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TUBERCULOSIS IN LIVER TRANSPLANT RECIPIENT : A SYSTEMATIC REVIEW

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Abstract

Background: *Despite claims, transplant recipients' TB rates are random. The rate of posttransplant tuberculosis depends on the organ transplanted, pre-transplant latent tuberculosis screening, and previous antituberculosis medication. This rate may also depend on recipient and donor tuberculosis rates. Active tuberculosis after solid organ transplantation increases the risk of graft loss and death four-fold compared to the general population.*

Aim: *This article examines the link between tubercolis and liver transplant recipient.*

Methods: *This study showed that it met all of the requirements by looking at the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines. So, the experts could make sure that the study was as current as possible. The search method used a number of electronic reference databases, such as Pubmed and SagePub, to look for papers that were published between 2000 and 2023. We didn't look at review papers, articles that had already been published, or articles that were only half done.*

Result: *In the PubMed database, the results of our search brought up 66 articles, whereas the results of our search on SagePub brought up 23 articles. The results of the search conducted for the last year of 2013 yielded a total of 23 articles for PubMed and 18 articles for SagePub. In the end, we compiled a total of 20 papers, 16 of which came from PubMed and four of which came from SagePub. We included five research that met the criteria.*

Conclusion: *Patients who have undergone organ transplantation are at high risk of developing latent TB. This shows the importance of administering prophylactic drugs such as isoniazid in post-liver transplant patients.*

Keyword: *Immunocompromised; Isoniazid; Liver transplant; Tuberculosis*

INTRODUCTION

Tuberculosis (TB) is one of the main infectious diseases and has become a public health concern worldwide. The World Health Organization (WHO) estimates that there are around 8.6 million incident cases of TB and 1.3 million deaths caused by the disease. More than half a million cases occur in children and 320,000 deaths are reported among people infected with HIV.[1,2] Eight countries accounted for two-thirds of the global total, including: India (26%), Indonesia (8.5%), China (8.4%), Philippines (6.0%), Pakistan (5.7%), Nigeria (4.4%), Bangladesh (3.6%) and South Africa (3.6%).[3]

The bacterium known as Mycobacterium tuberculosis (MTB), which causes tuberculosis, enters the body through the respiratory system. Mycobacterium tuberculosis is an aerobic bacterium that can primarily dwell in the lungs and numerous other organs of the body that have a high partial pressure. It is the causative agent of tuberculosis. Germs that cause tuberculosis take the form of rods and have unique features that make them resistant to acids when they are stained. Germs that cause tuberculosis can only survive for a short period of time in bright sunshine; however, they can live for several hours in a cool, dark environment.[4,5]

TB is one of the leading causes of death among liver transplant (LT) recipients. Infection typically results from the reactivation of a latent infection or, on rare occasions, an infected organ transplant. Diagnosis and treatment of tuberculosis after LT present numerous obstacles.[6] First, the diagnosis may be delayed due to subtle and uncommon clinical manifestations, a higher rate of extra-pulmonary tuberculosis (60%) in solid organ transplant recipients, and a paucity of accurate diagnostic tools. In addition, drug-drug interactions between anti-tuberculosis therapy and cyclosporine could result in a variety of adverse medical conditions.[7]

The estimated mortality rate associated with TB infection is 29%, making it one of the most life-threatening infectious diseases among transplant recipients. Immunosuppression is a well-known risk factor for tuberculosis relapse. This infection occurs in 1.2–6.4% of transplant cases worldwide, but the rate is 15% in endemic regions. Reactivation of latent infection is the most prevalent form of tuberculosis following transplant. 5–10% of immunocompetent patients exposed to MTB will develop tuberculosis over the course of their lifetime. While this risk is estimated 10-70 times greater in immunosuppression regimen recipients.[8–10] We will discuss about tuberculosis in liver transplant recipient.

METHODS

The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 checklist was used as the basis for the establishment of the criteria that were used to oversee the process of carrying out this systematic review. These standards were utilised to ensure that all of the relevant information was collected and analysed. Articles on " tuberculosis in liver transplant recipient " were the topic of this systematic review that was designed to research them. This review was designed to investigate them. These are the many aspects of the topics that were looked into during the research that is being considered right now.

The following conditions need to be fulfilled in advance in order for your work to be taken into consideration: 1) Articles have to be written in English; 2) Articles have to be able to be read online in their entirety; and 3) Articles had to have been published after 2013, but before this systematic evaluation was carried out. Under no circumstances will any of the following types of written submissions be considered for inclusion in the anthology: 1) Editorial letters, 2) submissions that do not have a DOI linked with them, and 3) article reviews and submissions that are comparable to one another.

The search for papers to be included in the systematic review began on July 18th, 2022 using the PubMed and SagePub databases with the search terms on "tuberculosis" and "liver transplant recipient" Where *(("tuberculosis, hepatic"[MeSH Terms] OR ("tuberculosis"[All Fields] AND "hepatic"[All Fields]) OR "hepatic tuberculosis"[All Fields] OR ("tuberculosis"[All Fields] AND "liver"[All Fields]) OR "tuberculosis liver"[All Fields]) AND ("transplant recipients"[MeSH Terms] OR ("transplant"[All Fields] AND "recipients"[All Fields]) OR "transplant recipients"[All Fields] OR ("transplant"[All Fields] AND "recipient"[All Fields]) OR "transplant recipient"[All Fields])) AND ((y_10[Filter]) AND (clinicaltrial[Filter]))* is used as search keywords.

After conducting a literature analysis and looking at the titles and abstracts of previously published studies, the author of the study revised the criteria for what should be included in the study and what should not be included in the study. These changes were made after the author considered what should not be included in the study. During the process of developing the systematic review that we carried out, we gave any and all consideration to only those research studies that were able to satisfy each and every one of our standards. Each study's title, author, publication date, study origin location, research study design, and research variables are all bits of information that can be gathered during the collection process.

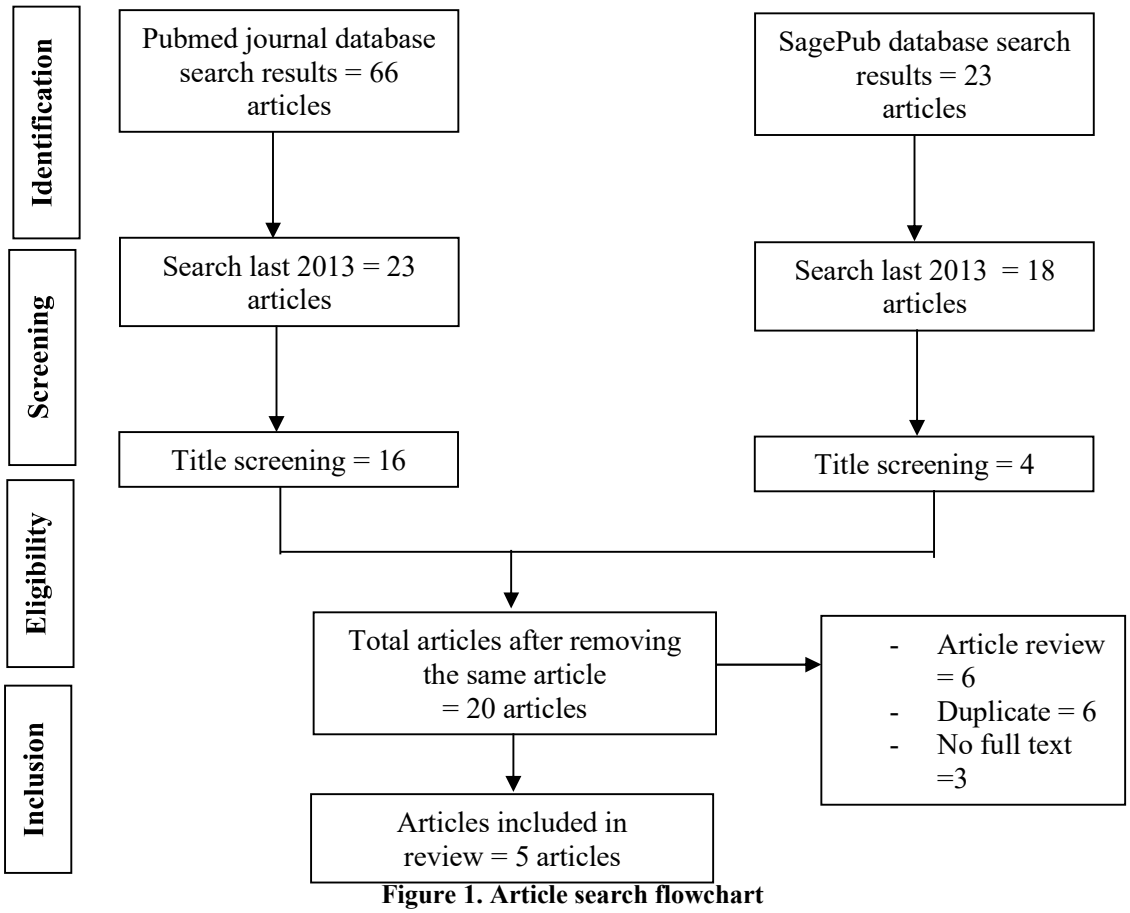

Figure 1. Article search flowchart

The writers did their own independent evaluations on a selection of the research that was given in the titles and abstracts of the publications in order to determine which studies ought to be taken into consideration. This allowed them to choose which studies ought to be taken into consideration. They were able to identify, as a result of this, which studies should be taken into consideration. The next thing that needs to be done is a study of the full texts of the studies that can be included in the systematic review since they fulfil the requirements. The objective of this analysis is to ascertain whether or not certain pieces of research may be pertinent to the goals of the review. This will be done so that the evaluation is as comprehensive as it possibly can be. This is the goal.

RESULT

In the PubMed database, the results of our search brought up 66 articles, whereas the results of our search on SagePub brought up 23 articles. The results of the search conducted for the last year of 2013 yielded a total of 23 articles for PubMed and 18 articles for SagePub. In the end, we compiled a total of 20 papers, 16 of which came from PubMed and four of which came from SagePub. We included five research that met the criteria.

Ahmadinejad, et al (2021) conducted a study with 675 people who got a transplant, 100 (14.8%) had a positive tuberculin skin test. Sixty-seven percent of the people who got the money were guys, and the average age was 72.6 ± 1.3 years. Before transplanting, Isoniazid was given to all patients as a preventive measure. Before the transplant, the average length of anti-tuberculosis treatment was 2.7 ± 1.9 months, and after the transplant, it was 3.6 ± 5.5 months. After an average of 45.2 ± 1 3 months of follow-up, none of these patients have gotten tuberculosis. During the time of the study, four of the people were sick with Mycobacterium tuberculosis, even though their skin tests had come back negative before the transplant.

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Result
Ahmadinejad, 2021[12]	Iran	Cross sectional study	675 liver transplant (LT) recipients	According to the findings of our research, the tuberculin skin test is an accurate and sensitive method for diagnosing latent tuberculosis in potential recipients of a liver transplant. Prophylaxis with isoniazid is well tolerated even in patients with end-stage liver disorders and in those who have received liver transplants.
Kim, 2021[11]	Republic of Korea	Cross sectional study	717 eligible LT recipients	According to the results of our study, chest imaging and IGRA should both be examined when trying to determine which risk groups should be treated for latent TB infection (LTBI).

Leong, 2021[13]	Taiwan	Cross sectional study	884 LT recipients	According to this study, the prevalence of TB was high among LT recipients. It is possible that aberrant CT findings and previous exposure to mTOR inhibitors are risk factors for tuberculosis in post-transplant recipients who have long-term immunosuppression.
Olithselvan, 2014[14]	India	Cross sectional study	214 transplant recipients	In an environment with a high prevalence of the disease, there is an immediate need for research to be conducted on the roles that routine IGRA testing and isoniazid prophylaxis play.
Liu, 2014[15]	China	Cross sectional study	166 liver transplant recipients	When compared to the overall Chinese population, the incidence density of tuberculosis was much greater among recipients of liver or kidney transplants. The presence of preoperative indications of latent tuberculosis in a recipient and obtaining a graft from a cadaveric donor were two important risk factors for the development of tuberculosis in recipients of a liver or kidney transplant.

Kim, et al (2021)[11] conducted a study with twenty-one patients and showed out of a total of 717 eligible LT recipients who were included in this study acquired active TB. After transplantation, the incidence rates of tuberculosis were as follows: 2,261, 724, and 119 cases/100,000 person-years in the first, second, and less than third years, respectively. Both a history of TB that was successfully treated (hazard ratio [HR] = 18.92; 95% confidence interval [CI] = 4.10–87.25) and a positive picture (+) / IGRA (HR = 10.86; 95% CI = 2.75–42.89) were independent risk factors for developing active TB. Having a positive IGRA but a negative image was not considered a risk factor.

Leong, et al (2021)[13] showed 744 TB cases per 100,000 patient-year were 18-fold higher than the Taiwanese general population. TB developed 20 months after liver transplant. 15 TB cases were pulmonary, 10 extra-pulmonary. The first year post-transplant saw five extra-pulmonary TB cases. 63.3% survived five years. Apical fibrotic change in pre-transplant computed tomographic (CT) findings and exposure to mammalian target of rapamycin (mTOR) inhibitors before TB event were independent risk factors for TB development (odds ratio [OR] = 10.79, 95% confidence interval [CI] 1.73–67.49, p = 0.01; OR = 3.847, 95% CI = 0.80–18.51, P = 0.09, respectively).

After transplantation, TB varied (median = 72 days, interquartil range [IQR] = 534 days). 80% of cases were extrapulmonary or disseminated. Compared to similar healthy LTRs, only unexplained granulomas in explants (2/5 or 40%, P = 0.01) were related with posttransplant TB. TB (52.9%) was the most common cause of granulomas in all explants, but almost half (47.1%) had other reasons. A normal daily regimen was used for 12 months (IQR = 7.5 months). Posttransplant TB caused 2/5 or 40% mortality. LTRs from a high-prevalence region had low TB prevalence. Isoniazid should be given to liver explants with TB-like granulomas. Post-liver transplant TB is deadly.[14]

Liu, et al (2014)[15] showed median time for tuberculosis to manifest was 20.0 months (interquartile range: 5.0-70.0). Receiving a graft from a cadaveric donor (odds ratio [OR] = 3.7; 95% confidence interval [CI] = 1.4-10.0; P = 0.010) and preoperative evidence of latent TB (OR = 6.8, 95% CI = 2.0-22.7; P = 0.002) were identified as two risk factors for TB in liver or kidney transplant recipients. People who got liver or kidney transplants were much more likely to get TB than the rest of the Chinese population. Liver or kidney donation recipients were more likely to get TB if they got a graft from a donor who had died and if there was evidence of latent TB before surgery.

DISCUSSION

Tuberculosis is a contagious infection caused by the bacterium Mycobacterium tuberculosis (MTb). The infection is generally characterized by the formation of granulomas in the infected. In most cases, transplant recipients have 20–74 times the risk of contracting tuberculosis compared to the normal population. There is no pattern to the incidence of tuberculosis among transplant recipients, despite what some have said. The reported incidence of tuberculosis among transplant recipients has been quite diverse, ranging from 1.2% to 6.4% in developing nations and up to 15% in TB endemic regions. among developing countries, the incidence of TB has been reported to be highest.[16]

The type of organ that was transplanted, pre-transplant screening for latent tuberculosis infection, and previous treatment with antituberculosis drugs are all factors that can play a role in the rate of posttransplant tuberculosis. Other factors that can play a role in this rate include the prevalence of tuberculosis in the recipient community and the prevalence in the donor population. Post-transplant active tuberculosis is related not only with an increased risk of graft loss, but also with a four-fold increase in the likelihood of a fatal result following solid organ transplantation in comparison with the general population.[17]

The majority of tuberculosis infections in immunocompetent individuals happen in the lungs, either because of a new infection or because of the reactivation of an old infection that had been dormant. This is true for the general population as well as for individuals. Extra-pulmonary involvement is seen in only 15–20 percent of people who have active

tuberculosis in the general population.[18] In fact, most transplant recipients get tuberculosis when a dormant infection comes back to life. It can also be caused by the type of organ transplanted, the amount of immunosuppression, and opportunistic infections that happen at the same time. Holty et al. said that more than 60% of people who got a liver donation and had active TB had involvement outside of the lungs.[14]

The most commonly used TCM test is the GeneXpert MTB/RIF (sensitivity test for Rifampicin). Currently, other TCM tests are becoming commonly known, although they are not yet widely known. The Xpert MTB/RIF is an automated, cartridge-based diagnostic test that can identify MTB and Rifampicin resistance. Xpert MTB/RIF based on Cepheid GeneXPert platform, quite sensitive, easy to use with nucleic acid amplification test (NAAT) method. This method purifies, concentrates and amplifies (by real time PCR) and identifies the nucleic acid sequences in the TB genome. The length of test administration to completion takes 1-2 hours.[19]

After a solid organ transplant, it's hard to tell if someone has active tuberculosis because a higher percentage of transplant recipients get extra-pulmonary or disseminated tuberculosis than in the general population, and some transplant-related conditions, especially allograft organ rejection, can look like tuberculosis. Since most anti-tuberculosis drugs need a fully functional liver, the risk of drug-induced side effects is higher for liver transplant recipients, whether you look at the hepatotoxic effect of each drug (like isoniazid and pyrazinamide) or the interactions between drugs (like rifampicin with immunosuppressants and corticosteroids).[17]

Interferon-Gamma Realease Assays (IGRA) is a tool for diagnosing M. TB infection including TB infection and latent TB. The specimen will be mixed and exposed to antigen from M.tuberculosis. Leukocytes of patients infected with TB will produce interferon-gamma (IFN-γ) when in contact with antigen from M.tuberculosis. Currently there are several IGRA kits that can be used. These kits have the same working principle, but differ in the processing technique, for example there is a kit that measures the immune response by measuring the amount of IFN-γ that is produced when blood is exposed to an antigen that is already in the specimen collection tube. Another kit measures the immune response by measuring the number of cells that produce IFN-γ.[19]

Isoniazid was first discovered in the 1920s and used as an antimycobacterial compound in the 1950s. This agent exhibits mycobactericidal effects on mycobacterial replication, whereas isoniazid is bacteriostatic against mycobacteria in a latent form. Isoniazid works by activating the mycobacterial KatG enzyme to produce reactive oxide species (ROS) that destroy the mycobacterial cell wall. Oral, intramuscular, and intravenous isoniazid are available. Isoniazid inhibits the cytochrome P450 system and acts as a monoamine oxidase (MAO-I) inhibitor. Isoniazid (INH) inhibits mycolic acid synthesis, which is necessary for mycobacterial cell walls. It kills Mycobacterium tuberculosis.[20]

Without knowing the number of donors with active TB and recipients with donor-derived TB, this lenient donor selection policy cannot be assessed. One centre said they hadn't encountered the questionnaire's clinical settings. They felt they could not appropriately assess the deceased donor for TB before harvest. Medical professionals may contract TB from organ donors with open pulmonary TB. Finally, this assessment of present practise rather than proper practise emphasises the necessity for the Indian transplant community to evaluate outcomes in light of their center's policies.[21]

CONCLUSION

Patients who have undergone organ transplantation are at high risk of developing latent TB. This shows the importance of administering prophylactic drugs such as isoniazid in post-liver transplant patients.

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