Prevalence, risk factors and Impact of Post-transplant Tuberculosis on Live Donor Kidney Transplant Recipients: A Retrospective Study

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ABSTRACT

Background: TB is encountered worldwide more frequently among renal transplant recipients than in the general population. It is reported to be nearly 50 times higher in the renal transplant population because of immunosuppression. TB may arise from unrecognized infection in the allograft or acquisition of new infection after transplantation. **Objective:** The aim of the current work was to determine prevalence and risk factors for development post-transplant TB, and the impact of post-transplant TB in live donor renal transplantation on both patient and graft survival. **Patients and methods:** This retrospective cohort study carried out in the Nephrology Unit, Mansoura Urology and Nephrology Centre in Association with Nephrology Unit, Zagazig University Hospitals in the period between January 2020 to December 2020. Included 210 patients out of 3200 kidney transplant recipients (KTRs) who underwent renal transplantation in the period between March 1976 and December 2019, divided into 2 main groups according to development of post-transplant tuberculosis, a group of 70 (KTRs) who developed tuberculosis after transplantation served as a study group and a matched group of 140 (KTRs) who did not develop tuberculosis after transplantation served as control group and evaluation of two groups through risk factor to develop TB, demographical data, clinical, laboratory and radiological evaluation. After that TB group was subdivided into 2 groups according to the site of infection: pulmonary and urinary TB. **Results:** Body mass index was higher among control group with statistically significant difference. Associated medical disorders as post-transplant diabetes, post-transplant bacterial and CMV infection had higher incidence among TB group. Liver enzymes and calcineurin (CNI) levels showed statistically significant difference among TB group before and during anti tuberculous treatment, in which liver enzymes were elevated while CNI levels were significantly reduced during antituberculous treatment. Post- transplant CMV infection was higher in patients who developed pulmonary TB. Graft and patient survival were comparable among both groups with no significant difference. **Conclusions:** It could be concluded that post-transplant diabetes, bacterial and CMV infections increase risk of development of post-transplant TB. There was no effect of post-transplant tuberculosis on both patient and graft survival.

Keywords: Post transplant tuberculosis, Live donor, Kidney transplantation.

INTRODUCTION

For the majority of patients with end-stage kidney disease, kidney transplantation is the treatment of choice. Patients and health-care providers benefit from long-term transplantation because mortality is lower than with maintenance dialysis and quality of life is improved also the annual cost of transplantation is substantially less than that of dialysis [1].

TB is encountered worldwide more frequently among renal transplant recipients than in the general population. It is reported to be nearly 50 times higher in the renal transplant population because of immunosuppression [2].

The total TB incidence rate in Egypt was 12 (11–14) per 100,000 people according to the World Health Organization estimates of TB burden, 2018. Screening, diagnosis, notification, and registration of TB cases were implemented all over Egypt according to the National TB Strategy of the National Tuberculosis Control Program (NTP) [3].

In developed countries, the prevalence of active tuberculosis among transplant patients has ranged from 1.2 to 6.4 percent but has been as high as 10 to 15 percent in endemic regions [4].

TB is most transmitted from the donor allograft to the recipient as a result of reactivation of latent infection in the recipient, but it can also occur as a result of unrecognized infection in the allograft or acquisition of new infection after transplantation. There have been numerous reports of TB transmission from the donor allograft to the recipient, particularly when the donor country of origin is endemic for TB [5].

TB can also emerge as a result of a higher risk of contracting a new Mycobacterium tuberculosis infection, which can quickly proceed to miliary TB due to immunosuppressive therapy. Because the symptoms and indicators of latent and active TB in donors and transplant recipients are ambiguous, the diagnosis is readily disregarded unless there is a high degree of suspicion of TB. Transplant patients' tuberculosis clinical picture is claimed to differ from that of the normal population, with an increased prevalence of extrapulmonary tuberculosis [6].

Antituberculosis drugs act as a double-edged weapon despite treating tuberculosis, they cause

enzyme induction that increase the metabolism of almost all immunosuppressive drugs and though decrease the plasma trough level which expose the transplant recipient to the risk of rejection [7].

In this study we aimed to determine prevalence, risk factors and impact for development of post-transplant tuberculosis (TB) in live donor renal transplantation on both patient and graft survival.

PATIENTS AND METHODS

This retrospective cohort study included a total of 210 patients out of 3200 kidney transplant recipients (KTRs) who underwent renal transplantation in the period between March 1976 and December 2019. The study was carried out in the nephrology unit, Mansoura Urology and Nephrology Centre in Association with Nephrology Unit, Zagazig University Hospitals in the period between January 2020 to December 2020.

Patients were divided into 2 main groups according to history of post-transplant tuberculosis:
I. Control group: (140 KTRs) with no history of post-transplant tuberculosis (TB).
II. Study group: (70 KTRs) with history of post-transplant tuberculosis (TB).

The TB group was subdivided into 2 subgroups according to the site of infection:
I. Urinary TB (42 KTRs): Positive urine culture for TB bacilli.
II. Pulmonary TB (28 KTRs): Positive sputum culture.

Our study included (KTRs) Living with functioning graft at least for 6 months post transplantation. From our work we excluded Recipients who lost their grafts in the first 6 months, lost follow up for more than 3 months, age less than 16 years old or refused to participate in this study.

The transplant registry was reviewed for the following:
Pre-operative details:
Demographic data as recipient age, sex and BMI, donor age, sex and consanguinity, causes of end stage renal disease, dialysis duration, pre- transplant medical disorders like hypertension, diabetes mellitus and chronic liver disease, Immunologic data as regard HLA and DR mismatching, History and number of blood transfusion and History of tuberculosis.

Operative details: ischemia time and time to diuresis.
Post-operative details: Induction immunosuppressive drugs, Maintenance immunosuppressive protocol, Frequency of acute and chronic rejection episodes etc.
Transplant preparation: In addition to routine work up, both donor and recipient were evaluated for TB by Tuberculin test, urinary Ziehl-Neelsen, TB PCR, and/or Quantiferon test.

Induction immunosuppression: Patients received different regimens of induction therapy as Antithymocyte globulin (ATG) (1.5 mg/kg/day administered by IV infusion for 7 to 14 days), Basiliximab (Simulect) (20 mg infused over 20-30 minutes by central or peripheral intravenous administration. The first 20 mg dose given within 2 hours prior to transplantation surgery. The recommended second 20 mg dose given 4 days after transplantation), Alemtuzumab (Campath 1-H) (60 mg by slow IV infusion on day zero).

Maintenance immunosuppression:
All recipients received different regimens of immunosuppression as Cyclosporine-based protocol, Alemtuzumab (Campath) protocol, Sirolimus-based protocol Tacrolimus-based Protocol.

Graft function:
During hospitalization, renal function was monitored daily by: *Serum creatinine*, *Urine analysis*, *Serum bilirubin*, *Serum ALT*, *Fasting blood sugar*: *Complete blood picture*, Estimation of calcineurin inhibitors (tacrolimus or cyclosporine) trough level in Blood Sonographic examination and Histopathological examination of the graft biopsy in cases of graft dysfunction.

Criteria for suspicion of TB:
Patients with relevant clinical manifestations (cough lasting more than two weeks, lymphadenopathy, fevers, night sweats, weight loss) and epidemiologic factors (history of prior TB infection or disease, known or possible TB exposure, and/or past or present residence in or travel to an area where TB is endemic).

Also, TB suspicion was made if there is sterile pyuria (urinary TB) and /or apical lung patches by chest radiology (pulmonary TB).

Diagnosis of post-transplant TB:
Urinary TB was diagnosed based on the results of acid-fast stain and TB PCR in 3 urine samples collected over 3 consecutive days. Pulmonary TB was diagnosed based on the results of acid-fast stain and TB PCR in 3 sputum samples collected over 3 consecutive days. In some cases, diagnosis was confirmed by QuantiFERON-TB (QFT).

Treatment of TB:
Pre-transplantation TB. Patients first received a complete course of anti-tuberculous therapy for at least 9 months and bilateral nephroureterectomy in cases of urinary TB.

In case of post-transplant TB: isoniazid (5mg/kg/day, max 300mg/day), rifampin (10mg/kg/day, max 600mg/day) or (5mg/kg/day, max 300mg/day), pyrazinamide (40-55 kg: 1000mg, 56-

75kg: 1500 mg, 76-90kg: 2000mg {use lean bodyweight}), and ethambutol (15-20mg/kg/day, max 1.6 g/day) for the first 2 months (intensive phase) followed by isoniazid and rifampin daily alone for an additional 4 months (continuation phase).

Fluoroquinolones including moxifloxacin (400mg/day no renal modification) and levofloxacin (500-1000mg/day needs renal modification) were used as second-line agents for active TB treatment in transplant patients who have hepatotoxicity on standard TB therapy or who have poor liver function.

Pyridoxine (vitamin B6) 25-50 mg/d was given with INH to all persons at risk of neuropathy and 100 mg/d to all persons on ethionamide.

Treatment of latent TB:

Isoniazid (INH) for 9 months given daily, Pyridoxine (vitamin B6) 25-50 mg/daily, 4-month course of rifampin monotherapy. If Isoniazid was started pre-transplant, it was held peri-transplant and resumed when the patient became in a stable condition and able to take oral medications.

Ethical consent:

An approval of the study was obtained from Mansoura University academic and ethical committee. Every patient signed an informed written consent for acceptance of the operation.

This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

Qualitative data were displayed in cross tabulation and quantitative data were described in terms arithmetic mean ± SD (standard deviation). Bivariate techniques were used for initial evaluation of contrasts. Thus, the chi-square and fisher's exact test were used for comparisons of frequencies of qualitative variables; the Mann-Whitney test and the unpaired t-test were used for comparisons of means of two quantitative variables. A p-value <0.05 was considered significant.

Graft and patient survival rates were assessed using Kaplan-Meier method. Significant variables in the univariate analysis were further analyzed in the multivariate to determine those who act independently (p<0.05). All analysis was carried out using the computer package SPSS for windows: An IBM Company, version 22, IBM Corporation, Armonk, NY, USA.

RESULTS

There was no statistically significant difference among both groups regarding age and sex of the recipient and donor. Body mass index in TB group was significantly lower in study group**.**

Transplantation from live related donors was predominant in both groups with no statistical significance and the cause of end-stage renal disease in the majority of both groups was unknown **(Table 1)**.

Table (1): Demographic data among studied groups.

		Control group (140 KTRs)	TB group (70 KTRs)	P-value
Recipient age (years)	Mean ±SD	31.3 ±9.9	31.7±11.2	0.54
Recipient Sex	Male	105 (75%)	55 (78.6%)	
	Female	35 (25%)	15 (21.4%)	0.56
Recipient BMI	Mean ±SD	29.3±1.3	21.6±0.9	**0.023***
Donor age (years)	Mean ±SD	37.2 ±10.5	36.3±10	0.51
Donor Sex	Male	68 (48.6%)	27 (38.6%)	
	Female	72 (51.4%)	43 (61.4%)	0.17
Consanguinity	Related	120 (85.7%)	61 (87.1%)	
	Unrelated	20 (14.3%)	9 (12.9%)	0.77

KTRs: Kidney transplant recipients, SD: Standard Deviation.

Prevalence of hypertension, diabetes, and hepatitis B and C infection and Urinary TB and pulmonary TB incidence before transplantation was comparable. The majority of patients in both groups received hemodialysis before transplantation for variable duration and the difference was statistically insignificant.

The difference between both groups regarding either HLA class I or 2 mismatches was of no statistical significance. No statistically significant difference among both groups regarding donor-recipient blood groups difference.

Comparable percent of population in both groups received blood transfusion before transplantation. There was no statistically significant difference among both groups regarding ischemia time and time to diuresis. No statistically significant difference among both groups regarding type of induction therapy or primary plan of immunosuppression.

Exposure to rejection episodes (either acute or chronic) is comparable among both groups. Also, both groups showed no statistical significance regarding incidence of acute tubular necrosis **(Table 2)**.

Table (2): Rejection episodes.

		Control group (140 KTRs) No. (%)	TB group (70 KTRs) No. (%)	P-value
Acute rejection:	No Hyper-acute Acute cellular rejection Vascular rejection	87 (62.1%) 1 (0.7%) 50 (35.7%) 2 (1.4%)	39 (55.7%) 0 (0%) 30 (42.9%) 1 (1.4%)	0.69
Number of rejection episodes:	0 1-2 3-4	66 (47.1%) 60 (42.8%) 14 (10.1%)	31 (44.3%) 30 (42.8%) 9 (12.9%)	0.74
Acute tubular necrosis	Yes No	8 (5.7%) 132 (94.3%)	6 (8.6%) 64 (91.4%)	0.43
Chronic rejection	Yes No	33 (23.6%) 107 (76.4%)	19 (27.1%) 51 (72.9%)	0.57

KTRs: Kidney Transplant Recipients

Post-transplant medical complications incidence including hypertension, gastro-intestinal troubles and malignancy (Kaposi's sarcoma) was comparable among both groups.

While, Post-transplant diabetes incidence was higher among TB group with statistically significant difference. CMV and Bacterial infection incidence including pneumonia, urinary tract infection and gastroenteritis were associated with higher incidence of TB with statistically significant difference.

There was no statistically significant difference among both groups regarding incidence of surgical complications including bleeding, hematomas, wound dehiscence, lymphocele and vascular problems. Incidence of wound infection post-transplantation was higher among TB group with statistically significant difference **(Table 3)**.

Table (3): Post-transplant medical complications.

		Control group (140 KTRs) No. (%)	TB group (70 KTRs) No. (%)	P-value
Time of TB diagnose after transplantation (months)	Mean± SD		45.3±13.2	
Hypertension	Yes No	78 (55.7%) 62 (44.3%)	41 (58.6%) 29 (41.4%)	0.69
Diabetes	Yes No	18 (12.9%) 122 (87.1%)	19 (27.1%) 51 (72.9%)	**0.01***
Hepatic impairment	Yes No	19 (13.6%) 121 (86.4%)	10 (14.3%) 60 (85.7%)	0.88
Pancreatitiss	Yes No	2 (1.4%) 138 (98.6%)	0(0%) 70 (100%)	0.31
Bacterial infection	Yes No	14(10%) 126(90%)	16(22.9%) 54(77.1%)	**0.012***
CMV infection	Yes No	1 (0.7%) 139 (99.3%)	4 (5.7%) 66 (94.3%)	**0.02***
Malignancy (Kaposi's sarcoma)	Yes No	4(2.9%) 136 (97.1%)	6(8.6%) 64 (91.4%)	0.067

KTRs: Kidney Transplant Recipients

Serum creatinine over 5 years after transplantation did not show any difference of statistical significance among the studied groups. Despite the number and percent of patients who were alive with functioning graft at last follow up were higher in the control group, the difference was statistically insignificant. Similar percent of patients were alive with failed graft and comparable percent was dead either with functioning graft or with failed graft. Among the study group there were two main groups of patients suffering from pulmonary TB (28 patients) and urinary TB (42 patients) there was no statistically difference between two groups regarding baseline characteristics, medical conditions and immunosuppressive medications. CMV infection incidence was significantly higher among pulmonary TB groups **(Table 4)**.

Table (4): Differences between pulmonary and urinary TB among the study group (TB group).

	Urinary TB (KTRs) No. (%)	Pulmonary TB (KTRs) No (%)	P-value
Number	42 (60%)	28(40%)	
Age (mean±SD)	33.4±11.1	29±11.02	0.12
Sex (male)	34 (81%)	21 (75%)	0.55
Pre-transplant pulmonary TB	1 (0.02%)	3 (3.5%)	0.54
Pre-transplant urinary TB	2 (4.76%)	0	0.5
Type of induction:			
ATG	5 (11.9%)	2 (7.1%)	
Basiliximab	18 (42.9%)	13 (46.4%)	0.8
Maintenance immunosuppression:			
Triple therapy	23 (54.8%)	13 (46.4%)	0.49
Steroid-based	32 (76.14%)	20 (71.4%)	0.78
Cyclosporine-based	20 (47.6%)	12 (42.9%)	0.69
Tacrolimus-based	15 (35.7%)	12 (42.9%)	0.54
Mycophenolate-based	15 (35.7%)	12 (42.9%)	0.54
Azathioprine-based	23 (54.8%)	11 (39.3%)	0.20
Post-transplant medical complications:			
CMV infection	0	4 (14.2%)	**0.02***
Bacterial infection	9 (21.4%)	7 (25%)	0.7
Acute rejection	19 (45.2%)	11 (39.3%)	0.43
ATN	4 (9.5%)	2 (7.1%)	0.72
Chronic rejection	11 (26.2%)	8 (28.6%)	0.82

CMV cytomegalovirus, KTRs: Kidney Transplant Recipients

Liver enzymes and Calcineurin (CNI) levels show statistical significant difference among study group (TB group) before, during antituberculous treatment and after treatment, in which liver enzymes were elevated and CNI levels were low during treatment. No statistically significant difference among TB group and control group regarding 5, 10and 15 years graft and patient survival (**Figures 1 and 2**).
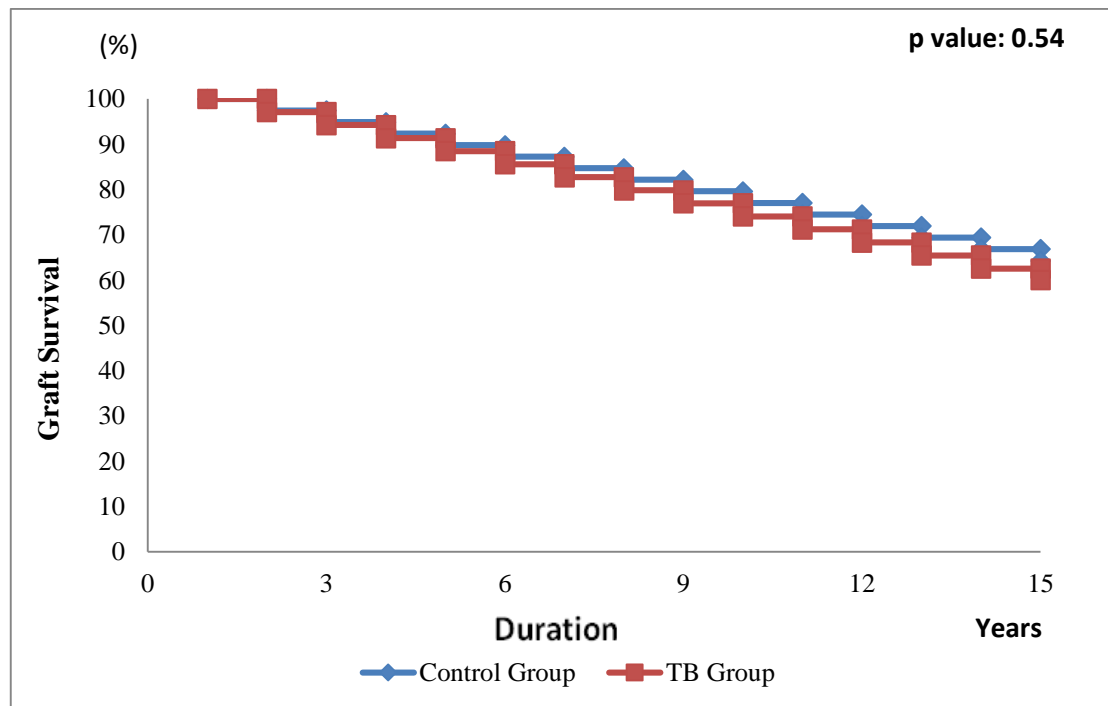

Figure (1): Kaplan-Meyer curve show no statistically significant difference regarding 5-, 10- and 15-years graft survival among control and TB groups.
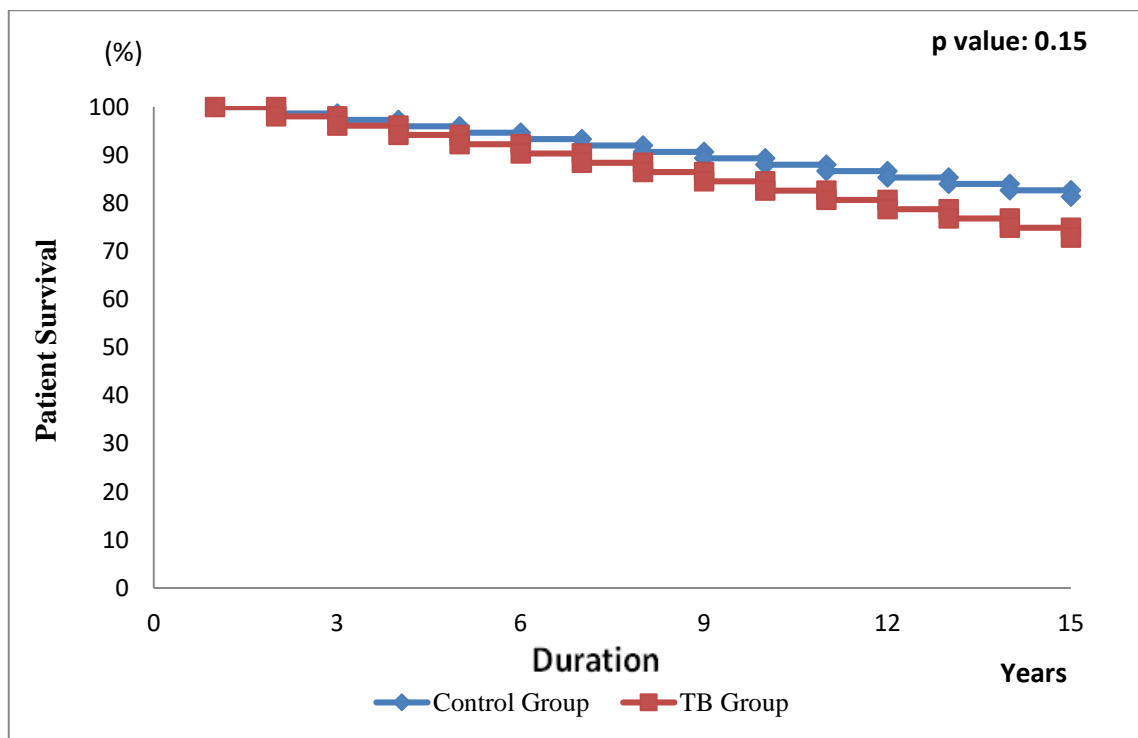
Figure (2): Kaplan-Meyer show no statistically significant difference regarding 5, 10 and 15 years patient survival among control and TB groups.

DISCUSSION

Our study is a retrospective cohort study concerned with the impact of post-transplant TB on live donor kidney transplant recipients.

The incidence of post-transplant TB varies from 0.5-1% in the USA [8] to 1-4% in Europe [9], whereas up to 11% have been reported from developing countries [10]. In our study, of 3200 live donor renal allograft recipients, 70 patients developed post-transplant TB with an incidence of 2.1%, which is moderately high probably because of the relatively high frequency of TB in Egypt. This was also reported by El-agroudy et al. [7].

In our study there was no significant difference regarding age and sex of recipients, and age, sex and consanguinity of donors of both groups. This is parallel to the results by Ha et al. [11] and Meinerz et al. [12]. On the other hand, Chen et al. [13] reported higher TB incidence among males.

Also, BMI was higher in control group. These results are parallel to Casha and Scarci [14]. However, Rungruanghiranya et al. [15] found no association between BMI and TB incidence.

Regarding original kidney disease there was no statistically significant differences between the two groups, in agreement with Meinerz et al. [12].

Our study showed that there was no statistical significance between two groups regarding pre-transplant medical conditions, this is consistent with the results of Marques et al. [16] and Jung et al. [17]. However, these results are inconsistent with Davies [18] and Chen et al. [13] who showed that pre-transplant diabetes increases risk of post-transplant TB two to four folds to normal people, also hemodialysis increases risk 10 to 15 folds.

Regarding immunological workup before transplantation there was no difference between two groups, the results are matched with John et al. [19] and Jung et al. [17], whereas HLA mismatch isn't a risk factor for TB infection in kidney transplantation.

In the current study, there is no difference among both group regarding blood transfusion. These results are inconsistent with Machado and Levi [20] who reported blood-borne transmission of TB.

Immunosuppressive therapy is thought to be the most important factor associated with the development of tuberculosis in transplant recipients [21, 22]. Our results show no statistically significant difference among both groups regarding type of immunosuppressive protocols, these results are parallel to the results of Marques et al. [16]. But this is against Agarwal et al. [23] who showed that cyclosporin increases risk of post-transplant TB.

in our study there was no difference among the groups regarding either acute or chronic rejection episodes, In agreement with **Qunibi** *et al.* [24], **Lopez and Schluger** [25] **and Ha** *et al.* [11] but It was reported that acute rejection episodes were more common in TB group by **Marques** *et al.* [16] **and Agarwal** *et al.* [23].

The time to onset of TB symptoms post-transplantation varies. Some investigators have found a bimodal distribution. The majority of their cases appeared early during the first 12 months post-transplantation [24, 26]. However in our study majority of cases developed TB within (2-4) years after transplantation, this was also reported by **El-Agroudy** *et al.* [7].

Our study also showed that post-transplant bacterial infections including pneumonia, urinary tract infections and wound infections were significantly higher in TB group, this was also reported by **Ha** *et al.* [11], **John** *et al.* [19], **Lattes** *et al.* [27] **and Currie** *et al.* [28].

In this study, the mean serum creatinine over 5 years post-transplantation showed no significant difference between TB group and control group. Similar findings were reported by **Marques** *et al.* [16].

In our study despite that the number and percent of patient who were alive with functioning graft at last follow up were higher in control group, the difference was statistically insignificant .Similar percent of patients was alive with failed graft and comparable percent were dead either with functioning graft or with failed graft. Also, there was no statistically significant difference between both groups on long term graft and patient survival.

Our results are parallel to the results of **El-agrody** *et al.* [7] **and arques** *et al.* [16] as careful management of immunosuppression allowed graft survival. In contrast graft and patient survival were significantly low in post-transplant TB cases as reported by **Meinerz** *et al.* [12] where the patients in Meinerz *et al.* died within 6 months and had more severe disease. Their atypical presentation could have delayed the diagnosis and initiation of treatment. Most patients who lost their grafts already had chronic dysfunction, and kidney function was gradually decreasing after treatment.

Our results showed a similar distribution of TB among transplant recipients as was emphasized by **Rubin** [29], urinary TB was the predominant site of infection(60%)(42 patients)and 40% suffered from pulmonary TB(28 patients).

Our results showed no statistically significant difference between two groups (urinary and pulmonary TB) regarding baseline characteristics, medical conditions and immunosuppressive medications. However post- transplant CMV infection was higher in patients who developed pulmonary TB as reported by **Ha** *et al.* [11].

In our cohort study, there were 5 patients suffered from pre-transplant pulmonary TB. All of them received treatment before transplantation. One patient did not develop TB after transplantation. Three patients developed post-transplant pulmonary TB and 1 patient developed urinary TB.

Also, 5 patients treated from urinary TB before transplantation. Three patients did not develop TB after transplantation. While, 2 patients suffered from post-transplant urinary TB. Despite that all of these patients who had pretransplant TB were maintained on INH for 1-year post-transplant.

Post-transplant TB patients (70 patients) received four-drug anti-tuberculous regimen for 2 months then INH and isoniazid for additional 4 months. Response to treatment was assessed clinically and laboratory by Acid-fast stain and TB PCR. Five patients needed hospital admission due to respiratory distress. 2 patients died during treatment course with no response to treatment. 16 patients suffered from graft impairment during treatment due to either state of infection or fluctuation of immunosuppressive trough levels. And one of them passed to graft failure.

Antituberculus drugs, especially rifampicin and isoniazid are associated with distinct problems in transplant recipients. Our results showed that liver enzymes were significantly elevated in TB group during antituberculus treatment. As the most common adverse effect of antituberculosis therapy in transplant recipients is hepatotoxicity, resulting from direct hepatic cell injury, which is most often attributed to isoniazid or rifampin. Similar findings were reported by **Meinerz** *et al.* [12] **and Marques** *et al.* [16] **and van Hest** *et al.* [30].

The study has limitations being retrospective and lack of randomization also number who developed post-transplant tuberculosis was small.

CONCLUSION

It could be concluded that BMI before transplantation, development of post-transplant diabetes, bacterial and CMV infections increase risk of development post-transplant TB.

Antituberculous treatment cause elevation of liver enzymes and reduction in calcineurin levels so higher doses are needed in order to maintain stable blood levels in kidney transplant recipients. CMV infection increase risk of pulmonary TB. There was no effect of post-transplant tuberculosis on both patient and graft survival we have moderate prevalence level of post-transplant TB.

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