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Current status of liver transplantation for human immunodeficiency virus-infected patients in mainland China

Tang JX *et al*. LT with HIV-infection in China

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Abstract

According to the report from the Chinese Center for Disease Control and Prevention, the prevalence of human immunodeficiency virus (HIV) infection exceeded 1.2 million individuals by the year 2022, with an annual increase of about 80000 cases. The overall prevalence of hepatitis B surface antigen among individuals co-infected with HIV reached 13.7%, almost twice the rate of the general population in China. In addition to the well-documented susceptibility to opportunistic infections and new malignancies, HIV infected patients frequently experience liver-related organ damage, with the liver and kidneys being the most commonly affected. This often leads to the development of end-stage liver and kidney diseases. Therefore, organ transplantation has emerged as an important part of active treatment for HIV infected patients. However, the curative effect is not satisfactory. HIV infection has been considered a contraindication for organ transplantation. Until the emergence of highly active anti-retroviral therapy in 1996, the once intractable replication of retrovirus was effectively inhibited. With prolonged survival, the failure of important organs has become the main cause of death among HIV patients. Therefore, transplant centers worldwide have resumed exploration of organ transplantation for HIV-infected individuals and reached a positive conclusion. This study provides an overview of the current landscape of HIV-positive patients receiving liver transplantation (LT) in mainland China. To date, our transplant center has conducted LT for eight end-stage liver disease patients co-infected with HIV, and all but one, who died two months postoperatively due to sepsis and progressive multi-organ failure, have survived. Comparative analysis with hepatitis B virus-infected

patients during the same period revealed no statistically significant differences in acute rejection reactions, cytomegalovirus infection, bacteremia, pulmonary infections, acute kidney injury, new-onset cancers, or vascular and biliary complications.

Key Words: Liver transplantation; Human immunodeficiency virus; Infection; Hepatitis B virus; End-stage liver disease; Mainland China

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Core Tip: In mainland China, human immunodeficiency virus (HIV) infection has long been considered an absolute contraindication for liver transplantation (LT). Until June 2004, Chinese scholars performed LT on two HIV patients, but these cases were only followed up for 24 and 22 months, respectively. Subsequently, there were no reported cases of LT in mainland China for patients with HIV infection until April 2019, when our transplant center performed ABO-incompatible LT for a patient with liver failure co-infected with HIV and hepatitis B virus. This study provides an overview of the current landscape of HIV-positive patients receiving liver transplantation in mainland China.

INTRODUCTION

Human immunodeficiency virus (HIV) remains a significant global health concern, with the latest data from the Joint United Nations Programme on HIV/acquired immunodeficiency syndrome (AIDS) indicating a staggering 38 million individuals infected worldwide in 2021. Approximately 4000 people contract HIV daily, resulting in an annual increase of 1.5 million new infections[1]. According to a report from the Chinese Center for Disease Control and Prevention, it is projected that by 2023, over 1.2 million individuals in China will be living with HIV, with an annual increment of around 80000 cases (https://www.chinacdc.cn. Accessed 30 November 2023). Since the

advent of highly active antiretroviral therapy (HAART) in 1996, substantial progress has been made in controlling HIV infection, managing opportunistic infections, reducing mortality rates, and prolonging life expectancy among infected individuals[2]. HIV/AIDS has become a chronic, manageable condition. However, liver-related mortality remains a formidable challenge, particularly for HIV-positive individuals undergoing HAART, who are increasingly susceptible to complications associated with co-infections, notably hepatitis C virus (HCV) and hepatitis B virus (HBV), leading to hepatocellular carcinoma, end-stage liver disease (ESLD), or alcohol-related liver disease[3,4]. Given the shared transmission routes, co-infections with chronic HCV and chronic HBV are prevalent[5].

GLOBAL TRENDS IN LIVER TRANSPLANTATION FOR HIV-POSITIVE PATIENTS

Liver transplantation (LT) is the only effective method for treating various ESLDs. Initially, HIV-positive patients were excluded from LT due to concerns about their compromised immune system, potential acceleration of HIV progression with immunosuppressive drugs, and limited organ resources[6,7]. However, by the year 2000, as the number of HIV-positive patients requiring LT significantly increased, the focus shifted towards addressing ESLD and end-stage renal disease in these individuals. The United States and the United Kingdom initiated two pilot trials for LT in HIV-positive individuals, yielding favorable outcomes without evidence of immunosuppressive drugs exacerbating the progression of HIV[8]. Then, a prospective multicenter study confirmed that LT in HIV patients exhibited excellent patient and graft outcomes[9].

In 2020, a large retrospective study enrolling LT recipients from the Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients from 2008 to 2015 elucidated the survival trends and characteristics of HIV-infected LT recipients[10]. Among 73206 LT patients, 658 (0.9%) were HIV-infected. From 2008 to 2011, patients survival rates at 1 year and 3 years for the HIV-infected group were 78.2% and 64.1%, respectively. From 2012 to 2015, the 1-year and 3-year survival

rates for the HIV-infected group improved significantly to 86.2% and 75.4%, respectively. The cumulative graft survival rates during 2012-2015 also showed substantial improvement, likely attributed to the rational use of anti-HIV drugs, immunosuppressants, and advancements in surgical techniques. Currently, LT outcomes and survival for HIV-positive recipients are comparable to those of HIV-negative recipients[11,12]. However, during the years 2012-2015, the 3-year graft survival rates for HIV-infected recipients with and without concurrent HCV infection were 62.6% and 84.7%, respectively, with similar results observed in patient survival rates. HIV/HCV co-infected recipients exhibited significantly lower survival rates than HCV mono-infected patients, possibly due to a higher rate of post-transplant HCV recurrence leading to graft failure and recipient mortality[13,14]. Cohort studies from France and Spain indicated a 5-year survival rate below 55% for HIV/HCV co-infected LT recipients[15,16]. Therefore, the question of whether LT should be pursued for this patient population remains contentious. To comprehensively evaluate the long-term postoperative survival of HIV-positive LT recipients, a retrospective cohort study with a follow-up exceeding 10 years examined 180 cases in the United States from 2002 to 2011[17]. At 5 years after transplantation (64.8% for HIV+/HCV- *vs* 51.8% for HIV+/HCV+, $P = 0.15$) and 10 years after transplantation (43.9% for HIV+/HCV- *vs* 44.1% for HIV+/HCV+, $P = 0.20$), there was no statistically significant difference in long-term survival rates between mono-infected (HIV+/HCV-) and co-infected (HIV+/HCV+) recipients. However, when compared to the general transplant population with HCV-positive recipients, the long-term survival and graft survival rates for HIV/HCV co-infected recipients after transplantation were suboptimal. Therefore, further research is necessary to investigate the long-term postoperative outcomes for HIV/HCV co-infected LT recipients.

In contrast to co-infection with HCV, HIV-infected patients concurrently affected by HBV appear to have a more favorable prognosis after LT when an appropriate HBV recurrence prevention strategy is implemented. Optimal prevention for recurrent HBV infection in HIV/HBV co-infected patients seems to involve the combination of antiviral

therapy with hepatitis B immunoglobulin (HBIG)[18]. In a prospective multicenter study in the United States, with passive prophylaxis using HBIG and antiviral treatment, there was no significant difference in graft and patient survival rates between HIV/HBV co-infected and HBV mono-infected LT recipients, with 3-year survival rates reaching 85%[11]. Studies by Anadol *et al*[19] demonstrated a 5-year survival rate of 80% for HIV/HBV co-infected patients, with no clinically relevant HBV-related ESLD observed after LT. Tateo *et al*[20] reported a cumulative graft and patient survival rate of 100% at an average follow-up of 32 months for 13 HIV/HBV co-infected LT recipients. To assess the postoperative prognosis and the risk of complications for HIV/HBV co-infected patients, we reviewed the literature on LT in HBV/HIV co-infected patients, revealing 1-year and 3-year cumulative survival rates of 85.9% and 77.3%, respectively. Moreover, due to the high recurrence rate of HBV viremia, lifelong prophylactic medication is recommended[21].

LIVER TRANSPLANTATION FOR HIV-POSITIVE PATIENTS IN MAINLAND CHINA

According to a cross-sectional study in China, the hepatitis B surface antigen infection rate among HIV-infected individuals can reach 14.5%, nearly three times higher than the general population[22]. In mainland China, HIV infection has long been considered an absolute contraindication for LT. The advent of HAART in 1996 improved the prognosis for HIV-infected individuals and encouraged some transplant centers in China to accept organ transplant candidates who were HIV positive. Until June 2004, mainland Chinese scholars performed LT on two HIV patients[23], but these cases were only followed up for 24 months and 22 months, respectively. Subsequently, there were no reported cases of LT in mainland China for patients with concomitant HIV infection until April 2019, when our transplant center performed LT for a patient with liver failure co-infected with HIV and HBV. This case is the first reported instance of ABO-incompatible LT for HIV/HBV co-infection[24]. As of the latest follow-up, the patient has survived healthily for over 4 years, with normal liver enzyme levels and no transplant

rejection reactions. To date, our transplant center has conducted LT for eight ESLD patients co-infected with HIV, and all but one, who died two months postoperatively due to sepsis and progressive multi-organ failure, have survived. There were no statistically significant differences in acute rejection reactions, cytomegalovirus infection, bacteremia, pulmonary infections, acute kidney injury, new-onset cancers, and vascular or biliary complications compared to HBV-infected patients during the same period.

The preoperative CD4(+) T cell count for the first ABO-incompatible patient in our preliminary report was only 42 cells/μL, while the preoperative CD4(+) T cell counts for the remaining patients were all below 200 cells/μL. With the exception of one case resulting in mortality, all other patients have maintained good health postoperatively.

CONCLUSION

Our study findings suggest that the criteria for preoperative CD4(+) T cell counts in LT recipients co-infected with HIV still require further exploration. Also, a comprehensive assessment beyond preoperative CD4(+) T cell counts is essential to ensure the safety of LT recipients in this category. Despite the relatively low number of cases of LT in HIV-infected individuals in mainland China, postoperative survival rates are comparable to those in Western countries. Given the limited number of cases included in the study, our next step will involve expanding the sample size and conducting more in-depth clinical research.

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