium development goal.\(^4\) In 2014, total 37,025 cases of TB were registered in Nepal. Most of the cases were reported in middle aged group, the highest among 15 to 24 year of age group. Among them 51% were pulmonary TB and 23% were extra pulmonary. In 2014, total death from TB was 1049. The overall treatment success rate (all forms) of drug susceptible TB was 91%, with 1.1% failure rate, 2% defaulted rate, and 3.3% death rate.\(^5\) The disease frequently leads to hospitalization, thus significantly increasing National Health Service cost. The incidence of active TB among patients on long-term dialysis is 10 to 25 times higher than that of the general population owing to the immunosuppressant effects of uremia.\(^6\) The rate varies according to regional factors; in developed countries, the incidence ranges in between 1.6% to 5.8%.\(^7\) The prevalence of tuberculosis in patients under maintenance dialysis has been reported to be 10.5 %\(^8\), 15%\(^9\) and 20%\(^10\) from India, Belgium and Berlin respectively. Diagnosing TB in CKD and dialysis patient can be complicated and difficult because of the increased frequency of extra-pulmonary involvement, which may result in atypical manifestations and non specific symptoms.\(^8,11\) An increased risk of TB in dialysis patient was first reported by Pradhan et al.\(^12\) in 1974. Impaired immune response in CKD patients may also lead to delayed response to therapy and increased mortality.\(^8,11\) Moreover, nutritional status, and vitamin D deficiency\(^13\) further contribute to impaired immunity in CKD patients. Given the globally increasing prevalence of CKD, a merger of CKD and TB epidemics could have significant public health implications in low- to middle-income countries like Nepal. In Nepal where the burden of TB is high, adequate data on TB in patients with CKD is not available. We set out to study the prevalence, clinical presentations and outcomes of TB in patients with CKD in a hospital set up.

Methods

Study design and setting
It was a hospital-based, descriptive, observational, cross sectional study conducted over a period of 12 months (June 2017 to May 2018) at Tribhuvan University Teaching Hospital (TUTH), Institute of Medicine (IOM), Nepal. TUTH is a 700 bedded tertiary care referral hospital located in the capital city, Kathmandu and provides multi-specialty health care services to patients from all 77 districts of Nepal.

Study methods

Patients attending the Nephrology Out Patient Department (OPD) and Hemodialysis ward and those admitted to the Internal Medicine and Nephrology wards of TUTH were included in the study. Ethical clearance for the study was obtained from the Institutional Review Board (IRB) of IOM. Written informed consent was taken from all the participants or their legal guardians if patients were under 18 years old. A total of 401 patients meeting the inclusion criteria were included in the study. A diagnosis of CKD was made by the treating physician or nephrologist based on KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease.\(^1\) Cases with confirmed CKD were evaluated and their stage of CKD was calculated using the CKD EPI equation.\(^{14}\) We included patients older than 16 years with the diagnosis of CKD stage 3, 4, 5, and 5D (CKD 5 on maintenance dialysis); renal transplant recipients and patients living with HIV/AIDS were excluded.

The diagnosis of tuberculosis was established by the treating physician or nephrologist based on clinical, radiological, microbiological, biochemical or histological findings. This study included TB cases which were already diagnosed by treating physician or nephrologist. Demographic profiles and clinical features were noted and laboratory and imaging results were recorded in the predesigned proforma. When calculating the prevalence of tuberculosis, the number of previously diagnosed cases and newly diagnosed cases were included. For the clinical features, we collected the current information; we followed up these cases until the duration of admission (if admitted) and until the duration of confirmation of TB diagnosis if they were in OPD and being evaluated for suspected TB.

CKD patients with newly diagnosed TB were followed at two month of starting anti-tubercular therapy (ATT). The patients and their relatives were advised to take/give ATT after dialysis only on the dialysis days. They were assessed at OPD by treating physician or nephrologist. Those patients who couldn’t
attend the OPD were followed via telephone by the researcher. These patients were assessed for improvement in their symptoms such as subsidence of fever and cough, overall improvement in the wellbeing, weight gain, increased appetite, improvement in strength and stamina, or improvement in dyspnea. Those requiring investigations to see for their improvement, for example: regression of lymph node size, pleural effusion, pericardial effusion, and ascites, disappearance of consolidation etc went for necessary investigations / assessments as decided by the primary care giver. Smear positive TB patients had a repeat acid fast bacilli (AFB) stain at completion of two months of ATT.

**Defining the case**

**Chronic kidney disease (CKD):** A diagnosis of CKD was made by the treating physician or nephrologist based on KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease (Details included in Supplementary material 2).

**Tuberculosis:** A diagnosis of tuberculosis was established by the treating physician or nephrologist based on clinical, radiological, microbiological, biochemical or histological findings (Details included in Supplementary material 3).

Definitions of the variables

The study variables like current smoker, alcohol consumption, diabetes mellitus, corticosteroid use, immunosuppressive use, and history of contact with TB were defined. (Details included in Supplementary material 4)

**Sample size**

Sample size was calculated by applying following formula:

Due to technical limitations, Equation 1 has been placed in the Supplementary Files section.

Where,

n= Number of sample required

z= Value of the normal deviated considered level of confidence (=1.96)
\( p_0 = \text{Reference proportion (taken as 0.1)} \)
\( p = \text{Proportion of interesting outcome (taken as 0.15)} \)
\( \alpha (\alpha) = \text{A significance level (taken as 0.05)} \)
\( \beta (\beta) = \text{A type II error probability (taken as 0.2)} \)
\( \epsilon = p - p_0 \)

Using above formula the sample size was estimated to be 401

Statistical analysis
Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables were expressed as frequency and percentage. Prevalence of TB in patients with CKD was calculated. A z-test was employed to compare the mean laboratory values between two groups (CKD patients with newly diagnosed TB and without TB). Bivariate analysis using Chi-square test was performed to establish the relationship between TB and its risk factors. Multivariate logistic regression analysis was performed for those variables that were significant in bivariate analysis to independently predict risk of TB. A p-value of < 0.05 was considered to be statistically significant. Data entry and statistical analysis were performed using SPSS 21 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.).

Results

**Demographic characteristics of the study population**

The mean age of the patients included in the study was 50.92 years (SD=17.98). There were 260 (64.8%) males; male to female ratio was 1.8:1. The demographic profile and etiology of CKD has already been published elsewhere, though chronic glomerulonephritis (36.2%), diabetes mellitus (31.9%), and hypertension (21.7%) were the top three causes of CKD.

**Prevalence of Tuberculosis in patients with CKD**

The prevalence of tuberculosis in patients with CKD was found to be 13.7% (55 out of 401). Out of 55 cases, 6 were previously diagnosed and were already under ATT, and 49 were newly diagnosed with tuberculosis. The proportion of CKD patient who developed TB was higher in stage 3 (16.7%), under
MHD for less than one year (41.9%), and session of MHD for one per week (33.3%) [Table 1].

**Clinical presentation of TB in patients with CKD**

The four most common clinical presentations were decreased appetite (85.7%), fever (83.7%), weight loss (51%) and cough (49%) [Table 2]. The duration of clinical presentations in 75.5% (n = 37) cases was more than or equal to two weeks and 24.5% (n = 12) cases was less than two weeks.

**Types of Tuberculosis in patients with CKD**

Extrapulmonary TB (EPTB), (69.1%; n= 38) was more common than pulmonary TB (PTB), (21.8%; n= 12), followed by disseminated TB (5.5%; n= 3), and miliary tuberculosis (3.6%; n= 2) [Figure 1]. The most common EPTB was tubercular pleural effusion (34.2 %; n=13), followed by TB lymphadenitis (18.4%; n=7), abdominal TB (13.2%, n=5), TB pericardial effusion (13.2%; n=5), renal TB (5.3%, n=2), TB meningitis (7.5%; n=3), pott’s spine (5.3%, n=2), and TB of middle ear cavity (2.6%, n=1) [Figure 2].

The mean duration of CKD diagnosis was 23.46 months (SD=23) in patients with TB, compared to 15.7 months (SD=21.8) in CKD patients without TB; this difference was statistically significant (p-value 0.02).

**Diagnosis of tuberculosis in patient with CKD**

In the newly diagnosed cases of tuberculosis (n= 49), 23 (46.9%) were diagnosed by analysis of body fluid (ascitic, pleural, pericardial and CSF), 14 (28.6%) by clinical presentations and radiological findings, 6 (12.2 %) by FNAC or biopsy, 2 (4.1%) by Urine AFB; which was further confirmed by urine PCR for *Mycobacterium tuberculosis*, 2 (4.1%) by sputum AFB examination, and 2 (4.1 %) by sputum geneXpert. Taken together, there were only six (12.3%) bacteriologically confirmed cases of tuberculosis.

**Analysis of risk factors associated with tuberculosis**

On bivariate analysis, we found that corticosteroid, immunosuppressive drugs, and history of contact with TB patients were risk factors for TB compared with their control group without TB (p < 0.05). However, we didn’t find statistically significant correlation of TB with smoking, and alcohol (p > 0.05).
On multivariate logistic regression analysis, we found that only history of contact with TB patients (OR: 0.4, 95% CI: 0.2-0.7, p=0.004), and corticosteroid use (OR: 5.7, 95% CI: 2.2-14.8, p < 0.001) were independent predictors for development of tuberculosis. Details of the risk factors associated with TB is represented in Table 4.

**Comparison of laboratory parameters of CKD patients with and without tuberculosis**

We observed that intact parathyroid hormone (iPTH) was lower and corrected calcium was higher in the newly diagnosed cases of tuberculosis compared to control group without TB (p < 0.05). CKD patients with TB tended to be more anemic, had lower level of vitamin D and serum albumin compared to CKD patients without TB, though these did not reach statistical significance (p > 0.05) [Table 5].

**Chest imaging (chest radiograph or CT scan chest) in CKD patients with tuberculosis**

Out of 49 newly diagnosed cases of TB, 16 (32.7%) had normal chest imaging. The most common abnormal finding was pleural effusion (n=8, 16.3%). Findings of chest imaging are shown in Table 6.

**Tuberculin skin test (TST) in CKD patients with tuberculosis**

TST was positive (> 5mm) only in nine patients (18.4%).

**Analysis of body fluid (pleural, ascitic, cerebrospinal, and pericardial)**

On analysis of body fluid it was found that, total leukocyte count was increased with monomorph predominance. Mean protein, and ADA were found to be elevated. Analysis of body fluid is shown in Table 7.

**Outcome of CKD patients with tuberculosis at two months of starting ATT**

Out of 49 newly diagnosed cases of TB, 29 (59.2%) patients improved at 2 months of starting ATT, 4 (8.2%) didn’t improve, 14 (28.6%) died during 2 months of starting ATT and 2 (4%) patients were lost to follow up [Figure 3].

**Outcome of TB patients at two months of starting ATT as per different types of TB**

Seventy percent of the patients with pulmonary tuberculosis improved at two months of ATT compared with 62% extrapulmonary TB cases. None amongst the three cases of disseminated TB
improved at two months, while one of the two cases of miliary TB improved and the other one died at two months of starting ATT. The outcomes of TB patients as per different types of TB are presented in Table 8.

The proportion of TB patients who improved at 2 months of ATT was higher in CKD stage 5D (20 out of 31; 64.5%), patients presenting with duration of symptoms for ≥ 2 weeks before diagnosis of TB (24 out of 31; 64.9%), patients receiving MHD for 6 months to one year (6 out of 8; 75%), patients who were not under corticosteroid (26 out of 41; 63.4%) or immunosuppressive drugs (27 out of 46; 58.7%), and patients without history of diabetes mellitus (23 out of 36; 63.9%). Similarly, the mortality in TB patients at 2 months of ATT was higher in CKD stage 4 (4 out of 7; 57.1%), patients presenting with duration of symptoms for < 2 weeks before diagnosis of TB (4 out of 12; 33.3%), patients receiving MHD for more than one year (2 out of 7; 28.5%), patients under corticosteroid (5 out of 8; 62.5%) or immunosuppressive drugs (1 out of 3; 33.3%), and patients with history of diabetes mellitus (4 out of 13; 30.8%) [Table 9].

Discussion

CKD is one of the modern day epidemics of increasing public health importance globally. Prevalence of tuberculosis is still high in developing countries, which are associated with significant morbidity and mortality. Cases of treatment resistant tuberculosis are increasing. Immunodeficiency is a feature of CKD, making these patients more susceptible to reactivation of TB or new infection. The prevalence of tuberculosis in patients under maintenance dialysis has been reported to be 10.5 %, 15% and 20% from India, Belgium and Germany respectively.

Patients under MHD living in low and low-middle income are at increased risk of developing active tuberculosis compared to their counterparts in developed countries. A report from Australia showed that the incidence of TB in CKD patients under MHD was significantly higher in patients born in the highest TB incidence countries (698 per 100,000 per year) compared to those born in low TB incidence countries (18 per 100,000 per year). This is because, active TB results from reactivation of latent tuberculosis infection (LTBI) acquired before dialysis initiation rather than from recent
exposure and infection. In our study we found the prevalence of TB in patients with CKD was 13.7%, which is higher than that reported from India, though paradoxically lower to those reported from Belgium and Germany. The TB rates in dialysis patients are higher than they are in the general population. A low threshold for suspicion and diagnosis of tuberculosis in CKD patients would be warranted.

Cough and hemoptysis, the classic symptoms of TB in the general population, are less frequently reported in dialysis patients. In this study we discovered varied clinical presentation of tuberculosis: decreased appetite (85.7%), fever (83.7%), weight loss (51%), cough (49%), dyspnea (46.9%), chest pain (20.4%), and hemoptysis (4.1%) [Table 2]. These features may be attributed to inadequate dialysis, volume overload, uremic symptoms or complication of hemodialysis in patients with CKD and this may lead to delay in the diagnosis and treatment of TB ultimately leading to worse prognosis.

Diagnosis of TB is more complex and difficult in dialysis patients because of atypical clinical presentations, non-specific symptoms, and increased frequency of extrapulmonary involvement. In our study, extrapulmonary TB was found in 38 patients (69.1%); this observation is consistent with other several other studies conducted in India and Turkey. In general population pulmonary tuberculosis is more common than the extrapulmonary; however in patients with CKD the ratio is reversed. High prevalence of extrapulmonary TB in patient with CKD is due to impaired cellular immunity with poorly formed granuloma. Different studies have found that the most common form of extrapulmonary TB in patients with CKD is TB lymphadenitis. However, in our study, we found that TB pleural effusion was the predominant type of extrapulmonary TB seen in 34.2% cases amongst all extrapulmonary TB cases followed by TB lymphadenitis in 18.4%. Similar finding was reported in a prospective study performed in India by Rao et.al.

Tuberculosis in patients with CKD remains a diagnostic challenge. In the current study, sputum for AFB was found to be positive only in 4.1% of cases. Tuberculosis was diagnosed in two patients
(4.1%) by urine AFB examination and two patients (4.1 %) by sputum geneXpert. Taken together, there were only six (12.3%) bacteriologically confirmed cases of tuberculosis.

The main modality of TB diagnosis was based on pathological and biochemical analysis of body fluid (46.9%), which must have required good amount of clinical judgment without established solid scientific rationale. Since pathological and biochemical analysis of fluid is not available in every centre, it is more challenging to find and treat TB in CKD patients in the peripheries of low income countries like Nepal. Initial screening with chest imaging seems to be a good investigation modality for the screening of tuberculosis in patients with CKD as 63.7% of CKD patients with TB had abnormal chest imaging in our study. It is highly recommended that the global medical community must put in extra effort and resources to discover newer diagnostic modalities to make definite diagnosis of tuberculosis.

We discovered that the prevalence TB was higher in the patients who had received MHD for less than one year (41.9%). Several studies have reported a high frequency of TB cases discovered in the first year of dialysis; this has been attributed to the poor general health at the start of dialysis when host immunity might be most profoundly depressed.24

On bivariate analysis, we found that corticosteroids, immunosuppressive drugs, and history of contact with TB patient were risk factors for TB. On multivariate logistic regression analysis, we found that only history of contact with TB patients and corticosteroid use was independent predictors of TB. A study done by Chagas et al. discovered that history of contact with TB patient was present in 80% of the patients with latent TB infection.27 Similarly, corticosteroid as risk factor for TB was found in study of Jick et al.28 These findings could suggest for isolation of active cases of TB till sputum conversion and judicial use of corticosteroids in advanced stages of glomerulonephritis weighing the risks and benefits of therapy. However, we didn’t find statistically significant association of TB with smoking, and alcohol consumption.

The mean age of TB diagnosis in our study was found to be 44 year, which is comparable to other studies conducted by Unsal et al.25, El Kabbaj et al. 29 and Hussein et al.30 This young age of TB
patients in our study was because the mean age of CKD patients in our study was 50.92 years. However several other studies showed that hemodialysis patients aged greater than 65 years were at the highest risk of developing TB.\textsuperscript{31} The reasons appears to be that, the detection of latent TB infection by tuberculin skin test (TST) is masked as advanced age is known to be associated with decreased delayed type of hypersensitivity.\textsuperscript{32, 33} CKD patients with TB were found to be more anemic, had lower level of serum albumin and serum vitamin D compared to CKD patients without TB, though these did not reach statistical significance (p > 0.05) [Table 5]. This observation compares with a recent observational study from United States which concluded that lower serum albumin is one of the risk factor for TB.\textsuperscript{34} A meta-analysis done by Huang SJ et.al\textsuperscript{35} showed that vitamin D deficiency is a risk factor for TB. This is because activated vitamin D is required for interferon-γ mediated antimicrobial activity of macrophages against \textit{M. tuberculosis}.\textsuperscript{36}

In a study conducted by Ravi et al., TST was found to be positive 16% patients of end stage renal disease (ESRD) which is significantly lower than in the general population (44%).\textsuperscript{37} The reason being T-cell dysfunction in ESRD for TST-hypo responsiveness. In the present study, we found that TST was positive (>5 mm induration considered positive) in only 18.4% of TB cases.

In the present study, out of the 49 newly diagnosed cases of tuberculosis, 29 patients (59.2%) improved at 2 months of starting ATT, 4 (8.2%) didn’t improve, 14 (28.6%) died during 2 months of starting ATT and 2 (4%) patients lost the follow up [Figure 3]. This response rate to ATT is very low compared to the general population and the early death rate is very high.\textsuperscript{5} Mortality rate was relatively higher in miliary TB (one out of two patients died), and disseminated TB (one out of three patients died).

The proportion of TB patients who improved at 2 months of ATT was higher in CKD stage 5D (20 out of 31; 64.5%), patients presenting with duration of symptoms for ≥ 2 weeks before diagnosis of TB (24 out of 31; 64.9%), patients receiving MHD for 6 months to one year (6 out of 8; 75%), patients not under steroid (26 out of 41; 63.4%) or immunosuppressive drugs (27 out of 46; 58.7%), and patients
without history of diabetes mellitus (23 out of 36; 63.9%). Similarly, mortality in TB patients at 2 months of ATT was higher in CKD stage 4 (4 out of 7; 57.1%), patients presenting with duration of symptoms for < 2 weeks before diagnosis of TB (4 out of 12; 33.3%), patients receiving MHD for more than one year (2 out of 7; 28.5%), patients who were under steroid (5 out of 8; 62.5%) or immunosuppressive drugs (1 out of 3; 33.3%), and patients with history of diabetes mellitus (4 out of 13; 30.8%) [Table 9]. The unusual finding of higher proportion of response rate in patients presenting with duration of symptoms for ≥ 2 weeks before diagnosis of TB and higher mortality in patients presenting with duration of symptoms for < 2 weeks before diagnosis of TB in our study could have occurred by a chance because of small sample size.

Studies from the early years of dialysis and some recent reports suggested a high mortality of 17-75% in hemodialysis patients with tuberculosis. The delayed diagnosis and treatment played a major role in some instances. In other cases, the mortality was apparently not caused by the TB itself or its treatment, however, by co-morbid conditions. There are reports of favorable outcome in studies done in Saudi Arabia, most likely due to early diagnosis and treatment. This suggests that if timely diagnosis and intervention is done, patients of CKD with TB can have better outcome in terms of improved survival and quality of life, which in turn will reduce the hospital stay and total health care costs.

To the best of our knowledge, this is the first study of its kind from Nepal. The study has included a reasonable size, nationally representative cohort of CKD patients attending a tertiary care hospital in Nepal. Meticulous documentation of the various sociodemographic profiles, clinical features, investigations findings and associated medical treatment details followed by rigorous statistical analysis and elaborated discussion of the findings comparing with contemporary literature has been done. The follow up period of two months for patients initiated on ATT, with only two patients lost to follow up is good. The high prevalence of tuberculosis in CKD, its risk factors, varied and atypical presentations, diagnostic challenges and limitations compounded by high initial mortality even in treated cases as demonstrated in this study demands for further large scale discussions and
researches in the field of tuberculosis in general and TB in CKD in particular.

Since the study was a cross sectional, we couldn't calculate the incidence of tuberculosis in patients with CKD. We evaluated the patients with TB for clinical improvement at two months and assessed their mortality during this period. However, we couldn’t assess their overall response and mortality at the completion of ATT. Since the majority of the diagnosis of TB was clinical, the diagnosis can always be questioned especially when nearly 40% of the patients given ATT either did not respond to therapy or died. The actual cause of death in CKD patients with TB could not be assessed, and from the current study we can’t say whether this high mortality is due to TB itself or because of other co-morbidities. Further, issues related to clearance of ATT drugs during hemodialysis could not be ascertained. Adherence to therapy could not be stringently verified since the majority of the patients received modified ATT drug dosages due to their renal function and this regimen was not provided by DOTS scheme of Nepal. Two patients were lost to follow up; so, their clinical improvement at two months of starting ATT couldn’t be assessed.

Conclusions
Prevalence of tuberculosis in Nepalese patients with CKD was higher compared to that in the general population. Extrapulmonary TB was more common than pulmonary TB; tubercular pleural effusion was the most common form of extrapulmonary tuberculosis. Decreased appetite, fever, weight loss, and cough were the four most common presenting symptoms. At two months of treatment, only 59.2% cases of tuberculosis responded to ATT. More than a quarter (28.6%) of CKD patients with diagnosis of tuberculosis died within two months.

We conclude that tuberculosis should be considered in the differential diagnosis of any CKD patient presenting with nonspecific symptoms such as anorexia, fever and weight loss. An empirical trial with anti tubercular medication is justified (especially in endemic areas) in strong clinical suspects if timely definitive diagnosis is not possible. We recommend larger scale, multicenter, multinational studies on tuberculosis in CKD and request the scientific community to develop better tools to confirm diagnosis of tuberculosis.

References
1. Levin A, Stevens PE, Bilous RW, Coresh J, De Francisco AL, De Jong PE, Griffith KE, Hemmelgarn BR, Iseki K, Lamb EJ, Levey AS. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney International Supplements. 2013 Jan 1;3(1):1-50.

2. Jha V, Garcia-Garcia G, Iseki K, Li Z, Naicker S, Plattner B, Saran R, Wang AY, Yang CW. Chronic kidney disease: global dimension and perspectives. The Lancet. 2013 Jul 20;382(9888):260-72.

3. Sharma S, Dhakal S, Thapa L, Ghimire A, Tamrakar R, Chaudhary S, Deo R, Manandhar D, Perico N, Perna A, Remuzzi G. Community-based screening for chronic kidney disease, hypertension and diabetes in Dharan. Journal of the Nepal Medical Association. 2013;52(189):205-12.

4. Stalker P. Millenium development goals. Nigerian Journal of Clinical Practice. 2008;14(3):318-21.

5. National Tuberculosis Program Nepal Annual Report 2014 [Internet]. National TB Center-TB Free Nepal. Government of Nepal Ministry of Health Department of Health Services National Tuberculosis Center; 2014 AD [cited 2018Mar1]. Available from: http://nepalntp.gov.np/wp-content/uploads/2018/03/Final-Annual-Report-NTPN-2018.pdf.

6. Chia S, Karim M, Elwood RK, FitzGerald JM. Risk of tuberculosis in dialysis patients: a population-based study. The International Journal of Tuberculosis and Lung Disease. 1998 Dec 1;2(12):989-91.

7. Levey AS, Coresh J. Chronic kidney disease. The Lancet. 2012 Jan 14 ; 379:165-80.

8. Rao TM, Ram R, Swarnalatha G, Pai BS, Ramesh V, Rao CS, Naidu GD, Dakshinamurty KV. Tuberculosis in haemodialysis patients: A single centre experience. Indian journal
9. Wauters A, Peetermans WE, Van den Brande P, De Moor B, Evenepoel P, Keuleers H, Kuypers D, Stas K, Vanwallegem J, Vanreenterghem Y, Maes BD. The value of tuberculin skin testing in haemodialysis patients. Nephrology Dialysis Transplantation. 2004 Feb 1;19(2):433-8.

10. Pilsczek, Florian H. Kaufmann, Stefan H.E. Prevalence and predictors of positive tuberculin skin test results in a research laboratory. Revista da Sociedade Brasileira de Medicina Tropical. 2008 Aug;41(4):416-8.

11. Lundin AP, Adler AJ, Berlyne GM, Friedman EA. Tuberculosis in patients undergoing maintenance hemodialysis. The American journal of medicine. 1979 Oct 1;67(4):597-602.

12. Pradhan RP, Katz LA, Nidus BD, Matalon R, Eisinger RP. Tuberculosis in dialyzed patients. Jama. 1974 Aug 12;229(7):798-800.

13. Nnoaham KE, Clarke A. Low serum vitamin D levels and tuberculosis: a systematic review and meta-analysis. International journal of epidemiology. 2008 Feb 1;37(1):113-9.

14. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J. A new equation to estimate glomerular filtration rate. Annals of internal medicine. 2009 May 5;150(9):604-12.

15. National Tuberculosis Center. National Tuberculosis Program Clinical Manual, 2074. Government of Nepal, Ministry of Health, Department of Health Service, National Tuberculosis Centre, Thimi, Bhakatapur 2074.

16. Ray S, Talukdar A, Kundu S, Khanra D, Sonthalia N. Diagnosis and management of miliary tuberculosis: current state and future perspectives. Therapeutics and clinical risk management. 2013;9:9.
17. Ponniah S. Monitoring tobacco use in New Zealand. A technical report on defining smoking status and estimates of smoking prevalence. Ministry of Health; 2008.

18. American Diabetes Association. Introduction: standards of medical care in diabetes—2018.

19. Jick SS, Lieberman ES, Rahman MU, Choi HK. Glucocorticoid use, other associated factors, and the risk of tuberculosis. Arthritis Care & Research: Official Journal of the American College of Rheumatology. 2006 Feb 15;55(1):19-26.

20. Sigdel MR, Pradhan RR. Chronic Kidney Disease in a Tertiary Care Hospital in Nepal. JIOM 2018;40:104-11.

21. Hill NR, Fatoba ST, Oke JL, Hirst JA, O’Callaghan CA, Lasserson DS, Hobbs FR. Global prevalence of chronic kidney disease—a systematic review and meta-analysis. PloS one. 2016 Jul 6;11(7):e0158765.

22. Sharma A, Hill A, Kurbatova E, van der Walt M, Kvasnovsky C, Tupasi TE, Caoili JC, Gler MT, Volchenkov GV, Kazennyy BY, Demikhova OV. Estimating the future burden of multidrug-resistant and extensively drug-resistant tuberculosis in India, the Philippines, Russia, and South Africa: a mathematical modelling study. The Lancet Infectious Diseases. 2017 Jul 1;17(7):707-15.

23. Romanowski K, Clark EG, Levin A, Cook VJ, Johnston JC. Tuberculosis and chronic kidney disease: an emerging global syndemic. Kidney international. 2016 Jul 1;90(1):34-40.

24. Hussein MM, Mooij JM, Roujouleh H. Tuberculosis and chronic renal disease. InSeminars in dialysis 2003 Jan (Vol. 16, No. 1, pp. 38-44). Malden, US: Blackwell Science Inc.

25. Unsal A, Ahbap E, Basturk T, Koc Y, Sakaci T, Arar AS, Kayabasi H, Sevinc M. Tuberculosis in dialysis patients: a nine-year retrospective analysis. The Journal of
Infection in Developing Countries. 2013 Mar 14;7(03):208-13.

26. Kayabasi H, Sit D, Kadiroglu AK, Kara IH, Yilmaz ME. The prevalence and the characteristics of tuberculosis patients undergoing chronic dialysis treatment: experience of a dialysis center in southeast Turkey. Renal failure. 2008 Jan 1;30(5):513-9.

27. Chagas AC, Hans Filho G, Oliveira SM, Ivo ML, Corrêa Filho RA, Donatti MI. Prevalence of latent tuberculosis and treatment adherence among patients with chronic kidney disease in Campo Grande, State of Mato Grosso do Sul. Revista da Sociedade Brasileira de Medicina Tropical. 2014 Apr;47(2):204-11.

28. Jick SS, Lieberman ES, Rahman MU, Choi HK. Glucocorticoid use, other associated factors, and the risk of tuberculosis. Arthritis Care & Research: Official Journal of the American College of Rheumatology. 2006 Feb 15;55(1):19-26.

29. El Kabbaj D, Bahadi A, Oualim Z. Prevalence of tuberculosis in hemodialysis patients. Saudi Journal of Kidney Diseases and Transplantation. 2010 Jan 1;21(1):164.

30. Hussein MM, Bakir N, Roujouleh H. Tuberculosis in patients undergoing maintenance dialysis. Nephrology Dialysis Transplantation. 1990 Jan 1;5(8):584-7.

31. Christopoulos AI, Diamantopoulos AA, Dimopoulos PA, Goumenos DS, Barbalias GA. Risk factors for tuberculosis in dialysis patients: a prospective multi-center clinical trial. BMC nephrology. 2009 Dec;10(1):36.

32. Dworsky R, Paganini-Hill A, Arthur M, Parker J. Immune responses of healthy humans 83-104 years of age. Journal of the National Cancer Institute. 1983 Aug 1;71(2):265-8.

33. Yung RL. Changes in immune function with age. Rheumatic disease clinics of North America. 2000 Aug 1;26(3):455-73.

34. Klote MM, Agodoa LY, Abbott KC. Risk factors for Mycobacterium tuberculosis in US
chronic dialysis patients. Nephrology Dialysis Transplantation. 2006 Sep 12;21(11):3287-92.

35. Huang SJ, Wang XH, Liu ZD, Cao WL, Han Y, Ma AG, Xu SF. Vitamin D deficiency and the risk of tuberculosis: a meta-analysis. Drug design, development and therapy. 2017;11:91.

36. Fabri M, Stenger S, Shin DM, Yuk JM, Liu PT, Realegeno S, Lee HM, Krutzik SR, Schenk M, Sieling PA, Teles R. Vitamin D is required for IFN-γ-mediated antimicrobial activity of human macrophages. Science translational medicine. 2011 Oct 12;3(104):104ra102-.

37. Ravi Shankar MS, Aravindan AN, Sohal PM, Kohli HS, Sud K, Gupta KL, Sahuja V, Jha V. The prevalence of tuberculin sensitivity and anergy in chronic renal failure in an endemic area: tuberculin test and the risk of post-transplant tuberculosis. Nephrology Dialysis Transplantation. 2005 Sep 27;20(12):2720-4.

38. Chou KJ, Fang HC, Bai KJ, Hwang SJ, Yang WC, Chung HM. Tuberculosis in maintenance dialysis patients. Nephron. 2001;88(2):138-43.

39. Taskapan H, Utas C, Oymak FS, Gülmez I, Ozesmi M. The outcome of tuberculosis in patients on chronic hemodialysis. Clinical nephrology. 2000 Aug;54(2):134-7.

40. Al-Homrany M. Successful therapy of tuberculosis in hemodialysis patients. American journal of nephrology. 1997;17(1):32-5.

Abbreviations
ACR : Albumin creatinine ratio
ADA : Adenosine deaminase
AER : Albumin excretion rate
AFB : Acid fast bacilli
ATT : Anti-tubercular therapy
CKD : Chronic kidney disease
| Abbreviation | Full Form |
|--------------|-----------|
| CKD-EPI      | CKD-Epidemiology Collaboration |
| CSF          | Cerebrospinal fluid |
| CT           | Computed Tomography |
| DOTS         | Directly Observed Treatment, Short Course |
| EPTB         | Extra-pulmonary tuberculosis |
| ESRD         | End stage renal disease |
| FNAC         | Fine needle aspiration cytology |
| GFR          | Glomerular filtration rate |
| HIV          | Human Immunodeficiency Virus |
| IOM          | Institute of Medicine |
| iPTH         | intact parathyroid hormone |
| IRB          | Institutional Review Board |
| JIOM         | Journal of Institute of Medicine |
| KDIGO        | Kidney Disease Improving Global Outcomes |
| LDH          | Lactate dehydrogenase |
| LTBI         | Latent TB infection |
| MDR-TB       | Multi drug resistant TB |
| MHD          | Maintenance Hemodialysis |
| MRI          | Magnatic Resonance Imaging |
| OPD          | Out Patient Department |
| PCR          | Polymerase chain reaction |
| SD           | Standard Deviation |
| TB           | Tuberculosis |
| TST          | Tuberculin skin test |
| TUTH         | Trib huvan University Teaching Hospital |
| USG          | Ultrasonography |
| ZN           | Ziehl Neelsen |
Declarations

Ethics approval and consent to participate:

It was approved by Institutional Review Board (IRB) of Institute of Medicine (IOM), Tribhuvan University Teaching Hospital, Kathmandu, Nepal on 7th June, 2017. Ref no: 381 (6-11-E)^2/073/074. Prior written informed consent was taken from all the participants or their legal guardians if patients were under 18 years old after explaining the nature and purpose of the study.

Consent to publish:

Not applicable.

Availability of data and materials:

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The research work was submitted to library, IRB, and department of Internal Medicine of IOM, TUTH as a part of thesis. The demographic profile and etiology of CKD has already been published in Journal of Institute of Medicine (JIOM), vol40, issue2, August 2018. The abstract was presented on 14th International Conference of Society of Internal Medicine of Nepal (SIMON) held from May 2 to 4, 2019 at Kathmandu, Nepal.

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RRP and MRS conceived the study; RRP and MRS participated in the design; RRP collected the data; and RRP and MRS performed statistical analyses. RRP and MRS drafted the manuscript. RRP and MRS edited and checked the manuscript. All of the authors have read and approved the final manuscript.

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Tables

Table 1: Prevalence of TB in different groups
| Parameters          | Total number of CKD patients | Number of CKD patients with TB | Within prevalence (%) |
|---------------------|-----------------------------|--------------------------------|-----------------------|
| CKD stage           |                             |                                |                       |
| Stage 3             | 18                          | 3                              | 16.7                  |
| Stage 4             | 51                          | 8                              | 15.7                  |
| Stage 5             | 108                         | 9                              | 8.3                   |
| Stage 5D            | 224                         | 35                             | 15.6                  |
| Duration of Dialysis|                             |                                |                       |
| Less than 6 month   | 172                         | 17                             | 9.9                   |
| Six month to one year| 25                          | 8                              | 32                    |
| More than one year  | 27                          | 10                             | 37                    |
| Session of MHD per week |                    |                                |                       |
| One                 | 3                           | 1                              | 33.3                  |
| Two                 | 207                         | 32                             | 15.5                  |
| Three               | 10                          | 2                              | 20                    |

Table 2: Clinical presentation of TB in patients with CKD (n=49)

| Clinical presentation | Frequency | Percentage |
|-----------------------|-----------|------------|
| Decreased appetite    | 42        | 85.7       |
| Fever                 | 41        | 83.7       |
| Weight loss           | 25        | 51         |
| Cough                 | 24        | 49         |
| Dyspnea               | 23        | 46.9       |
| Chest pain            | 10        | 20.4       |
| Hemoptysis            | 2         | 4.1        |
| Others                | 7         | 14.3       |

Table 3: Risk factors associated with tuberculosis

| Parameters          | Number of patient with TB (%) | Number of patient without TB (%) | Total |
|---------------------|-------------------------------|---------------------------------|-------|
| Condition                        | Yes                | No      | Statistic | P-value |
|---------------------------------|--------------------|---------|-----------|---------|
| Smoking                         | 29 (14.2)          | 26 (13.2) | 204       |         |
| Alcohol                         | 28 (13.5)          | 27 (14)  | 207       |         |
| Corticosteroid                  | 10 (24.4)          | 45 (12.5) | 41        | <0.01   |
| Immunosuppressive drugs         | 4 (36.4)           | 51 (13)  | 11        | <0.01   |
| History of contact with TB patient | 16 (25.8) | 39 (11.5) | 62        |         |
| Diabetes mellitus               | 13 (10.2)          | 42 (15.4) | 128       |         |
*p-value was calculated using Chi-square test

Table 4 : Risk factors associated with tuberculosis

| Parameters                              | OR  | 95% CI       | p-value |
|-----------------------------------------|-----|--------------|---------|
| Diabetes mellitus                       | 1.6 | 0.8-3.2      | 0.2     |
| History of contact with TB patient     | 0.4 | 0.2-0.7      | 0.004   |
| Corticosteroid                          | 5.7 | 2.2-14.8     | <0.001  |
| Immunosuppressive drugs                 | 0.5 | 0.09-2.3     | 0.333   |

Table 5 : Laboratory parameters of CKD patients with and without tuberculosis
| Parameters                              | CKD with TB (n=49) | CKD without TB (n=346) | *p-value |
|----------------------------------------|--------------------|------------------------|----------|
| Hemoglobin (gm/dL)                     | 8.21               | 8.6                    | 0.1      |
| Hematocrit (%)                         | 26.46              | 26.91                  | 0.55     |
| Total leukocyte count (per microlitre) | 10267              | 8679                   | 0.04     |
| Urea (mmol/L)                          | 26.36              | 27.27                  | 0.61     |
| Creatinine (umol/L)                    | 752.83             | 781.1                  | 0.64     |
| iPTH (pg/dL)                           | 251.43             | 328.61                 | 0.036    |
| Phosphorus (mg/dL)                     | 4.76               | 4.61                   | 0.65     |
| Vitamin D (ng/dL)                      | 24.45              | 28.48                  | 0.06     |
| Uric acid (umol/L)                     | 425.12             | 448.92                 | 0.34     |
| Albumin (gm/L)                         | 31.69              | 33.40                  | 0.06     |
| Corrected calcium (mmol/L)             | 2.02               | 1.92                   | 0.02     |
*p-value was calculated using Z-test

Table 6: Chest imaging in CKD patients with tuberculosis

| Chest imaging                                      | Frequency | Percentage |
|----------------------------------------------------|-----------|------------|
| Normal                                             | 16        | 32.7       |
| Pleural effusion                                   | 8         | 16.3       |
| Consolidation                                      | 1         | 2.0        |
| Bilateral pulmonary infiltrate                     | 4         | 8.2        |
| Consolidation with effusion                        | 5         | 10.2       |
| Unilateral infiltrate                              | 2         | 4.1        |
| Miliary pattern                                    | 2         | 4.1        |
| Fibrosis in upper lobe with mediastinal lymphadenopathy | 4     | 8.2        |
| Pericardial Effusion                               | 5         | 10.2       |
| Consolidation with tree in bird appearance         | 1         | 2.0        |
| Lung Abscess                                       | 1         | 2.0        |
| Total                                              | 49        | 100        |

Table 7: Findings of body fluid analysis in patients with TB and CKD

| Parameters (Mean) | Pleural fluid (n=12) | Ascitic fluid (n=4) | Cerebrospinal fluid (n=3) | Pericard (n=4) |
|-------------------|----------------------|---------------------|---------------------------|---------------|
| Total leukocyte count per uL | 1835 | 583 | 402 | 4910 |
| Polymorph (%)    | 37       | 27      | 10       | 21        |
| Monomorph (%)    | 63       | 73      | 90       | 79        |
| Protein (gm/L)   | 33.3     | 34      | 29       | 25.2      |
| LDH (U/L)        | 522      | 277     | -        | -         |
| Sugar (mmol/L)   | 9        | 7.5     | 5.1      | 10.4      |
| ADA (U/L)        | 32.4     | 28      | 11       | 31.2      |

Table 8: Outcome of TB patients at two months of starting ATT as per different types of tuberculosis
| Outcome                  | Pulmonary TB (%) | Extrapulmonary TB (%) | Disseminated TB (%) | Miliary TB (%) | Total |
|--------------------------|------------------|-----------------------|---------------------|----------------|-------|
| Improved                 | 7 (70)           | 21 (62)               | 0 (0)               | 1 (50)         | 29    |
| Not improved             | 0 (0)            | 2 (6)                 | 2 (67)              | 0 (0)          | 4     |
| Mortality                | 3 (30)           | 9 (26)                | 1 (33)              | 1 (50)         | 14    |
| Lost to follow up        | 0 (0)            | 2 (6)                 | 0 (0)               | 0 (0)          | 2     |
| Total                    | 10               | 34                    | 3                   | 2              | 49    |

Table 9: Factors affecting outcome of TB patients at two months of starting ATT
| Parameters                                  | Improved (%) | Not improved (%) | Mortality (%) | Lost to follow up (%) |
|---------------------------------------------|--------------|------------------|---------------|-----------------------|
| Duration of symptoms before TB diagnosis    |              |                  |               |                       |
| < 2 weeks                                   | 5 (41.7)     | 2 (16.7)         | 4 (33.3)      | 1 (8.3)               |
| ≥ 2 weeks                                   | 24 (64.9)    | 2 (5.4)          | 10 (27)       | 1 (2.7)               |
| CKD stage                                   |              |                  |               |                       |
| Stage 3                                     | 2 (66.7)     | 0 (0)            | 1 (33.3)      | 0 (0)                 |
| Stage 4                                     | 3 (42.9)     | 0 (0)            | 4 (57.1)      | 0 (0)                 |
| Stage 5                                     | 4 (50)       | 0 (0)            | 3 (37.5)      | 1 (12.5)              |
| Stage 5D                                    | 20 (64.5)    | 4 (13)           | 6 (19.3)      | 1 (3.2)               |
| Duration of MHD                             |              |                  |               |                       |
| Less than 6 months                          | 11 (68.8)    | 2 (12.5)         | 2 (12.5)      | 1 (6.2)               |
| 6 months to 1 year                          | 6 (75)       | 0 (0)            | 2 (25)        | 0 (0)                 |
| More than one year                          | 3 (43)       | 2 (28.5)         | 2 (28.5)      | 0 (0)                 |
| Session of MHD per week                     |              |                  |               |                       |
| One                                         | 0 (0)        | 1 (100)          | 0 (0)         | 0 (0)                 |
| Two                                         | 19 (65.5)    | 3 (10.4)         | 6 (20.7)      | 1 (3.4)               |
| Three                                       | 1 (100)      | 0 (0)            | 0 (0)         | 0 (0)                 |
| History of contact with TB patient          |              |                  |               |                       |
| Yes                                         | 10 (66.7)    | 0 (0)            | 3 (20)        | 2 (13.3)              |
| No                                          | 19 (55.8)    | 4 (11.8)         | 11 (32.4)     | 0 (0)                 |
| Corticosteroid                              |              |                  |               |                       |
| Yes                                         | 3 (37.5)     | 0 (0)            | 5 (62.5)      | 0 (0)                 |
| No                                          | 26 (63.4)    | 4 (9.8)          | 9 (22)        | 2 (4.8)               |
| Immunosuppressive drugs                     |              |                  |               |                       |
| Yes                                         | 2 (66.7)     | 0 (0)            | 1 (33.3)      | 0 (0)                 |
| No                                          | 27 (58.7)    | 4 (8.7)          | 13 (28.3)     | 2 (4.3)               |
| Diabetes mellitus                           |              |                  |               |                       |
| Yes                                         | 6 (46.2)     | 2 (15.4)         | 4 (30.8)      | 1 (7.6)               |
| No                                          | 23 (63.9)    | 2 (5.6)          | 10 (27.8)     | 1 (2.7)               |

Figures
Figure 1

Types of tuberculosis in patients with CKD (n=55)
Figure 2

Types of extrapulmonary TB in patients with CKD (n=38)
Figure 3

Outcome of CKD patients with tuberculosis at two months of starting ATT (n=49)

Supplementary Files

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Equation 1.png