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MINIREVIEWS

Solid organ transplantations and COVID-19 disease

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Abstract

Tens of thousands of people worldwide became infected with severe acute respiratory syndrome coronavirus-2. Death rate in the general population is about 1%-6%, but this rate rises up to 15% in those with comorbidities. Recent publications showed that the clinical progression of this disease in organ recipients is more destructive, with a fatality rate of up to 14%-25%. We aimed to review the effect of the pandemic on various transplantation patients. Coronavirus disease 2019 (COVID-19) has not only interrupted the lives of waiting list patients'; it has also impacted transplantation strategies, transplant surgeries and broken donation chains. COVID-19 was directly and indirectly accountable for a 73% surplus in mortality of this population as compared to wait listed patients in earlier years. The impact of chronic immunosuppression on outcomes of COVID-19 remains unclear but understanding the immunological mechanisms related to the virus is critically important for the lifetime of transplantation and immune suppressed patients. It is hard to endorse changing anti-rejection therapy, as the existing data evaluation is not adequate to advise substituting tacrolimus with cyclosporine during severe COVID-19 disease.

Key Words: COVID-19; SARS-CoV-2; Solid organ transplantation; Mortality; Immunosuppression; Comorbidity

Core Tip: Coronavirus disease 2019 (COVID-19) has not only interrupted the lives of waiting list patients'; it has additionally impacted transplantation policies, transplant surgeries and broken donation chains. Revised guidelines should advise to continue cyclosporine use as an immunosuppressant to the patients during COVID-19 disease excluding some of patients having kidney failure, severe leucopenia or high serum cyclosporine levels.

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INTRODUCTION

Introduction and aim

Tens of thousands of people worldwide became infected with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)[1]. When the disease is clinically symptomatic; it presents with fever, cough, lymphopenia, dyspnea and, multiorgan failure in severe cases[2]. Death rate in the general population is about 1%-6%, but this rate rises up to 15% in those with comorbidities[3]. Current publications showed that the clinical progression of this disease in organ recipients is more destructive, with a fatality rate of up to 14%-25%. We aimed to review the effect of the pandemic on various transplantation patients[4].

Negative effects of coronavirus disease 2019 in increasing waiting list of organ transplantations

Coronavirus disease 2019 (COVID-19) has not only interrupted waiting list patients' lives; it has also affected transplantation strategies, transplant surgeries and broken donation chains. COVID-19 was directly and indirectly accountable for a 73% surplus in mortality of this population as compared to wait listed patients in former years[5].

High COVID-19 afflicted areas observed more than a 2.2 times greater waiting list fatality as compared to prepandemic mortality in the United States[6]. In the United Kingdom, 10% of wait listed patients who developed COVID-19 died[7]. In France, as many as 42% of wait listed deaths in March and April 2020 were caused by COVID-19 [5].

Kidney transplant waiting list deaths increased by 43%, the largest in any solid organ transplantation (SOT) patient group on the waiting list[8,9]. In perspective, there was a 12% increase in deaths in patients on the lung transplant waiting list, an 8% increase in deaths on a liver transplant waiting list, and a 36% increase in deaths in patients on a heart transplant waiting list[10].

Transplant and waiting list patients have similar death rates after admission to the hospital for COVID-19 disease. A study has demonstrated a low absolute fatality risk from COVID-19 in transplanted and waitlisted cases, but a high and similar death rate when admitted to the hospital, of around 30%. Death rate was higher in elderly transplant recipient cases[11].

UNDESIRABLE EFFECTS OF IMMUNOSUPPRESSION ON COVID-19 IN TRANSPLANTATION PATIENTS

The impact of chronic immunosuppression on outcomes of COVID-19 remains unclear but understanding the immunological mechanisms related to the virus is critically important for the lifetime of transplantation and immune suppressed patients.

Given the reduced T-cell immunity, transplant recipients are estimated to be at a greater risk for serious bacterial and viral infections. The difficult problem is when a coronavirus-infected immunosuppressed and SOT patient is taking either intravenous immunoglobulin (IVIG), steroids, calcineurin inhibitors or mycophenolic acid. SOT itself covers various clinical conditions/issues resulting from kidney, liver, heart and lung transplantations (Table 1).

Angiotensin-converting enzyme-2 and dipeptidyl peptidase, expressed in proximal tubular cells, are identified as receptors for SARS-CoV and MERS-CoV[12]. The possible explanation for acute renal injury is the uptake of SARS-CoV-2 virus into the proximal tubular epithelium and virus infection inducing CD68+ -macrophage infiltration and enhancing complement C5b-C9 deposition on tubules[13].

Acute renal injury is one of the most common complications of COVID-19. It was seen in 30%-89% of patients with kidney transplantation. Acute renal injury has developed as a result of many factors like decreased renal perfusion and cytokine storm[14]. To date, minimizing the utilization of antivirals and immunosuppressive

Table 1 Therapeutic agents used during solid organ transplantation period and their side effects

Agents	Mechanism	Side effects
IVIG	Reduces HLA sensitivity. The goal of the IVIG therapy is to lower the level of HLA antibodies and limit their ability to attack a transplanted organ	Headache, fever, urticaria, eczema, hypotension, anaphylactic shock, TRALI, immune thrombocytopenic purpura. Delayed side effects: Renal impairment, transfusion related infection
Glucocorticosteroids	Mimic the effects of cortisol side effects block T-cell derived and antigen presenting cell derived cytokine expression	Hypertension, hirsutism, susceptibility to infection, osteoporosis, necrosis, insulin resistance, growth retardation
Calcineurin inhibitors (cyclosporine, tacrolimus)	Inhibition the key signaling phosphatase calcineurin, which is an enzyme that activates T-cells of the immune system	Nephrotoxicity, promoting of the *de novo* cancers, metabolic disorders such as diabetes, dyslipidemia, gingival hyperplasia, hirsutism, hypertension, susceptibility to infection
Antiproliferative agents (Mycophenolic acid, azathioprine)	Inhibiting purine base synthesis and arresting T- and B-cell proliferation	Nausea, sleep disturbance, headache, constipation, diarrhea, weakness, fever, hematuria
mTOR inhibitors (sirolimus, everolimus)	Alternative for calcineurin inhibitors and antiproliferatives. T-cell proliferation inhibition. Binds to the specific cytosolic protein FKBP-12	Hypertension, hyperlipidemia, anemia or thrombocytopenia, headache, proteinuria, interstitial lung disease, mouth ulcers
Azathioprine	Decrease DNA and RNA synthesis reduce the production of lymphocytes	Nausea, hepatotoxicity, leukopenia, thrombocytopenia, malignancies

FKBP: FK506 (tacrolimus) binding protein; IVIG: Intravenous immunoglobulin; TRALI: Transfusion related acute lung injury; mTOR: Mechanistic target of rapamycin.

therapy has been recommended, but the evidence has been weak to support these recommendations[1]. Hypothetically, conversion to cyclosporine, in kidney transplant patients with COVID-19 has both antiviral potency and immunomodulatory effects; it may also help to avoid graft rejection during the infection[1].

Several studies have reported that immunosuppression may be a possible risk factor for coronavirus-related pneumonia in a patient[13]. For kidney transplant recipients diagnosed with SARS-CoV-2, it may be reasonable to use cyclosporine because of its antiviral and immune modulatory effects[13]. According to various clinical studies, severe pneumonia has been more widely reported in patients receiving anti-rejection and induction therapies, possibly due to immunosuppression[15].

The management of heart transplant recipients becomes more complex as these heart transplant patients require more intense immunosuppression than other SOT recipients[16]. In addition to the present complexity, COVID-19 has a potential effect on both primary and secondary myocardial injuries[17]. These cases are constantly utilizing long-term immunosuppressive therapy and at a high risk to develop unwanted effects. Although they have adequate heart function, this population must be thought of as very brittle owing to the existence of several comorbidities like chronic renal disease associated with a long exposure to immunosuppressants. In a transplanted cases' cohort, time-dependent comorbidities along with older age, such as calcineurin inhibitor nephrotoxicity and other common complications of immunosuppressive management, could also be harmful[18].

Transplant recipients are thought by some authors as a high-risk group for COVID-19 since they take lifetime immunosuppressive treatment. Immunomodulatory agents could improve immune reaction, but this could yield to an escalation in viral load and postponed disease salvage. Remarkably, calcineurin inhibitors, the most commonly used immunosuppressive agent in lung transplant recipients, have shown impressive capacities to inhibit the replication of coronaviruses. Therefore, it was suggested that basic immunomodulation could defend lung transplant patients against the most severe clinical pictures of COVID-19 disease[19].

Calcineurin inhibitors, antimetabolites, and glucocorticosteroids are the most commonly used as standard immunosuppressants; nonetheless, in COVID-19 confirmed patients, antimetabolites were generally stopped while prescription of glucocorticosteroids was continued in management or even amplified in dosage. It was thought as essential to use suitable doses of glucocorticosteroids through the process, as it could subdue hyperinflammatory reaction and stimulate the recovery from pneumonia without severe unwanted effects[20].

Impact of co-infections (fungal) with COVID-19 in transplantation patients

Impact of co-infections (bacterial or viral) with COVID-19 disease in SOT patients

could be severe and lethal. To the best of our knowledge, specific co-infections (bacterial or viral) related with SARS-CoV-2 in SOT patients have not been widely reported. However, SARS-CoV-2 might raise the risk of invasive pulmonary aspergillosis (İPA) development in these patients. Although several case reports and small series have been described in the literature, infrequent information is obtainable concerning COVID-19-related İPA in SOT cases. A case of a renal SOT recipient with severe COVID-19 was later diagnosed with IPA. After beginning of isavuconazole with nebulized liposomal amphotericin B combination treatment and the withdrawal of immunosuppression, İPA was improved[21].

Other risk factors for COVID-19 development and mortality in transplantation patients

SOT cases with COVID-19 had a tendency to greater mortality compared with non-SOT controls, although it was not always found to be statistically significant[20,22]. Immunosuppression and comorbidities might put SOT patients at a higher risk from COVID-19, as proposed by new case series[23]. In the overall literature, some factors were shown to be independently related with COVID-19 which included non-white race and comorbidities, comprising obesity, diabetes, asthma and chronic obstructive pulmonary disease[24]. Nevertheless, no factors were demonstrated to be related with fatality, other than being elderly in those who had been transplanted[11].

A few studies have clearly compared consequences between SOT and non-SOT patients with COVID-19 disease. A retrospective matched cohort single-center study evaluated effects of COVID-19 and the effect of immunomodulation on cytokine release syndrome of COVID-19 in SOT patients. Overall, SOT recipient cases had equal fatality to non-SOT cases, although more SOT cases received tocilizumab (63% *vs* 48%) and steroids (37% *vs* 20%)[25]. In another study, 45 SOT *vs* 2427 non-SOT cases hospitalized with COVID-19 to a health-care system were compared. There were no statistically meaningful differences between SOT and non-SOT in maximum illness severity score, length-of- stay, or mortality. Regardless of a greater risk profile, SOT recipients had a significantly faster drop in disease severity over time compared with non-SOT cases[23]. Chaudhry *et al*[26] compared consequences of 35 SOT cases with 100 non-SOT cases that were admitted with COVID-19 at a single center, and detected that a combined consequence [intensive care units (ICU) admission, intubation, hospital fatality] was similar between these 2 groups, even though comorbidities and acute renal damage were more usual in the SOT case group[26]. Generally, SOT cases were more likely to take COVID-19 specific treatments and to need ICU admission. However, fatality (23.08% in SOT *vs* 23.14% in non-SOT) and highest level of supplementary oxygen needed during admission did not significantly vary between these groups[27].

As a result of the comprehensive literature, mortality in SOT recipients compared to controls (non-SOT recipients) has been detected as similar and the SOT programs should not be stopped and are best to be continued during the SARS-CoV-2 pandemic.

VARIOUS THERAPEUTIC OPTIONS OF COVID-19 DISEASE IN TRANSPLANTED PATIENTS

Convalescent immune plasma (CIP) infusion has been utilized in the therapy of other infectious diseases for more than a century[28], under the notion that passive immunization can push the immune system to prevent the disease progression until a specific immune response is developed in the afflicted person[29]. However, the use of CIP did not improve survival in non-transplant patients with severe COVID-19 disease [29]. According to a randomized control trials study at day 30, no significant difference was reported between the CIP and the placebo groups[29].

A course of IVIG at a dose of 1 g/kg was given as an immunomodulatory therapy in patients with serum immunoglobulin G (IgG) level < 700 mg/dL. Antiviral treatment was not administered in any group. According to a large, randomized open-label trial, dexamethasone was related with lower fatality in patients necessitating mechanical ventilation or supplemental oxygen, compared with standard care[30].

Mycophenolate has a cytostatic effect on activated lymphocytes. In COVID-19, the virus SARS-CoV-2 has a direct cytotoxic effect on CD8+ -lymphocytes, thus explaining the relation between lymphopenia and poorer outcomes. Consequently, mycophenolate and SARS-CoV-2 may reveal a synergic side effect on diminishing peripheral lymphocytes, which would be accountable for a deviant immune modification as

shown with other viruses. On the contrary, mechanistic target of rapamycin (mTOR) inhibitors enhance the quality and functionality of memory T-cells and lessen the replication of numerous viruses[31].

Cyclosporine can be beneficial at any moment through the progress of the disease given its impact on the inhibition of viral replication, maintenance of renal graft and down regulation of the immune reaction. Cyclosporine and tacrolimus are the most utilized calcineurin inhibitors in regular clinical practice for inhibition of alloimmune response in transplantation. Calcineurin inhibitors subdue the immune system and the primary action is inhibition of interleukin-2 (IL-2) production in T-cells. Cyclosporine and tacrolimus are chemically different molecules. Calcineurin inhibitors attach to intracellular cyclophilin, which is an immunophilin, and this calcineurin inhibitor-immunophilin complex inhibits nuclear factor of activated T-cells (NFAT). As a result of NFAT inhibition, cytokine transcription and T-cell activation are blocked[32]. The cyclosporine level needed to prevent virus replication surpasses by far the serum levels that characteristically are well below 200 ng/mL[32]. This indicates that the dose utilized to manage most patients with cyclosporine is too low to successfully eliminate the virus. One of the issues is to reach adequate tissue level, as the key virus load is in the respiratory tract and lungs rather than in serum and the cyclosporine concentration in the lungs is lesser than in serum[32]. Additionally, the necessary dosage for vigorously treating severe COVID-19 patients would be 3-6 times greater, which in turn would trigger severe adverse and possible toxic effects, specifically nephrotoxicity[32]. Inhaled cyclosporine has been tried in animals, healthy volunteers and pulmonary transplantation recipients and the pulmonary amount of inhaled cyclosporine is three times more than when systemically administered[32].

Calcineurin inhibitors, such as cyclosporine A and tacrolimus, have a significant role in continuing immunosuppression after SOT. Those medications have a slight therapeutic window, and individual doses and drug management are required. A significant number of cases suffer from short- or long-term calcineurin inhibitors toxicity, with renal dysfunction, hypertension, neurotoxicity and metabolic instabilities [33]. Dose minimization is related to a modest improvement in kidney function, but persistent injury is detected on biopsies if the calcineurin inhibitors are sustained. Calcineurin inhibitor cessation may be the best option by providing calcineurin inhibitors through the early period of immunologic graft damage and then changing them to less nephrotoxic drugs before imperative renal damage happens[34].

Prophylactic lessening of immunosuppression due to fear of COVID-19 disease is not recommended in SOT recipients. With maintenance immunosuppressive management, glucocorticosteroids can be sustained during COVID-19 disease[35]. Sustaining other immunosuppressive medications with lowest effective dose/blood concentration is recommended for cases having mild to moderate COVID-19. Withdrawal of antimetabolites, *e.g.*, mycophenolate mofetil, and maybe inhibitors of mTOR such as sirolimus is recommended in moderate to severe COVID-19. Calcineurin inhibitors may be sustained or replaced for mTOR inhibitors with lower therapeutic levels in moderate to severe COVID-19. If sustained in COVID-19 cases, therapeutic drug watching of calcineurin/mTOR inhibitors and proper dose lessening is suggested in combination with protease inhibitors, hydroxychloroquine/chloroquine, or IL-1/IL-6 receptor antagonists. Checking the hemogram is suggested in cases using antimetabolite drugs or mTOR inhibitors. Drug dose adjustment/evasion should be contemplated for chloroquine, atazanavir, oseltamivir, ribavirin, anakinra, and Janus associated kinase (Jak) inhibitors in cases with organ dysfunctions[36].

Anti-COVID-19 medications, *e.g.*, lopinavir/ritonavir and hydroxychloroquine, have not been tested by laborious clinical trials. These medications may be utilized cautiously for common patients with COVID-19, but for SOT recipients using long-term immunosuppressive management, antiviral medications should be meticulously chosen. Moreover, the senior SOT patients are frequently afflicted with hepatic and renal dysfunction of varying degrees, resulting in worse drug metabolism. The combination of lopinavir/ritonavir and hydroxychloroquine is implicated in extreme tacrolimus trough whole blood levels with unwanted effects[37].

COVID-19 VACCINATION IN TRANSPLANTATION PATIENTS

In transplant recipient patients, the COVID-19 vaccine is a way to protect these patients when there is no definitive cure for COVID-19. On the waiting list of cases with COVID-19, serologic studies have showed that IgM levels increase 5–10 d after infection onset. IgG development classically follows an IgM response development

within 12–14 d of symptom onset in most patients[9]. Follow-up studies suggest that these responses last for at least 5 mo succeeding infection and can confer immunity against repeated SARS-CoV-2 infections[9].

Growing evidence indicates that SOT recipients who take mRNA-based vaccines have low immunization rates[38]. Less than half of the vaccinated transplant cases demonstrated antibodies against the SARS-CoV-2 spike protein[38]. Although immunosuppressant agents are thought to have a key role during this course, the appearance of severe COVID-19 disease after mRNA-based vaccination in immunocompetent or immunocompromised individuals has not yet been described[38]. A possible reason for this might owe to lack of humoral response, together with a restricted or deficient T-cell response, even after the second dose of the vaccination [38]. Live (replication-competent) vaccines are usually contraindicated in immunocompromised subjects due to a risk of vaccine-acquired disease[39]. These vaccines contain intact virions that are engineered to incorporate the gene encoding the SARS-CoV-2 spike protein, and somehow influences the viral vector's capacity to competently infect cells and increases spike gene delivery[39]. It should be emphasized that immunosuppression isn't considered as a contraindication to their use, despite the theoretical concerns with replication-deficient viral vector-based vaccines. SARS-CoV-2 vaccines have significant potential to decrease COVID-19-associated morbidity and mortality among recipients of SOT, including kidney transplants[39].

In a study, 14 SOT recipients were diagnosed with COVID-19 24 d after injection of vaccines. One patient died, 2 patients were hospitalized and 11 patients were recovering at home. 50% of infected cases were hospitalized for the management. There was enough data to issue warnings that immunologically incompetent people should continue to practice firm COVID-19 precautions after vaccination and directions given to the overall population may not be relevant to the SOT patients[40].

SOME ISSUES OF TRANSPLANTATION PATIENTS DURING COVID-19 PANDEMIC

As access to hospitals becomes easier; the determination of SARS-CoV-2 infected patients with mild symptoms which would otherwise be missed in the overall population is increasing.

Fatality rates were lesser than those detected in the age- and gender-matched common population, thereby signifying that chronic immunosuppression could result in a certain protective effect against the most severe types of COVID-19. According to a multi-center study in Istanbul, the usage of cyclosporine was related with a lesser incidence of fatality. On the contrary, rejection treatment was recognized as a risk factor for mortality[15]. Nevertheless, in cases taking mycophenolate, dose lessening, or temporary change to calcineurin inhibitors or everolimus may be considered until complete rescue from COVID-19[31].

It is hard to endorse changing anti-rejection therapy, as the existing data appraised is not adequate to endorse substituting tacrolimus with cyclosporine during severe COVID-19 disease[32]. Nonetheless, revised guidelines should advise to continue cyclosporine use to the cases during COVID-19 except in some of the patients having kidney failure, severe leucopenia or increased serum cyclosporine levels. A change from tacrolimus to cyclosporine would be found only on affirmative observational documents with a supposed advantage for COVID-19 illness, but with a likely greater risk of refusal and controlled studies are necessary to examine whether this change is suitable or not[32]. We need to identify which SOT recipients benefit from specific therapies, the ideal timing of these therapies and the balance of benefits and risks of these therapies, such as late secondary infections. We have to encourage clinical trials and observational researches in the future to incorporate SOT recipients. Long-term follow up of SOT recipients will be important in order to clarify these guidelines. For the safety of recipients, testing donors for SARS-CoV-2 has become a cornerstone of kidney transplant practice[9].

CONCLUSION

Although both negative effects of COVID-19 on increasing waiting list and undesirable effects of immunosuppression on COVID-19 disease in SOT patients; the current literature data support continuation of transplant programs during the COVID-19 era

[11].

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ORIGINAL ARTICLE

Retrospective Study

Latent tuberculosis: Risk factors, screening and treatment in liver transplantation recipients from an endemic area

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Abstract

BACKGROUND

Patients undergoing solid organ transplantation, particularly those who live or have lived in tuberculosis (TB) endemic areas, are at a high risk of developing TB. The majority of post-transplantation TB cases are associated with reactivation of latent TB infection (LTBI). Brazil is in a single position with overlapping areas of high TB endemicity and high transplant activity. In liver transplant (LT), one should be aware of the potential hepatotoxicity associated with the treatment regimens for LTBI.

AIM

To evaluate the frequency of LTBI in LT patients and treatment-related issues.

METHODS

This was a retrospective analysis of a cohort of cirrhotic patients aged ≥ 18 years, who underwent LT at a high-complexity teaching hospital from January 2005 to December 2012.

RESULTS

Overall, 429 patients underwent LT during the study period. Of these, 213 (49.7%) underwent the tuberculin skin test (TST) during the pre-transplant period, and 35

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(16.4%) of them had a positive result. The treatment for LTBI was initiated after LT in 12 (34.3%) of the TST-positive patients; in 3 (25.0%), treatment was maintained for at least 6 mo.

CONCLUSION
The prevalence of LTBI was lower than expected. Initiation and completion of LTBI treatment was limited by difficulties in the management of these special patients.

Key Words: Latent tuberculosis; Liver transplantation; Tuberculosis; Infection; Transplantation; Risk factors

Core Tip: In liver transplant, one should be aware of the potential hepatotoxicity associated with the treatment regimens for latent tuberculosis infection (LTBI). The aim of this study was to evaluate the frequency of LTBI in liver transplant patients and treatment-related issues. The prevalence of LTBI was lower than expected, probably due to low tuberculin skin test sensitivity in patients with impaired liver function. In addition, the initiation and completion of LTBI treatment was limited by difficulties in the management of patients in the presence of elevated liver enzymes and a potential risk of hepatotoxicity.

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INTRODUCTION

In 2018, the World Health Organization estimated that 1.7 billion people, 23% of the world's population, were infected with *Mycobacterium tuberculosis* (MTB). Among these, 5%-20% will develop tuberculosis (TB) during their lifetime[1]. Patients undergoing solid organ transplantation (SOT) have a 36-fold to 74-fold higher risk for developing TB, with an associated lethality of 10% to 40% (up to 10 times higher) when compared with the general population[2,3].

The reactivation of latent TB infection (LTBI) is responsible for the majority of post-transplantation TB cases[4,5]. In areas of limited resources, the tuberculin skin test (TST) is commonly used to investigate LTBI, and it is recommended for all SOT candidates regardless of previous Bacillus Calmette-Guérin vaccination[4,5]. Unfortunately, the sensitivity and specificity for the TST in this population is not well defined due to the absence of a gold standard test for LTBI diagnosis.

When available and affordable, interferon-gamma release assays (IGRAs) may be performed to detect interferon-gamma production in response to MTB antigens. The clinical history of the patient must be investigated. Patients diagnosed with TB infection should be questioned about symptoms and undergo chest radiography or computed tomography to rule out an active TB infection[6-8].

Treatment for LTBI is an effective strategy for the prevention of active TB in SOT recipients and is recommended in the following conditions: SOT candidates positive for the TST or IGRA who have not been previously treated; those at high-risk of pre-transplant exposure to MTB, even if their TST or IGRA results are negative; those with a history of active TB infection who were inadequately treated; and previous untreated TB, as suggested by chest imaging reports[9,10]. For the treatment of LTBI, isoniazid (INH) 300 mg daily supplemented with vitamin B6 for 9 mo[3,5,10] is recommended and is usually started before transplantation. However, in patients undergoing liver transplantation (LT), hepatotoxicity may be associated with INH or other anti-TB drug treatment. Therefore, the treatment for LTBI is commonly provided in the post-transplant period[4,5] considering that LTBI treatment may result in worsening of liver

function in a patient with an already borderline condition and taking into account the impact on the outcome since transplantation may not be possible at that time. Nevertheless, in patients with compensated liver cirrhosis, preventive therapy could be initiated before LT, with strict monitoring for possible toxicities[10-12].

One should highlight that Brazil presents a particular epidemiological context for the development of TB in transplant recipients, considering the high absolute number of transplants performed in an area of high TB endemicity. Despite the efforts to reduce the incidence rates, the burden of TB continues to remain high. In 2018, there were 33.5 cases per 100000 inhabitants. During the period of this study (2005–2012), the incidence rate of TB in Brazil ranged from 37.0 to 41.5 cases per 100000 habitants per year[13,14].

The identification and treatment of LTBI in patients undergoing LT is a very relevant subject; however, publications on this topic are still scarce, especially in the context of higher endemicity. A better understanding of LTBI is needed in areas with a high risk of infection and limited resources. The aim of this study was to determine the prevalence of LTBI (by using the TST) and to evaluate the frequency of and tolerance to treatment for LTBI in LT recipients. It is worth mentioning that this landscape illustrates the majority of countries endemic for TB with an active and public transplant system and limited resources.

MATERIALS AND METHODS

Population study

This is a retrospective analysis of a cohort of cirrhotic patients aged ≥ 18 years who underwent LT at a high-complexity teaching hospital from January 2005 to December 2012. The hospital provides medical care for patients from all regions of Minas Gerais state and has been responsible for the majority of LT performed in the state (81.6%) during the period of the study[15]. It is worth mentioning that Minas Gerais state presented a TB incidence of 15.8 cases per 100000 inhabitants in 2017, without marked difference among different cities[13,14].

A TB screening program began at the beginning of transplant activities in 1994, but it was restructured in 2009/2010 when institutional protocols were reviewed. Screening includes epidemiological, clinical, radiological and TST data.

The study was approved by the Federal University of Minas Gerais Research Ethics Committee (Approval number: 0614.0.203.000-11).

Data collection

A TST result was considered positive when the diameter of the indurate area was ≥ 5 mm 48-72 h after intradermal injection of 2 UT of purified protein derivative RT23. Results after a second TST were not analyzed because it was rarely performed, despite the current recommendation for two-step TST.

The patients' data were collected from electronic medical records and included sex, age at LT, the etiology of cirrhosis, clinical laboratory test results at the nearest date of completion of the TST [albumin, creatinine, sodium (Na+), bilirubin, hemoglobin, international normalized ratio], model for end-stage liver disease (MELD) score, MELD-Na and Child-Turcotte-Pugh scores, information regarding previous TB and LTBI diagnosis and treatment, and close contact with TB patients (positive epidemiology).

Treatment regimen for LTBI

Treatment of LTBI with INH at a dose of 5–10 mg/kg/d, with a maximum dose of 300 mg/d, was the protocol indicated for LT recipients since the beginning of transplant activities in the 1990s. After July 2010, when a TB protocol following international guidelines was implemented, an effort was made to standardize the approach. INH is currently initiated in the post-transplant period, after liver enzymes stabilization, with intended duration of 6 mo according to Brazilian official protocol recommendation. From the patients who received the treatment for LTBI, we collected data including the start and end date of treatment, dose of INH, the need for treatment discontinuation due to suspected INH-induced hepatotoxicity or other adverse events and serum levels of liver enzymes following the initiation of INH treatment.

Statistical analysis

Analyses were performed using the SPSS 2009 release (PASW Statistics for Windows,

Version 18.0. Chicago: SPSS Inc.) software package. Descriptive statistics were presented as frequencies and percentages for categorical variables and as measures of central tendency (mean and median) and dispersion (standard deviation and range) for the quantitative variables. The categorical variables were compared between groups with or without LTBI, using c^2 test and Fisher's exact test as appropriate. Differences between continuous variables were assessed using the Student's *t* test when the variables were normally distributed and Mann-Whitney *U* test when the variables did not present a Gaussian distribution. Logistic regression modeling was used in the multivariate analysis of variables with a $P < 0.20$ according to the univariate analysis. For post-transplant survival analysis, we used Kaplan-Meier survival curve and log-rank test to compare patients with and without LTBI. For all statistical analyses, a $P < 0.05$ was considered significant.

RESULTS

Overall, 497 patients underwent primary LT at our hospital. Of these, the following 68 patients were excluded from the analyses: 48 aged < 18 years and 20 who did not have liver cirrhosis. Among the remaining 429 patients, the TST was performed in 213 (49.7%), and the results were positive in 35 (16.4%) (Figure 1). In a chronological analysis of TST implementation, a progressive increase in LTBI screening from 7.0% in 2005 to 96.4% in 2012 was observed (Figure 2). The average follow-up time after LT was 3.2 ± 1.6 years.

Patients characteristics and TST results

The main clinical and laboratorial characteristics of patients who underwent TST and univariate analysis between TST-positive and -negative patients are shown in Table 1. Previous contact with TB patients was observed in 18 (8.5%) patients, without a significant association with TST positivity in univariate analysis ($P = 0.09$). The TST results were positive at a significantly lower frequency in patients with autoimmune hepatitis, primary biliary cholangitis and primary sclerosing cholangitis than in patients with other diagnoses and at a significantly higher proportion among the patients with hepatocellular carcinoma (HCC) than in those without HCC. Patients with positive TST results had higher serum Na levels and lower MELD-Na score than those with negative TST results. For other laboratory parameters, no significant difference was observed (Table 1).

In multivariate logistic regression analysis, seven variables were included (age, cirrhosis etiology, presence of HCC, Child-Turcotte-Pugh and MELD-Na scores, previous contact with TB patients, serum sodium levels and serum albumin levels). There was a significant association between the history of previous contact with TB patients and a positive TST result [odds ratio (OR): 6.66, 95% confidence interval (CI): 3.17–14.08; $P < 0.01$]. Additionally, patients classified as Child-Pugh class A had a greater chance of a positive TST result then those classified as Child-Pugh class C (OR: 3.18, 95%CI: 1.14–8.89; $P = 0.03$).

Survival

There was no significant difference in post-LT survival between patients with positive and negative TST results (log-rank $P = 0.44$).

LTBI treatment

INH was prescribed to 12 (34.3%) of the 35 patients who had a positive TST result before LT in a median of 11 (8-56) d after LT (Figure 1). Among the 23 (65.7%) patients who did not receive INH, 5 died early in the post-transplant period, without opportunity for liver enzymes stabilization and INH prescription. Nine patients underwent LT before July 2010 when our TB protocol indicating LTBI treatment was fully implemented and nine patients thereafter.

Among the 12 (34.3%) patients who were prescribed INH, 3 (25.0%) used INH for at least 6 mo (180-232 d) and 9 (75.0%) did not complete the 6 mo of INH treatment (Figure 1). Drug withdrawal was prompted by changes in the serum levels of liver enzymes in 2 patients who used INH for 57 d and 80 d, respectively, and due to a polyserositis in 1 patient who used it for 93 d. In 6 patients, drug withdrawal was not justified, with an average usage time of 143 d, ranging from 112–171 d (Table 2). No alternative regimen was tried for patients who had the drug withdrawn.

Table 1 Clinical characteristics and tuberculin skin test results of 213 cirrhotic patients who underwent liver transplantation between January 2005 and December 2012, *n* (%)

Characteristic	General (*n* = 213)	TST positive (*n* = 35)	TST negative (*n* = 178)	*P*[1]
Age (yr)	53.2 ± 11.0	56.1 ± 8.6	52.6 ± 11.3	0.13
Male	153 (71.8)	25 (71.4)	128 (71.9)	0.95
Cirrhosis etiology				
Viral hepatitis	68 (31.9)	12 (34.3)	56 (31.5)	
Alcoholic	64 (30.0)	13 (37.1)	51 (28.7)	
Cryptogenic	45 (21.1)	6 (17.1)	39 (21.9)	0.01
AIH, PBC, PSC	27 (12.7)	0 (0)	27 (15.2)	
Other etiologies	9 (4.2)	4 (11.4)	5 (2.8)	
Previous contact with TB patients	18 (8.5)	6 (20.0)	12 (8.3)	0.09
Hepatocellular carcinoma	41 (19.2)	11 (31.4)	30 (16.9)	0.046
MELD score	16.4 ± 5.0	15.4 ± 4.0	16.6 ± 5.1	0.22
MELD Na	18.2 ± 5.3	16.5 ± 4.5	18.5 ± 5.4	0.045
Child				
Child A	39 (18.3)	11 (31.4)	28 (15.7)	
Child B	107 (50.2)	14 (40.0)	93 (52.2)	0.136
Child C	67 (31.5)	10 (28.6)	57 (32.0)	
Hemoglobin	12.2 ± 1.9	12.6 ± 2.3	12.1 ± 1.7	0.257
Creatinine (mg/dL)	0.99 ± 0.62	0.93 ± 0.25	1.00 ± 0.67	0.471
Albumin (g/dL)	3.1 ± 0.6	3.3 ± 0.8	3.1 ± 0.5	0.181
Sodium (mEq/L)	137.7 ± 4.7	139.5 ± 4.6	137.3 ± 4.7	0.043
Bilirubin (mg/dL)	4.33 ± 5.96	2.92 ± 1.76	4.60 ± 6.44	0.364
INR	1.62 ± 0.43	1.59 ± 0.39	1.62 ± 0.44	0.795

[1]Differences between tuberculin skin test positive and negative.

TST: Tuberculin skin test; AIH: Autoimmune hepatitis; PBC: Primary biliary cholangitis; PSC: Primary sclerosing cholangitis; TB: Tuberculosis; MELD: Model for End-Stage Liver Disease; MELD-Na: Model for End-Stage Liver Disease with Sodium; Child: Child-Turcotte-Pugh; INR: International normalized ratio.

Post-transplant TB

There were no cases of active TB among patients evaluated and submitted to TST pre-transplant in a median follow-up of 37 mo.

DISCUSSION

Transplant recipients have a higher risk of developing TB in the post-transplantation period, which is associated with a high lethality rate. Since reactivation of LTBI is the main cause of the illness, development of preventive treatment strategies is recommended[4,5,10].

Based on our standard transplant protocol, all candidates with a history of inadequate treatment for the clinical or radiological features of TB should be treated for LTBI. If there is no history of past TB or treatment for LTBI, the TST or IGRA should be performed. If the TST result is positive, then the patient should be treated. Considering the low frequency of positive results, the high-risk candidates, such as household contacts of patients with active TB infection, may receive treatment even if the TST results are negative. For each patient, a risk-benefit assessment is required to decide the optimal time for providing the treatment for LTBI. We usually wait for the post-LT

Table 2 Usage time of isoniazid and reason for drug withdraw in patients with positive tuberculin skin test

Patient	Usage time (d)	Reason for drug withdraw
Patient 1	> 180	LTBI treatment complete
Patient 2	> 180	LTBI treatment complete
Patient 3	> 180	LTBI treatment complete
Patient 4	57	Changes in liver enzymes
Patient 5	80	Cholestasis
Patient 6	93	Clinical worsening - polyserositis
Patient 7	112	Not justified
Patient 8	142	Not justified
Patient 9	146	Not justified
Patient 10	162	Not justified
Patient 11	171	Not justified
Patient 12	172	Not justified

LTBI: Latent tuberculosis infection.

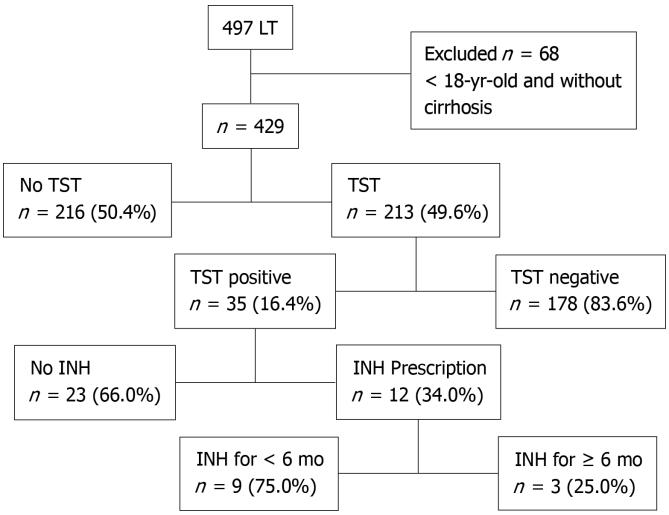

Figure 1 Population study. INH: Isoniazid; LT: Liver transplant; TST: Tuberculin skin test.

period to begin INH once liver function has been normalized. An active TB infection should be excluded in all candidates by checking for the presence of signs and symptoms, chest radiograph and imaging of other body sites if necessary. When evidence of active infection is obtained, appropriate clinical specimens are collected for microbiological confirmation.

Considering the possibility of protocol failures regarding adherence to LTBI diagnosis, therapy and hepatoxicity, we decided to study LTBI diagnosis and treatment in LT patients. Although advised by the American Society of Transplantation and European Society of Clinical Microbiology and Infectious Diseases[5,10], the performance of the TST or IGRA for LTBI screening is variable, ranging from 36%-100% of the patients from different liver transplant centers globally distributed[12,16-19]. In the present study, TST was performed in almost half of the patients, with progressive increase over the years, reaching 96.4% in 2012 (Figure 2). There was a sharp increase between 2009 and 2010 when the TB protocol was implemented in our center.

In our study, only 16.4% of the patients had a positive TST result, which was lower than expected. In countries with disease burden lower or similar to Brazil (Spain, Saudi Arabia and South Korea), a higher rate of TST positivity (between 24% and 38%) has been detected[7,13,20,21]. Studies conducted in Brazil and carried out in the states

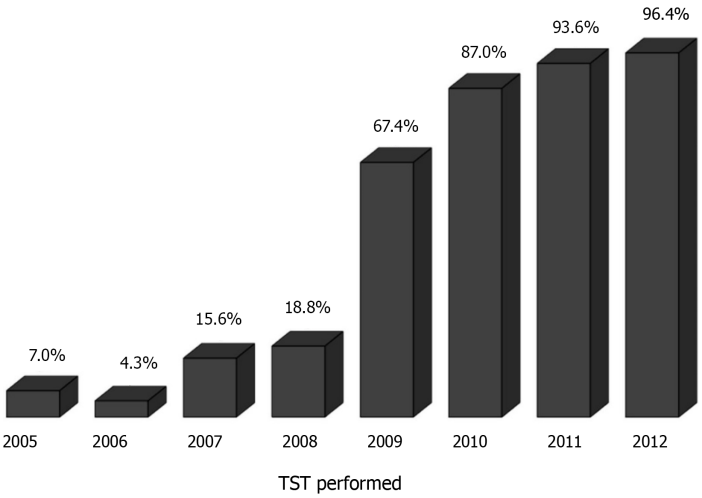

Figure 2 Tuberculin skin test implementation between 2005 and 2012. TST: Tuberculin skin test.

of Rio de Janeiro and São Paulo showed a positive TST result of 30.0% and 17.2% of the patients, respectively[12,18]. Notably, the incidence of TB in Brazil is not uniform. The incidence coefficient in the states of Rio de Janeiro is higher than São Paulo and Minas Gerais (63.5, 39.4 and 15.8 cases per 100000 inhabitants in 2017, respectively). The lower coefficient observed in Minas Gerais state may explain the low prevalence of LTBI in our study[13,14].

It should be highlighted that LTBI diagnosis using the TST presents several limitations, including false-negative results, especially in patients with end-stage liver disease. In addition, it is worth mentioning that IGRA was thought to be more sensitive and specific than the TST. However, regarding patients awaiting LT, the overall performance of IGRA was similar to TST[17,22-24]. None of our patients underwent IGRA, considering the higher costs and unavailability of the assay in our routine practice.

In the multivariate analysis, Child-Pugh class C cirrhosis was associated with a lower TST positivity rate than Child-Pugh class A cirrhosis, which can probably be explained by a higher grade of immunosuppression associated with more advanced liver disease. Patients with HCC had a higher frequency of positive TST results than those without HCC. Among HCC patients, we observed an absolute predominance of a MELD score < 20 (97.6%). The presence of a less advanced liver disease is a possible explanation for a better response to TST and a greater chance of positivity in HCC patients[17].

In the univariate analysis, a significant association was observed between TST positivity and serum Na levels; this was also reflected in the MELD-Na scores. A low Na level is an unfavorable prognostic factor for patients with liver diseases and therefore a marker of disease severity[25,26].

Patients with autoimmune liver diseases (autoimmune hepatitis, primary biliary cholangitis and primary sclerosing cholangitis) showed positive TST results less frequently. Immunosuppressors, which are used to treat autoimmune hepatitis, are a well-established factor responsible for increased false-negative TST results[27].

In the multivariate analysis, there was a positive association between TB epidemiology and TST positivity. Surprisingly, no data on prior TB contact were found in 17.8% of the patients, denoting that little importance was given to this item in the pre-transplant interview, despite this factor being associated with a higher risk of TB regardless of TST result[4], especially if a recent contact[10,28-30].

Concerning previous studies, even though LTBI treatment is widely recommended [5,10,31], INH prescription is quite variable, varying from 18% to 100%[7,17,32,33]. In the current study, treatment for LTBI was provided to 34.3% of the patients with a positive TST result; all treatments were in the post-transplant period. A total of 23 patients did not receive INH treatment: 5 patients died early in the post-transplantation period, 9 patients were transplanted before the full implementation of our TB protocol in July 2010, and 6 of the 9 remaining patients (transplanted after July 2010) had elevated or fluctuating serum liver enzymes, which may have been a problem while prescribing INH. According to our protocol as well as the international recommendations (American Society of Transplantation and European Society of Clinical Microbiology and Infectious Diseases) for liver transplant candidates, clinical

and graft function stability are required to initiate the treatment for LTBI[4,10]. The risk of INH-related hepatotoxicity is higher when aspartate transaminase levels are increased[21]. The change in the levels of liver enzymes is probably the biggest limitation for the prescription of INH; however, there may be additional factors that are difficult to explain. In 3 patients, although liver function was stable, INH was not prescribed.

Besides initiation, maintaining the treatment for LTBI was also difficult. Only 25.0% of the patients who were prescribed INH received the medication for at least 6 mo. LT candidates and recipients are more likely to discontinue medication when compared with other SOT patients[34,35]. Usually, treatment interruption is caused by the increased levels of liver enzymes. This was observed in 2 (16.6%) patients in this study. Although medication-related hepatotoxicity was not confirmed (increased liver enzymes were more likely related to viral hepatitis C recurrence and biliary stenosis), the drug was not restarted. A third patient had the medication discontinued because of worsening of the overall condition with polyserositis and was not restarted. However, the small number of patients limit further conclusions.

The efficacy of the treatment for LTBI in preventing TB varies with the duration of treatment[31,36-38]. The American Society of Transplantation and European Society of Clinical Microbiology and Infectious Diseases suggest INH treatment for 9 mo[5,10], whereas the Brazilian Ministry of Health recommends INH use for at least 6 mo[31]. For 6 (50.0%) patients in our study, INH was withdrawn without explanation before completing 6 mo, with average usage time of 143 d, ranging from 112–171 d. It is possible that the date of transplantation was considered as the start of INH instead of the date of prescription. Since there are difficulties in maintaining LTBI therapy due to possible drug interactions with immunosuppressants and hepatotoxicity, especially seen in this group of patients, shorter treatments would be desirable and possibly easier to manage.

Although we observed limitations on protocol adherence, there were no TB cases during this period. In a systematic review evaluating the incidence of TB in patients with a positive TST result, there was no significant difference between patients who received INH and those who did not. However, considering the incidence of TB in LT patients, in the presence of risk factors (TST positivity, clinical history, compatible radiological changes), the use of INH reduced the incidence of TB ($P = 0.02$)[16].

This study presents limitations that are inherent to retrospective studies, such as the quality of data depending on clinical records. The patient enrollment occurred over a long period of time, with the possible consequences of different protocols and no standardized management across the years. Also, during the time of recruitment, there was an improvement in screening and sometimes a lack of TST. Another limitation in assessing the impact of LTBI screening and treatment in TB cases is the fact that we are evaluating a disease with a relatively low incidence (15.8 per 100000 habitants per year in our state). Even though LT increases this incidence, we would still need a much larger number of patients to assess the impact of screening and treatment strategies. Multicentric studies could contribute to this assessment.

CONCLUSION

Despite the limitations, this study presents some important information regarding the approach and management of LTBI in liver transplant candidates and recipients in a middle income country. Therefore, we understand that since diagnostic methods available (TST and IGRA) for LTBI diagnosis have limitations, especially in patients with end-stage liver disease as observed in the present study, and ahead of the recent reduction in availability of TST, it is necessary to adopt other criteria to indicate the treatment of LTBI for patients submitted to LT. LTBI treatment is essential for patients with positive TST and for patients with a history of incompletely treated TB, history of direct contact with patients with TB and presence of residual lesions on imaging tests [5,9,10]. Patients with recent TST conversion, recent direct contact with MTB and more intense immunosuppression are at a greater risk of acquiring the infection[4,9,10]. The present study also demonstrated the difficulty to initiate and complete INH treatment due to the associated hepatotoxicity and the complex management of these patients. Further research is necessary to develop an effective and well-tolerated alternative therapeutic strategy for LTBI.

ARTICLE HIGHLIGHTS

Research background

In solid organ transplants, one should be aware of the potential risk for tuberculosis, usually because reactivation of latent tuberculosis infection (LTBI).

Research motivation

Dealing with tuberculosis risk is especially difficult in countries with high endemic rates. In liver transplant recipients, we also have to deal with hepatotoxicity associated with the treatment regimens for LTBI.

Research objectives

The aim of this study was to evaluate the frequency of LTBI in liver transplant patients and treatment-related issues.

Research methods

This is a retrospective analysis of a cohort of cirrhotic patients aged ≥ 18 years who underwent liver transplantation at a high-complexity teaching hospital from January 2005 to December 2012. LTBI diagnosis and treatment were analyzed.

Research results

The prevalence of LTBI was lower than expected, probably due to low TST sensitivity in patients with impaired liver function. In addition, the initiation and completion of LTBI was limited by difficulties in the management of patients in the presence of elevated liver enzymes and a potential risk of hepatotoxicity.

Research conclusions

The prevalence of LTBI was lower than expected, and the initiation and completion of LTBI treatment was limited by difficulties in the management of these special patients.

Research perspectives

It is necessary to search for other criteria to indicate the treatment of LTBI for patients submitted to liver transplantation, and further research is necessary to develop an effective and well-tolerated alternative therapeutic strategy for LTBI.

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