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ORIGINAL ARTICLE

The prevalence of latent/chronic infection in liver transplant candidates in Taleghani Hospital of Tehran, Iran, from 2020 until 2021

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ABSTRACT

Aim: The present study aimed to study the prevalence of various latent infections in pre-transplanted patients.
Background: Due to chronic immunosuppressive therapy, patients receiving organ transplants are at risk for reactivation of various infections. Due to the complications in the course of diagnosing and treating the post-transplant infection, screening transplant recipients and donors is vital.
Methods: This retrospective cohort study was performed between March 2020 and 2021. A total of 193 patients receiving a liver transplant in Taleghani Hospital, Tehran, Iran were enrolled.
Results: One-hundred and three (53.4%) patients were men, with an average age of 48.4 ± 13.3 years. Among viruses, 177 (91.7%) patients had a positive IgG titer for CMV. Anti-EBV IgG was positive in 169 (87.6%) patients. One-hundred and seventy-five (90.7%) patients had a positive IgG titer for the VZV. One-hundred and sixty-six (86.0%) cases had positive IgG anti-HSV antibodies. According to our findings, none of the patients were infected with HIV, but 9 (4.7%) cases and 141 (73.1%) had positive anti-HCV and anti-HAV IgG antibodies, respectively. HBV surface (HBs) antigen was also reported positive in 17 (8.8%) patients, while the HBs antibody was positive in 29 (15.0%) patients.
Conclusion: In our study, most of the patients had positive serology for latent viral infections such as CMV, EBV, VZV, and HSV, but the prevalence of latent tuberculosis and viral hepatitis was low among transplant candidates.

Keywords: Latent infections, Liver transplant, CMV IgG, Infection reactivation, Transplant candidate.

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Introduction

Many human diseases are eventually treated with solid organ transplants, and due to the advancement of surgical techniques and immunosuppressive therapies, this method has improved the quality of life and increased the survival of transplant recipients (1, 2). Cirrhosis caused by chronic liver disease is the twelfth leading cause of death in the United States, with liver transplantation being recognized as an effective treatment for these patients with irreversible liver failure (3). However, 10% of transplant recipients do not survive the first year of transplantation, while the five-year survival rate of these patients is about 70% (4, 5). Among the factors that cause mortality among these patients, infection is responsible for the death of more than 50% of the recipients' population (6). The prevalence of latent infections is different in various

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studies, for example CMV infection was found in 44 to 85% of liver transplant recipients (7) and the serum prevalence of HSV-1 virus in organ transplant recipients was seen up to 80% in people under 60 years of age, (8) while 90% of liver transplant recipients were infected with VZV (9).

The best course of action for infection in these people is to prevent catching the disease in the first place. This is because to their immunosuppressed state, the diagnosis of the infection is often more difficult due to the reduction of symptoms of the disease- non-specific symptoms such as fever may be of non-infectious root such as transplant rejection, which makes the diagnosis even more challenging (10, 11). On the other hand, many cases of antimicrobial therapies could exert hepatotoxic effects and induce drug interactions with immunosuppressive medications. Nevertheless, if an infection is suspected, prompt and intensive treatment is necessary (10, 11). Due to the complications mentioned in the course of diagnosing and treating the post-transplant infection, screening the transplant recipients and donors is vital to improve the outcome of organ transplantation (12), to identify and avoid conditions leading to disqualification of the donor and recipient of the targeted organ, and ultimately, to develop strategies for preventing post-transplant infection (13, 14).

This study aimed to determine the prevalence of latent infection among liver transplant recipients and demonstrate the need for strategies to identify and treat infections in these patients.

Methods

A retrospective cohort study was performed among 193 patients who underwent a liver transplant in Taleghani Hospital of Tehran, Iran, between March 2020 and 2021. In this study, we used two questionnaires which captured demographic information (age, sex, and history of underlying diseases) and paraclinical data on latent infections (positive or negative information about anti-herpes simplex virus (anti-HSV) IgG, anti-cytomegalovirus (anti-CMV) IgG, anti-Epstein-Barr virus (anti-EBV) IgG, anti-varicella zoster virus (anti-VZV) IgG, interferon-gamma release assay (IGRA) test, and venereal disease research laboratory (VDRL) test). The study protocol was approved by the Ethics Review Committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.RIGLD.REC.1400.007)

The latent tuberculosis (LTB) diagnosis of this study was based on the TB-IGRA method, an approved diagnostic test for screening active and latent Mycobacterium tuberculosis infection. In this method, TB7.7, CFP_10, and ESAT_6 proteins were used to stimulate cells in heparinized blood and measure interferon-gamma by the enzyme-linked immunosorbent assay (ELISA) method, specific in-vitro responses to Mycobacterium tuberculosis infection are measured. This test is not positive for environmental species of Mycobacterium or after bacillus Calmette-Guerin (BCG) vaccination, and evaluates the specific immune response for TB (15). VDRL test is also used to diagnose syphilis. This test was used as a screening test for detecting Treponema pallidum antibody, with high sensitivity and low specificity in the early stages of the disease. If this test was positive, the results would be confirmed using fluorescent treponemal antibody test absorption (FTA-ABS) or micro-hemagglutination assay for Treponema pallidum (MHA-TP) methods (16).

The patients were tested for anti-CMV IgG and anti-CMV IgM (PishtazTeb Co.), with all results evaluated by ELISA and reported as arbitrary units per milliliter (AU/mL). IgG and IgM antibodies (Zeus Scientific Company) were also employed to diagnose EBV, and the results were evaluated and reported using ELISA. IgG and IgM antibodies (PishtazTeb Co.) were tested in the case of HSV viruses, and ELISA reported the results. ELISA also detected VZV in patients using IgG and IgM antibodies (Vircell Co.).

Various diagnostic tests were used to detect the hepatitis B virus in patients - HBe Ag and HBe ab, which target a virus-soluble protein, HBc Ab, which targets the virus core antigen, HBS Ag, which is the hepatitis B virus surface antigen, and HBS Ab, which is an antibody against this surface antigen. Moreover, all these experiments were performed through the ELISA method. HBV Polymerase Chain Reaction (PCR)was also performed on patients' blood samples. PCR method was used to detect the hepatitis C virus.

Data were analyzed by statistical tests such as Chi-square and Mann-Whitney U tests, then via SPSS software v. 22.0 (Armonk, NY, USA), where p-value < 0.05 was considered significant.

Results

In this study, 190 patients were enrolled, among whom one hundred and three (53.4%) patients were men with age range of 14 to 79 years old, with an average age of 48.4±13.3 years. The demographic information of the patients is reported in Table 1.

Ten cases (5.4%) out of the 183 patients whose IGRA test data were recorded were diagnosed with LTB. One patient (0.5%) had also a positive VDRL test, while 186 patients were reported negative.

Among herpes viruses, 177 (91.7%) patients had a positive IgG titer for CMV, and 4 (2.1%) patients reported equivocal results, among them 96 (54.2%) were male with no significant difference between males and females (P=0.411). Anti-EBV IgG was positive in 169 (87.6%) patients. Out of the anti-EBV IgG-positive patients, 91 (53.8%) were male, with no significant difference between various genders (P=0.615). One-hundred and seventy-five (90.7%) patients had a positive IgG titer for the VZV. One-hundred and sixty-six (86.0%) had positive IgG anti-HSV antibodies. Regarding anti-HSV IgG titers, 87 (52.4%) patients were male, with no significant difference between various genders (P=0.508).

According to our findings, none of the patients were infected with HIV, but 9 cases (4.7%) and 141 (73.1%) had positive anti-HCV and anti-HAV IgG antibodies,

Table 1. Demographic and clinical characteristics in patients with COVID-19 and with influenza.

Parameters	Covid-19 (n=50)	influenza (n=50)	P <0.05
Age	63.26 ± 20.64	59.62 ± 21.27	0.38
Sex			
Male	29(58%)	22 (44%)	
Female	21 (42%)	28 (56%)	
Signs and symptoms			
Fever	38(76%)	46 (92%)	0.029
Cough	41 (82%)	33 (66%)	0.06
Myalgia	29(58%)	32(64%)	0.53
Dyspnea	37 (74%)	28 (56%)	0.059
Headache	14 (28%)	17 (34)%	0.51
Fatigue	32 (64%)	26 (52%)	0.22
Gastrointestinal symptoms	19 (38%)	2 (4%)	0.003
Anorexia	33 (66%)	23 (46%)	0.04
Laboratory assay results			0.94
Leukocytosis	14 (28%)	7 (14%)	
Leukopenia	7 (14%)	6 (12%)	
ESR	27 (54%)	26 (52%)	0.84
CRP	39 (78%)	24 (48%)	0.0001
Lymphocytopenia	27 (54%)	17 (34%)	0.04
Neutrophilia	10 (20%)	18 (36%)	0.07

Table 2. CT imaging findings in 50 patients with COVID-19 and 50 with influenza-like illness.

CT findings	COVID-19	influenza-like illness	P <0.05
Ground glass opacity	43 (86%)	25 (50%)	0.002
Consolidation	22 (44%)	23 (46%)	0.01
Pleural effusion	8 (16%)	11 (22%)	0.28
Air bronchogram	3 (6%)	6 (12%)	0.29
Pleural thickening	9 (18%)	3 (6%)	0.06
Nodules	11 (22%)	7 (14%)	0.051
single nodule	2 (18.2%)	5 (71.4%)	
two and more nodules	9 (81.8%)	2 (28.6%)	
Air space opacity	4 (8%)	3 (6%)	0.69
Pleurisy	4 (8%)	3 (6%)	0.69
Atelectasis	6 (12%)	3 (6%)	0.29
Emphysema	2 (4%)	4 (8%)	0.39
Distribution			<0.0001
peripheral distribution	27 (54%)	4 (8%)	
central distribution	14 (28%)	16 (32%)	
peripheral and central	8(16%)	6 (12%)	

respectively. HBV surface (HBs) antigen was also reported positive in 17 (8.8%) patients, while the HBs antibody was positive in 29 (15.0%) patients. Further, among the HBs antigen-positive patients, the HBe antigen and HBe antibody were positive in 4 (23.6%) and 12 (70.6%) patients.

Rgw serology data of our study groups are outlined in Table 2.

Discussion

Tuberculosis, an opportunistic infection in solid recipient patients, occurs in about 1% of solid organ recipients in North America and Europe (17, 18) .Also, this population is at increased risk of primary infection or reactivation, and diffuse form of the disease, due to suppression of their immune system (19). According to the World Health Organization (WHO), in 2018, it was estimated that about 23% of the world's population was infected with Mycobacterium tuberculosis. However, only 5 to 20% of them would develop LTB, which is 36 to 74 times higher in patients receiving solid organ transplants, and the death rate in these recipients is estimated to be up to 40% (20, 21).

Reactivation of LTB is responsible for most cases of LTB after transplantation (22). Regarding liver transplantation, the results show that the incidence of LTB in these patients is 2.25 times higher than their matched group, and people receiving transplantation have a lower survival rate if they have LTB than those without this condition (23). Since most cases of TB after transplantation are associated with reactivation of latent infection, all transplant recipients, especially in TB endemic areas, should have a PPD or IGRA test before transplantation (24). If they come out with a positive test or have a history of active TB, they should go under additional screening to check them for signs and symptoms, chest radiography, and imaging of other body parts, if necessary, to rule out active disease. Clinical specimens should be collected for microbiological confirmation if any evidence of active infection is obtained.

As mentioned earlier, LTB infection management is essential for transplant recipients' survival, but this process is facing challenges, as anti-mycobacterial treatment has significant drug interactions and toxicities (25). For example, rifampin and possibly isoniazid induce liver enzymes and increase the catabolism of corticosteroids plus cyclosporine, which, as reported in several cases, can lead to transplant rejection (26). Meanwhile, the treatment of latent infection in transplant recipients can increase the risk of liver failure due to the potential toxicity of the drugs (27).

In our study, only 5.4% of transplant recipients had a positive IGRA test result, among whom one test result was weakly positive, which requires further investigation. Our result is consistent with a report which showed the prevalence of LTB in transplant recipients between 0.26% and 6.4% based on patients' residences (28). In another study by Ozgen et al., 16.4% of the recipients had a positive result. In another study, 1.24% of liver transplant recipients were diagnosed with LTB (29). Activation of LTB infection often occurs early in post-transplantation (30). For example, in a study 7 out of 9 patients developed LTB within 12 months after liver transplantation; So proper identification and treatment of transplant recipients seems necessary (31).

Although primary active viral infection is uncommon in transplant recipients, if an active viral infection is detected in a recipient, the infection should be treated before transplantation, and the immune suppression process begins (32). Herpes viruses that are clinically important in transplant recipients include HSV, VZV, CMV, and EBV, which is the reason why HSV screening is performed in some transplant centers, and in other centers, global antiviral prophylaxis is performed for at least one month after transplantation. Screening for the VZV is also vital due to its lethality; if possible, vaccinating the negative serum recipient is necessary (32).

Cytomegalovirus, classified as a subfamily of beta-herpes viruses, has a serum prevalence of 30 to 50% in developed countries and 97% in other regions (33). Infection with the virus occurs in most solid organ recipients at the peak of immunosuppression, mainly within the first trimester post-transplantation (31). According to studies, the virus is found in 44 to 85% of liver transplant recipients and causes symptomatic disease in 29% of these recipients (34). There are three main patterns of CMV transmission in transplant recipients, the most dangerous of which is when the serum recipient is negative while the serum donor is

positive (35). This is important given that in our study 184 patients also tested negative for CMV (IgG).

Another state occurs when the recipient of the infection is latent, and after receiving a transplant from a positive serum, he or she would have a secondary infection or reactivation. Superinfection also occurs when a positive serum recipient re-receives hidden infected cells from a positive serum donor (36). In our study, 177 (92.7%) cases of transplant candidates had positive IgG for this disease, which indicates the possibility of the presence of the virus in the body of these patients in a latent manner; it is consistent with a study that considers the serum incidence of this virus in developing countries to be up to 100% (37).

HSV, one of the most common causes of infection in transplant recipients, often occurs as a reactivation, but there is also the possibility of primary infection through person-to-person contact or allografts (38). The serum prevalence of HSV-1 virus in organ transplant recipients has been observed to be up to 80% in people under 60 years of age; in the case of HSV-2 virus, it is 26.3% in those under 40 years of age (39). According to our study, 86% of the subjects had a positive IgG result for this virus, among whom 93% were under 65 years of age, but in this study, age was not a significant risk factor for infection with this virus. Another study found HSV antibodies in 75% of adult transplant candidates (40).

Transplant recipients can show mild symptoms such as fever, headache, and sore throat from EBV infection, but the virus can also cause post-transplantation lymphoproliferative disease (PTLD) in transplant recipients (41). This disease is one of the leading causes of death in transplant recipients (7). PTLD occurs in different types of transplants with different percentages and, in the case of liver transplantation, it affects 2.1 to 2.2% of transplant recipients (42). The highest risk of this disease occurs in a seronegative receiver from a seropositive donor. However, it may also take place in seropositive recipients following the suppression of the immune system, especially while using potent suppressors such as anti-thymocyte globulin (ATG) and belatacept (43). Thus, knowledge of EBV serology in all pre-transplant patients is essential. According to our study, liver transplant recipients had 88.9% of those with IgG. This statistic is consistent with a study in which 90 to 95% of people were positive for IgG antibodies (44).

The prevalence of the VZV infection has been observed to be two to five times greater among transplant recipients than general population (45);90% of recipients are infected, which increases the risk of reactivation after transplantation (46). The reactivation of the virus can lead to skin zoster as well as organ involvement and post-herpetic neuralgia (PHN) (50), which reduces the quality of life (51) (34, 40, 47).

Syphilis, also caused by Treponema pallidum, is commonly known as a sexually transmitted infection, which is more common in young men who have sex with other men (45, 46). However, due to the suppression of the immune system in transplant recipients, these people are also at greater risk of activating dormant hepatitis and syphilis infections (47). In our study, only one person had a positive result.

Hepatitis B virus, which causes recurrent infection in 80% of transplant recipients, is a virus in the Hepadnaviridae family and can cause significant complications in patients receiving it, leading to death in 50% of cases (48, 49). Due to the mildness of primary HBV caused by blood transfusions or liver donations from an infected donor, it is important to evaluate recipients who have HBV and may have a recurrent infection (50). The risk of active and fulminant HBV was higher in patients who had hepatitis surface antigen and were transplanted; this is important given that in our study, 17 patients also tested positive for this antigen (13). The hepatitis C virus, which often causes the recurrence of hepatitis C in positive recipients, is a single-stranded RNA virus and is a common cause of chronic liver disease and liver transplantation (51, 52). Liver enzymes show a higher prevalence of abnormalities after transplantation in patients receiving a positive serum compared to serum-negative individuals (53, 54). This virus can be considered the main cause of post-transplant hepatitis in patients receiving liver transplantation and kidney recipients (54, 55). Accordingly, monitoring the prevalence of infected people is very important. As seen in our study, 8 transplant recipients tested positive for the virus (4.1%) and this result is in line with a study in which 0.2% of the recipients were positive for IgG antibodies (54).

Conclusion

It is essential to have an accurate knowledge about the epidemiology of latent infections in liver transplant candidates to prevent reactivation of the infection. To the best of our knowledge it has been the first study to evaluate the prevalence of latent infections in liver transplant candidates in Iran.

In our study, most of the patients had positive serology for latent viral infections such as CMV, EBV, VZV, and HSV, but the prevalence of latent tuberculosis and viral hepatitis was low among transplant candidates.

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Conflict of interests

All authors have no relevant financial interests to be declared.

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