Hepatocellular carcinoma after kidney transplantation: analysis of Hong Kong Renal Registry

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Abstract
Kidney transplant recipients have increased risk of cancers when compared with the general population. Hepatocellular carcinoma (HCC) is extremely important in Asia where hepatitis B virus (HBV) infection is endemic. The aim is to study the epidemiological and clinical aspects of all de novo HCC in our kidney transplant recipients. Moreover, various preventive strategies which may help to optimize the outcome will also be discussed. A retrospective review of all patients who developed HCC after kidney transplantation between May 1972 and December 2011 in Hong Kong, based on the data from Hong Kong Renal Registry. After a follow-up period of 40,246 person-years, 20 patients (males 15; females 5) developed HCC. The annual incidence was 49.7/100,000 persons per year. Among them, 16 were HBV carriers, 2 were hepatitis C (HCV) carriers and 2 had HBV and HCV co-infection. Presence of HBV infection was associated with 78-fold higher risk for HCC development. Majority (85%) were asymptomatic when HCC was diagnosed by ultrasound or alpha-fetoprotein surveillance. All patients diagnosed by surveillance received active treatment while 2/3 of symptomatic patients could only receive symptomatic care and died rapidly. In conclusion, HBV infection is the major etiological factor for HCC development in kidney transplant recipients in HBV endemic areas. Regular HCC surveillance appeared to be able to detect early stage cancers which are amenable to treatment and offer the best hope of cure.

Keywords
Hepatocellular carcinoma, incidence, kidney transplantation

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Introduction
Kidney transplantation offers the best treatment option for patients with end stage renal disease in terms of survival and quality of life. However, cancer is one of the major causes of mortality and morbidity in kidney transplant recipients, and it has been shown that the risk of development of any cancers was approximately 3-fold when compared with the age- and gender-matched general population.1–3

Chronic viral hepatitis, related to hepatitis B virus (HBV) or hepatitis C virus (HCV), is the leading cause of hepatocellular carcinoma (HCC) in the general population worldwide. HCC is extremely important in Asia where HBV infection is endemic. A study in Taiwan showed that chronic HBV infection is associated with a 98-fold higher risk for HCC.4 In Hong Kong, approximately 8% of the general population is HBV carriers5 and HCC ranks the fourth most common cancer in our general population.6 HCC-related mortality is high because of its delayed presentation and surgical cure of HCC relies on early diagnosis. Traditional screening regimen for early HCC detection includes serum alpha-fetoprotein (AFP) levels and liver ultrasound (USG). However, the real benefits and cost-effectiveness of HCC surveillance in the general population remain the source of debate.7 Currently there is no consensus on which surveillance protocol can improve the disease-specific or all-cause mortality for HCC.8 Informal screening for high risk patients is commonly practised because cancers detected by screening are generally smaller and unifocal which are more likely to be amenable to surgical resection.7

Kidney transplantation has a variable effect on risk for specific cancers.1–3 Moreover, the incidence of specific post-transplant cancers also varies among different geographical areas. Previous studies showed that the incidence of HCC after kidney transplant is much higher in Asian countries where HBV infection is endemic, when compared with the Western countries.9,10 However, prophylactic use of antiviral therapy may theoretically suppress the HBV DNA levels and reduce the risk of HCC.11 In fact, there are only limited data
in literature regarding the development and management of HCC after kidney transplantation. In addition, there is also no firm and uniform guideline for HCC surveillance in kidney transplant recipients, although regular AFP and USG are recommended in high risk patients in most centers.

In this study, we present the epidemiological and various clinical aspects, including the etiologies, clinical presentation and diagnostic methods, as well as the long-term outcome of all de novo HCC in our kidney transplant recipients. Moreover, we will also discuss about the various preventive strategies which may help to optimize the outcome of kidney transplant recipients with HCC.

Patients and methods
We performed a retrospective review of all patients who developed de novo HCC after kidney transplantation between May 1972 and December 2011, based on the Renal Registry of the Hospital Authority (HA) of Hong Kong (accounts for >90% of patients who received renal replacement therapy in Hong Kong) and medical records from individual transplant centers. The data in the Renal Registry belonged to the Central Renal Committee, HA. Analysis and publication of data was approved by the Committee. HBV infection was confirmed by hepatitis B surface antigen (HBsAg) positive testing while HCV infection was defined by presence of HCV antibodies. Those cancers detected after graft failure were excluded from analysis. For purposes of the analyses and defining years of follow-up, patients were censored at the time of death, time of graft failure, diagnosis of cancer, the last reported contact or 31 December 2011.

SPSS (SPSS 15.0, Inc., Chicago, IL) was used to perform the statistical analyses. Standardized incidence ratio (SIR) was calculated as the number of observed cancer cases among the kidney transplant recipients divided by the expected number of cancer cases. The expected number of cases was based on the person-years at risk and the age-adjusted cancer incidence rates in the general population, which could be obtained from the Hong Kong Cancer Registry 2010, provided by the HA. The 95% confidence intervals (CIs) of the SIRs could be calculated by assuming that the observed cancers follow a Poisson distribution.

Results
A total of 4895 kidney transplants were performed in 4674 patients, among which 457 (9.8%) were HBV carriers, 191 (4.1%) were HCV carriers and 28 (0.6%) had co-infection with HBV and HCV. After a follow-up period of 40,246 person-years (mean: 8.2 ± 6.2 years, range: 2 months to 33.4 years), 20 patients (males 15; females 5) developed HCC. The annual incidence was 49.7/100,000 persons per year. HCC ranked the sixth most common post-transplant malignancies (6.7% of all cancers) in our cohort and the SIR was 2.53 (95% CI 1.63–3.91). The risk was higher in female (SIR 3.94, 95% CI 1.64–9.46) than male patients (SIR 2.26, 95% CI 1.36–3.74). All patients with HCC in our cohort had chronic viral hepatitis. Among them, 16 patients were HBV carriers, 2 were HCV carriers and 2 had co-infection with HBV and HCV. All 6 HBV carriers who had kidney transplant between 2002 and 2011 were put on antiviral therapy after transplantation. On the other hand, only 5 out of the 12 HBV carriers who had transplant before 2002 were on antiviral therapy. Ten patients were on lamivudine, whereas one was on entecavir. The mean age at transplant was 44.3 ± 12 years, whereas the mean age at HCC diagnosis was 51.4 ± 8.4 years (male 51.3 ± 9.1 years; female 51.6 ± 6.8 years). The duration from kidney transplant to the diagnosis of HCC were 7 years (range: 1 month to 17 years).

Among the total 485 patients (335 males and 150 females) who had chronic HBV infection (including 28 patients who also had HCV co-infection), 18 patients developed HCC after a follow-up period of 4178 person-years. Using these data, the calculated annual incidence rate of HCC in our HBV positive kidney transplant recipients was 430.8/100,000 persons. On the other hand, 4189 patients were non-HBV carriers. Among them, only 2 patients developed HCC after a follow-up period of 36,068 person-years and the annual incidence rate of HCC in our HBV negative kidney transplant recipients was 5.5/100,000 persons. In other words, presence of chronic HBV infection was associated with 78-fold higher relative risk for HCC in our kidney transplant recipients.

Clinical manifestations and treatment modalities were not properly recorded in 2 patients. For the remaining 18 patients, 3 (15%) were symptomatic when the diagnosis was confirmed. The clinical manifestations included ascites, weight loss and abdominal discomfort. On the other hand, 15 patients were asymptomatic and were diagnosed to have HCC by AFP and/or USG surveillance. However, the frequency of AFP and USG varied among different patients. Six patients were diagnosed to have HCC by abnormal AFP levels, which were later confirmed by imaging and histology. The median duration between normal and abnormal AFP were 5 months (range: 2–8 months). On the other hand, 9 patients who had normal serial AFP levels were subsequently diagnosed by USG screening. The median USG intervals of these 9 patients were 14 months (range: 8–30 months). Among them, only 4 patients had regular USG surveillance every 6–12 months, with HCC diagnosed at a median interval of 7.5 months between serial USG.

Among the 18 patients with known AFP levels at diagnosis of HCC, 16 patients had HBV infection (2 had HCV co-infection). Eleven patients were on antiviral therapy after transplant, whereas 5 were not. Sixty four percent of patients with antiviral therapy, compared with 20% of patients without antiviral therapy, had normal AFP levels but the difference was not statistically significant (p = 0.28).

The immunosuppressive regimen was adjusted in all patients after diagnosis of HCC. Eighteen patients either reduced or stopped the calcineurin inhibitors while sirolimus was added in 5 patients. None of them developed acute rejection. The treatment and outcome of these patients are summarized in Table 1. All 15 asymptomatic patients who were diagnosed by surveillance received treatment; 8 underwent hepatic resection, 2 received transarterial chemoembolization (TACE), 2 had radiofrequency ablation (RFA), 1 had percutaneous ethanol injection (PEI), 1 had surgery + TACE and 1 had RFA + TACE. On the other hand, none of the 3 patients diagnosed by symptoms received surgery. One of them received selective internal radiation (SIT) and died after 16 months. The other 2 received symptomatic treatment.
only and died 1 month and 5 months after diagnosis, respectively.

The median survival of all our HCC patients was 40 months (range: 1 month to 10 years). Total 11 patients died (8 due to cancer progression, 2 due to sepsis and 1 due to cerebrovascular accident). The crude rate of HCC mortality in our HBV positive kidney transplant recipients was 263/100,000 person-years. The median duration from cancer to death was 18 months (range: 1 month to 10 years). The patient who survived 10 years after diagnosis had hepatic resection but finally died of sepsis. On the other hand, 9 patients were still alive with a median follow-up of 54 months (range: 1–105 months) after diagnosis of HCC. Only 1 patient had graft failure due to unknown reason. All of them received treatment, 6 had surgical resection alone, 1 TACE, 1 RFA and 1 combined RFA and TACE.

**Discussion**

This is a large scale population-based study of all kidney transplant recipients who were diagnosed to have de novo HCC in Hong Kong. Similar to our general population, the male-to-female ratio for HCC in our kidney transplant recipients was also 3:1. However, HCC tends to occur at a younger age in our kidney transplant recipients than in our general population. In our study, the mean age of HCC diagnosis for men and women were 51.3 and 51.6 years, respectively. On the other hand, the median age of HCC diagnosis in our general population for men and women were 63 and 71 years, respectively. This difference in the age of HCC diagnosis may be partly attributed to the earlier detection of tumour during surveillance. Contrary to the low incidence in Western countries, HCC is a leading cause of post-transplant malignancies in Asia where HBV infection is endemic. HCC accounted for 37.9% of all cancers after kidney transplantation in Taiwan and only approximately half of the transplant recipients with HCC had chronic HBV or HCV infection. On the other hand, HCC is the sixth commonest post-transplant cancers (6.7% of all cancers) in our cohort, but all tumors were related to HBV and/or HCV infections. Various factors are shown to affect the development of HCC in HBV carriers in different geographical areas, including HBV genotype, HBeAg status, degree of liver fibrosis/cirrhosis, use of antiviral therapies, HBV DNA levels, family history of HCC and amount of alcohol consumption. Unfortunately such information was largely unavailable in our study. There is now universal consensus that all HBV positive kidney transplant recipients should receive pre-emptive antiviral therapies in order to maintain undetectable HBV DNA levels, which might lower the risks of HCC. Entecavir and tenofovir are preferred nowadays because of high risks of development of lamivudine resistant strains.

A recently published literature review showed that the overall HCC mortality rate among HBV positive kidney transplant recipients in high prevalence area was 775/100,000 person-years. The author compared the HCC mortality in HBV positive kidney transplant recipients with that of HBV positive general populations, and found that the HCC mortality rate was increased in low and intermediate seroprevalence areas, but inconclusive in high seroprevalence areas. Different surveillance programs may contribute to differences in HCC mortality in various studies. The HCC mortality rate in our HBV positive kidney transplant recipients was 263/100,000 person-years, which was comparable with that of the HBV positive general population in high seroprevalence areas such as Taiwan (283.5/100,000 person-years). The prognosis of HCC depends on the stage at diagnosis. The preferred therapy is surgical resection. However, most patients are not eligible because of tumour size and/or underlying liver dysfunction. For those who are not surgically resectable, liver transplantation remains the other potentially curative option. For patients who are not eligible for resection or liver transplantation, therapeutic options include nonsurgical methods of tumour ablation such as RFA, PEI, TACE, systemic chemotherapy or radiation therapy. The choice of treatment is determined by the size and distribution of the tumors, the severity of underlying liver disease, the vascular involvement and the patients' overall general health status.

A study showed that the median survival of patients with HCC in our general population was 11 months while up to 39.5% of the HCC were diagnosed with clinical symptoms. On the other hand, our kidney transplant recipients had a far better survival with a median survival of 40 months, which was probably related to the earlier stage of disease at diagnosis (only 15% of our patients presented with symptoms). In our cohort, surgical resection remains the mainstay of treatment and seems to provide a good prognosis to our patients with HCC. However, information concerning the HCC staging in our cohort was largely incomplete. Patients with early stage HCC can achieve 5-year survival rates near 70% after tumour resection and transplantation, while those with advanced HCC have a median survival of less than 1 year. As a result, the practice of regular surveillance for asymptomatic HCC in high-risk population is widely accepted. However, there is lack of evidence in randomized controlled trials (RCT) addressing the issues of mortality benefits and cost-effectiveness of HCC surveillance in kidney transplant recipients. Most of the current recommendations for cancer screening in kidney transplant recipients are entirely extrapolated from data in the general population.
However, RCT showing the benefits of HCC surveillance in general population is also scarce. There is only one RCT, which was performed in China and involved 18,816 patients with markers of current or prior HBV infection, showed that HCC related mortality could be reduced by 37% in surveillance arm when compared with those without surveillance.\textsuperscript{23} As a result, additional RCT are still considered necessary in order to confirm the benefits of surveillance.

To decide whether to put a patient in a surveillance program is determined by the level of risk for HCC, which in turn, is related to the incidence of HCC.\textsuperscript{24} However, there is no data to indicate what level of risk should trigger HCC surveillance in kidney transplant recipients. Theoretically guidelines published for HCC surveillance in general population should also be strictly applied to transplant population because of the significant higher risk of cancer in kidney transplant recipients. In our cohort, the SIR of HCC in kidney transplant recipients is 2.53. HBV infection is not only the main risk factor for HCC development in our general population, but also in kidney transplant recipients. Ninety percent (18/20) of our patients with HCC had HBV infection (2 had co-HCV infection). In addition, we found that HBV infection was associated with 78-fold higher relative risk for HCC in our kidney transplant recipients. In Caucasians, the risk of HCC is related to inflammatory activity and the presence of cirrhosis.\textsuperscript{25} This is not true for Asian HBV carriers, who remain at risk regardless of presence of cirrhosis or replication status.\textsuperscript{26} Taking into consideration of the excess risk of cancer and earlier onset of disease after kidney transplantation, it is therefore reasonable to recommend HCC surveillance in all Asian HBV kidney transplant recipients, irrespective of cirrhosis status and disease activity. For non-HBV carriers, HCC surveillance is also recommended for all patients with cirrhosis of various etiologies, although the risk of HCC development is likely not uniform across all patients.\textsuperscript{24}

The process of surveillance also involves deciding the optimal surveillance tools as well as the optimal interval. The American Association for the Study of Liver Diseases currently recommends USG with or without AFP at 6–12-month intervals for high risk group of patients.\textsuperscript{24} Although surveillance USG could detect majority of tumors before clinical presentation with a pooled sensitivity of 94%, it was less effective for detecting early HCC with a sensitivity of only 63%.\textsuperscript{27} It is controversial whether there was additional benefit in adding AFP to USG during surveillance.\textsuperscript{26} Moreover, use of antiviral treatment might reduce the AFP levels which could further reduce its sensitivity.\textsuperscript{28} In our study, more patients with antiviral therapy had normal AFP levels than patients without antiviral therapy. In fact, half (9/18) of our patients had normal serial AFP levels before HCC was diagnosed by USG surveillance, which might further indicate that AFP alone may not be an adequate screening test. On the other hand, the effectiveness of USG may be related to operator experience and technique, and scanning is difficult in patients with morbid obesity or a very nodular liver. As a result, AFP may still play an important role of HCC surveillance in kidney transplant recipients.

Surveillance intervals could result in significant differences in sensitivity for detection of early HCC. The pooled sensitivity of the studies with surveillance at least every 6 months was significantly higher than studies with surveillance program on an annual basis (70.1% vs. 50.1%, \(p = 0.001!\)).\textsuperscript{27} A study showed that surveillance interval of less than 6 months may be associated with early detection of HCC and improved survival in HBV endemic areas.\textsuperscript{29} However, underutilization of HCC surveillance is common with most studies reporting rates below 30%.\textsuperscript{30} Similar situation may also occur in kidney transplant recipients. In our cohort, only 4 out of the 20 patients diagnosed with HCC received USG surveillance at intervals between 6 and 12 months. As a result, further efforts should also focus on identifying appropriate intervention targets to increase surveillance rates.

In conclusion, chronic HBV infection is the major etiological factor for the development of HCC not only in the general population, but also in kidney transplant recipients in HBV endemic areas such as Hong Kong. As in our general population, regular surveillance with USG and AFP appeared to be able to detect early HCC which is amenable to liver transplantation or surgical resection and offer the best hope of cure. However, RCT assessing the benefits of surveillance are still considered necessary.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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