



Review Article

A review of nationwide population study of organ transplantation in Taiwan

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ABSTRACT

Solid organ transplantation has become the therapy of choice for patients with end-stage organ disease. The frequently transplanted organs in Taiwan include liver, kidney, heart, and lung, and the success rate has improved significantly worldwide for the past decades. However, organ recipients are known to be at a higher risk of post-transplant infections and *de novo* cancer due to immunosuppression and oncogenic viral infections. Organ recipients are known to be at a two- to fourfold increased risk of cancer and the risks are particularly high for malignancies caused by viral infections, including post-transplant lymphoproliferative disorders via Epstein-Barr virus, Kaposi sarcoma via Kaposi sarcoma herpesvirus, anogenital cancers via human papillomavirus, and hepatocellular carcinoma via hepatitis B and C virus. Population-based cohort studies may help better understand the pattern of infection and cancer risk in transplant recipients and clarify the role of the immune system, infection, and risk factors in the development of malignancy. Improvement of surgical techniques, advancement of immunosuppressant therapy in addition to early detection and prevention of infection, and regular surveillance of *de novo* cancer after transplantation have become the mainstay of successful organ transplantation.

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1. Introduction

Solid organ transplantation followed by immunosuppression to prevent graft rejection is a life-saving therapy for patients with end organ failure. However, organ recipients are at higher risk of infection¹ and a two- to fivefold increase of *de novo* cancer development² secondary to the exposure to oncogenic viruses and their immunosuppressed status compared with the general population. Worldwide, it has been approximated that one in five incident cancers can be attributed to infectious agents, through either a new infection or a reactivation of a latent virus. Several virus-related malignancies after organ transplantation have been identified [e.g., post-transplant lymphoproliferative disorders (PTLDs) via Epstein-Barr virus, Kaposi sarcoma via Kaposi sarcoma herpesvirus,

anogenital cancers via human papillomavirus, and hepatocellular carcinoma (HCC) via hepatitis B and C virus (HBV and HCV, respectively)].^{3–5}

The National Health Insurance (NHI) Program in Taiwan was launched in 1995 and the coverage was up to 99.5% by the year 2010. Using the NHI Research Database, many population-based studies have been conducted to elucidate morbidity and mortality associated with organ transplantation. This review will mainly discuss the four major types of organ transplantations in Taiwan, namely, liver, kidney, and cardiothoracic transplantations including heart and lung transplantations and their frequently associated infections and cancer risks.

2. Liver transplantation

Liver transplantation has become the treatment of choice for patients with end-stage liver disease, irreversible acute hepatic failure, and selected HCC.⁶ With the advancement in surgical techniques and the use of immunosuppressants, the survival rate worldwide has improved.⁷ Frequently used immunosuppressive drugs in Taiwan include calcineurin inhibitors (cyclosporine and

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tacrolimus), mammalian target of rapamycin inhibitors (sirolimus and everolimus), azathioprine, steroids, and mycophenolic acid, etc. all of which offer the recipients a variety of choices for immunosuppression required after transplantation. A recent population-based study conducted by Huang et al⁸ had revealed that the overall 1-year survival rate in Taiwan was 85.1% and the 5-year survival rate was 79.6% as compared with 92.7% and 80.9%, respectively, in living donor transplant recipients, which were reported from the United Network for Organ Sharing Database (and 89.1% and 73.7%, respectively, in deceased donor liver transplant recipients). Differential hepatitis virus infection distribution was thought to be attributable to the difference in survival rates between Taiwan and Western countries. More specifically, HCV infection was the leading indication for liver transplantation in the United States and Europe and recurrence of HCV infection was universal after liver transplantation and is associated with allograft dysfunction and loss,^{9,10} whereas HBV was the main indication for liver transplantation in Taiwan. The overall 1-, 3-, and 5-year mortality rates after liver transplantation in Taiwan were reported to be 14.9%, 18.8%, and 20.5%, respectively.¹¹ In addition, studies have shown that pre-existing diabetes mellitus (DM) was associated with significant postliver transplantation morbidity and mortality.^{12,13} However, Tsai et al¹⁴ demonstrated that patients with DM did not exhibit any increased risks of 30- and 90-day post-transplant mortality and morbidity rates. More interestingly, those DM patients with renal manifestations exhibited a significantly higher risk of 30-day postoperative mortality than the non-DM cohort, but not those with other DM-associated morbidities, such as ophthalmological involvement, peripheral vascular disorder, ketoacidosis, or coma, suggesting that pretransplant renal function would be predictive of patient survival after transplantation.^{14–16}

As infection is the major cause of mortality and morbidity in liver transplant recipients, several other studies have attempted to investigate the risks of various infections among liver recipients. Cytomegalovirus (CMV) is one of the most common infectious pathogen that can lead to graft loss and mortality in liver transplant recipients.¹⁷ CMV infection has been correlated with the occurrence of vanishing bile duct syndrome,¹⁸ a rare syndrome consisting of chronic cholestasis and loss of intrahepatic bile ducts, the hallmark of chronic allograft rejection.¹⁹ The estimated incidence of CMV disease in other countries was estimated to be 6–40%,^{20,21} whereas in Taiwan a 14.5/100 person-years prevalence and a cumulative incidence of 3.8%, 4.2%, and 4.9% at 1 year, 2 years, and 10 years, respectively, with the risk being highest in the first 6 months after liver transplantation and then declining were reported.¹¹ It has been suggested that the use of antiviral prophylaxis for CMV may improve allograft function and survival in solid organ transplantation recipients.^{22,23}

Besides infection, *de novo* malignancy remains a leading cause of mortality following transplantation, with liver cancer being the most commonly observed cancer in the United States.² In Taiwan, the evidence of cancer risk is limited among liver recipients because most studies had relatively small sample size and were based on a single-institution experience. One study included 444 recipients and showed the standardized incidence ratio of all *de novo* malignancy to be 3.26 compared with the general population, which was consistent with that reported by the Western studies.²⁴ Of all the *de novo* malignancies, the most common was PTLN and bladder cancer and of recurrent malignancy the most common was HCC, which may have a close association with HBV relapse.^{25,26} Low body weight, cancer history, non-HBV carrier status, and preoperative cirrhosis or fulminant hepatitis as indications for liver transplantation were risk factors for developing *de novo* malignancy post-transplantation. Patients

with recurrent malignancy after liver transplantation had a significantly higher mortality compared with patients with *de novo* malignancies.²⁴

3. Kidney transplantation

The incidence and prevalence of end-stage renal disease in Taiwan are relatively high.²⁷ Renal transplantation has become the definitive therapy for most patients with end-stage renal disease to improve life expectancy and quality.²⁸ Similar to liver transplant recipients, kidney recipients are at a higher risk of life-threatening infections and *de novo* malignancies secondary to long-term immunosuppression after transplantation. As the organ is usually scarce with long waiting list, transplant tourism from Taiwan to China has become more common in Taiwan.

BK polyomavirus (BKV) was considered as a potential cause of allograft loss in kidney transplant recipients, with BKV reactivation being a significant cause of morbidity.²⁹ It has been reported that the incidence of BKV-associated nephropathy at 2 years after transplantation in the United States appeared to increase at a steady rate from 1.5% in 2003 to 6.4% in 2009³⁰; however, evidence in Taiwan is limited. One study concerning BKV compared the incidence of BK viruria in transplant tourists with domestic recipients. A significantly higher rate of BK viruria was found in the transplant tourists than in the domestic recipients, although the prevalence of biopsy-proven BKV nephropathy was not statistically significant.³¹

An elevated risk of kidney cancer among kidney recipients has been well described.² In some studies conducted in the Western societies, nonmelanoma skin cancer was considered the most common cancer^{32,33}; however, the pattern appeared to be different in the Asian population. Transitional cell carcinoma was first reported to be the most common cancer in Hong Kong.³⁴ Li et al³⁵ found that kidney recipients were at three times higher risk of all cancers with higher incidences in kidney and bladder cancers. Female sex appeared to be an independent factor for *de novo* cancer post-transplant, which was supported by Hwang et al's³⁶ study demonstrating that female recipients tended to have a significantly higher urologic malignancy risk after renal transplantation. Li et al's³⁵ study found that patients younger than 20 years had the highest risk among all cancers and the risk progressively decreased with age. Hsiao and Hsu³⁷ similarly found that kidney and other unspecified urinary organs were the most common cancer sites, accounting for 18.5% of the malignancies diagnosed in kidney recipients. Other risk factors of *de novo* cancer included a history of chronic renal disease and ischemic heart disease prior to transplantation and older age at the time of transplantation, different from what was previously stated. Nevertheless, elevated cancer risk was consistent with another study conducted in the United States, in which 15 times or higher risk of developing *de novo* renal cell carcinoma was reported in kidney recipients as compared with the general population.³⁸ Interestingly, cancer risk appeared to vary by race/ethnicity in kidney recipients; more specifically, the risk increased more for black kidney recipients than for white or Hispanic recipients, suggesting that racial/ethnic differences might play an important role in cancer risk in addition to post-transplant immunosuppression.³⁹ Therefore, the immunosuppressive status, underlying renal disease, genetic background, and even environmental factors could all contribute to the different cancer risk patterns in Asian population as compared with the Western countries.

In terms of patient and graft survival, another area of interest was to compare outcomes between transplant tourists and domestic recipients as mentioned previously. Chung et al⁴⁰ reported that transplant tourists had a higher prevalence of DM,

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