

Hepatocellular carcinoma in patients with chronic kidney disease

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Abstract

AIM: To investigate outcomes of hepatocellular carcinomas (HCCs) in patients with chronic kidney disease (CKD).

METHODS: Four hundred and forty patients referred between 2000 and 2002 for management of HCCs were categorized according to their CKD stage, *i.e.*, estimated glomerular filtration rate (eGFR) > 90 (stage 1), 60-90 (stage 2), 30-60 (stage 3), 15-30 (stage 4), and < 15 (stage 5) mL/min per 1.73 m², respectively. Demographic, clinical and laboratory data were collected and mortality rates and cause of mortality were analyzed. The mortality data were examined with Kaplan-meier method and the significance was tested using a log-rank test. An initial univariate Cox regres-

sion analysis was performed to compare the frequency of possible risk factors associated with mortality. To control for possible confounding factors, a multivariate Cox regression analysis (stepwise backward approach) was performed to analyze those factors that were significant in univariate models ($P < 0.05$) and met the assumptions of a proportional hazard model.

RESULTS: Most HCC patients with CKD were elderly, with mean age of diagnosis of 60.6 ± 11.9 years, and mostly male (74.8%). Hepatitis B, C and B and C co-infection virus were positive in 61.6%, 45.7% and 14.1% of the patients, respectively. It was found that patients with stages 4 and 5 CKD were not only older ($P = 0.001$), but also had higher hepatitis C virus carrier rate ($P = 0.001$), lower serum albumin level ($P = 0.001$), lower platelet count ($P = 0.037$), longer prothrombin time ($P = 0.001$) as well as higher proportions of advanced cirrhosis ($P = 0.002$) and HCCs ($P = 0.001$) than patients with stages 1 and 2 CKD. At the end of analysis, 162 (36.9%) patients had died. Kaplan-Meier analysis revealed that patients with stages 4 and 5 CKD suffered lower cumulative survival than stages 1 and 2 CKD (log-rank test, $\chi^2 = 11.764$, $P = 0.003$). In a multivariate Cox-regression model, it was confirmed that CKD stage [odds ratio (OR) = 1.988, 95%CI: 1.012-3.906, $P = 0.046$], liver cirrhosis stage (OR = 3.571, 95%CI: 1.590-8.000, $P = 0.002$) and serum albumin level (OR = 0.657, 95%CI: 0.491-0.878, $P = 0.005$) were significant predictors for mortality in this population.

CONCLUSION: HCC patients with stages 4 and 5 CKD had inferior survival than stages 1 and 2 CKD. This warrants further studies.

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Key words: Hepatocellular carcinoma; Hepatitis B virus; Hepatitis C virus; Chronic kidney disease; End-stage renal disease

Core tip: There is a paucity of data regarding outcomes of hepatocellular carcinoma (HCC) in patients with chronic kidney disease (CKD), even though both hepatitis B virus and CKD are endemic in Taiwan. In a large-scale study, a total of 440 patients with HCC were categorized according to their CKD stage. At the end of analysis, it was found that HCC patients with stages 4 and 5 CKD suffered poorer survival than stages 1 and 2 CKD, which might be explained by inferior liver reserve. Interestingly, tumor stage was not a significant predictor for mortality according to a multivariate Cox regression model.

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INTRODUCTION

Taiwan has the highest prevalence and second highest incidence of end-stage renal disease (ESRD) in the world^[1,2]. According to the 2012 Renal Data System of the United States^[3], the United States, Taiwan and Japan continue to have some of the highest rates of incident ESRD, at 369, 361 and 288 per million population in 2010. In Taiwan, the prevalence of ESRD reached 2584 per million in 2010, while rates of 2260 and 1870 were reported in Japan and the United States. Similarly, hepatitis B virus (HBV) and hepatocellular carcinoma (HCC) are endemic in Taiwan^[4-6]. The carrier rate of hepatitis B surface antigen (HBsAg) in the general population is 15%-20%^[4]. Consequently, many Taiwanese patients with CKD or ESRD are also chronic HBV carriers^[7].

There is strong evidence of increased cancer risk in patients with CKD^[8], in patients with ESRD being treated with chronic dialysis^[9-11], and in recipients of renal transplant^[12]. The CKD was associated with malignancy and worse prognosis^[13-16]. Moderately reduced kidney function may be an independent risk factor for cancer in older men. The risk begins when estimated glomerular filtration rate (eGFR) falls to approximately 55 mL/min and progressively increases as eGFR declines to 40 mL/min, similar to the risk of patients on dialysis or of transplant recipients^[8]. Because survival time after the confirmation of recurrence was significantly shorter in the CKD group, their cumulative survival rate was significantly lower compared to that in the non-CKD group, although the difference in disease-free survival was not significant^[17].

Almost all cancers in the renal parenchyma are renal cell carcinoma, whereas cancers in the urinary tract are urothelial carcinoma. These two cancers differ markedly in terms of carcinogenesis and basic biology. Renal cell carcinoma is the most common urologic cancer in Western patients on dialysis, whereas urothelial carcinoma is

the most common urologic cancer in Asian patients on chronic dialysis^[11]. This is a unique and distinguishing epidemiologic characteristic of the Taiwanese population^[11]. On the other hand, very few data^[17-22] are available regarding the outcome of patients with HCC and CKD, even though both are endemic in Taiwan.

Therefore, this study analyzed the registry of the Chang Gung Memorial Hospital to examine the epidemiology of HCC in CKD populations in Taiwan.

MATERIALS AND METHODS

This retrospective observational study complied with the guidelines of the Declaration of Helsinki and was approved by the Medical Ethics Committee of Chang Gung Memorial Hospital, a tertiary referral center in northern Taiwan. Because of the retrospective nature of this study, Institutional Review Board approval was obtained and the informed consent of risk of HCC and all treatment modalities of all patients on their initial admission was used. Moreover, all individual information was securely protected (by delinking identifying information from the main dataset) and available only to the investigators. All the data were analyzed anonymously and all primary data were collected according to epidemiologic guidelines. This policy was based on previous publications^[23,24].

Patients

Four hundred and forty patients referred between 2000 and 2002 for management of HCCs were categorized according to their CKD stage, *i.e.*, eGFR > 90 (stage 1), 60-90 (stage 2), 30-60 (stage 3), 15-30 (stage 4), and < 15 (stage 5) mL/min per 1.73 m², respectively. Demographic, clinical, laboratory and mortality data were obtained for analysis.

Diagnosis of HCC

HCC was diagnosed by alpha-fetoprotein, imaging studies such as ultrasonography, radio-contrast enhanced triphasic dynamic computed tomography, magnetic resonance imaging, angiography, and/or documented tissue histopathology^[25].

Diagnosis of liver cirrhosis

Cirrhosis was diagnosed by histopathology or by laboratory tests, hepatic ultrasonography, and clinical manifestations of chronic hepatitis with portal hypertension (*i.e.*, varices, thrombocytopenia, or splenomegaly), and/or hepatic decompensation (*i.e.*, jaundice, prolonged prothrombin time, and ascites)^[26].

Diagnosis of CKD

The eGFR was computed using the four-variable modification of diet in renal disease (MDRD) study equation^[27]. The CKD stage was defined as 1, 2, 3, 4 and 5 according to eGFR; > 90, 60-90, 30-60, 15-30, and < 15 mL/min per 1.73 m², respectively^[27].

Table 1 Baseline characteristics of patients with hepatocellular carcinoma, stratified according to the stage of chronic kidney disease *n* (%)

Variable	Total (<i>n</i> = 440)	Stages 1 and 2 (<i>n</i> = 132)	Stage 3 (<i>n</i> = 263)	Stages 4 and 5 (<i>n</i> = 45)	<i>P</i> value
eGFR ¹	53.7 ± 27.1	73.5 ± 13.5	50.0 ± 26.4	17.6 ± 8.7	0.000
Age ¹ (yr)	60.6 ± 11.9	54.4 ± 12.3	63.1 ± 10.5	64.0 ± 11.7	0.000
Male	329 (74.8)	115 (87.1)	182 (69.2)	32 (71.1)	0.000
HBV carrier	271 (61.6)	97 (73.5)	152 (57.8)	22 (48.9)	0.002
HCV carrier	201 (45.7)	42 (31.8)	131 (49.8)	28 (62.2)	0.000
HBV and HCV carrier	62 (14.1)	15 (11.4)	39 (14.8)	8 (17.8)	0.488
Follow-up duration ¹ (mo)	37.6 ± 37.1	37.0 ± 37.6	40.7 ± 37.6	20.9 ± 27.4	0.013

¹Data are presented as mean ± SD. The *P* value represents comparison between patients with stages 4 and 5 and patients with stages 1 and 2. eGFR: Estimated glomerular filtration rate; HBV: Hepatitis B virus; HCV: Hepatitis C virus.

Table 2 Liver function tests of patients with hepatocellular carcinoma, stratified according to the stage of chronic kidney disease (mean ± SD)

Variable	Total (<i>n</i> = 440)	Stage 1 and 2 (<i>n</i> = 132)	Stage 3 (<i>n</i> = 263)	Stages 4 and 5 (<i>n</i> = 45)	<i>P</i> value
AFP (ng/mL)	6202.1 ± 83392.3	3564.6 ± 11906.0	8176.6 ± 106579.9	1866.3 ± 4866.0	0.911
AST (U/L)	84.8 ± 77.9	94.3 ± 76.1	77.4 ± 68.6	104.3 ± 126.5	0.495
ALT (U/L)	73.0 ± 90.4	79.4 ± 79.1	64.8 ± 49.2	103.0 ± 218.9	0.150
T-bilirubin (mg/dL)	1.8 ± 3.7	1.5 ± 1.6	1.8 ± 4.3	2.8 ± 4.4	0.198
ALP (U/L)	122.4 ± 92.1	124.0 ± 76.6	114.6 ± 79.7	164.5 ± 170.2	0.072
Albumin (g/dL)	3.5 ± 0.7	3.6 ± 0.6	3.5 ± 0.7	3.2 ± 0.7	0.001
Prolonged PT (s)	1.9 ± 4.3	1.4 ± 1.2	1.6 ± 2.1	5.1 ± 12.4	0.000
Platelet count (x 10 ³ /μL)	138.2 ± 90.7	163.7 ± 109.7	126.5 ± 80.1	131.4 ± 73.0	0.037

The *P* value represents comparison between patients with stages 4 and 5 and patients with stages 1 and 2. AFP: Alpha-fetoprotein; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; T-bilirubin: Total bilirubin; ALP: Alkaline phosphatase; PT: Prothrombin time.

Management of HCC

The HCC patients in the stages 1 and 2 groups underwent tumor resection, liver transplantation, or percutaneous interventional therapies for local tumor ablation, including radio-frequency ablation, pure ethanol injection therapy, pure acetic acid injection therapy, and transcatheter arterial chemo-embolization^[28]. Patients in the stage 3 group received trans-catheter arterial chemo-embolization and radio-frequency ablation^[28]. Those in stage 4 received palliative chemotherapy, trans-catheter arterial chemo-embolization, or radiotherapy, and medical care^[28].

Statistical analysis

Continuous variables are expressed as means and standard deviations and categorical variables as numbers with percentages in brackets. All data were tested for normality of distribution and equality of standard deviations before analysis. For comparisons between patient groups, we used General Linear Model (Least Significant Difference test) for quantitative variables and Cross-tabulation (χ^2 or Fisher's exact tests) for categorical variables. Mortality data were compared using the Kaplan-Meier method and the significance was tested using a log-rank test. An initial univariate Cox regression analysis was performed to compare the frequency of possible risk factors associated with mortality. To control for possible confounding factors, a multivariate Cox regression analysis (stepwise backward approach) was performed to analyze those factors that were significant in univariate

models ($P < 0.05$) and met the assumptions of a proportional hazard model. We considered results that rejected the null hypothesis with 95% confidence to be significant. All analyses were performed using IBM SPSS Statistics Version 20.

RESULTS

Baseline characteristics

Most HCC patients with CKD were elderly, with mean age of diagnosis of 60.6 ± 11.9 years (Table 1), and mostly male (74.8%). Hepatitis B, C and B and C co-infection virus were positive in 61.6%, 45.7% and 14.1% of the patients, respectively. It was found that patients with stages 4 and 5 CKD were older ($P = 0.001$) and had higher hepatitis C virus (HCV) carrier rates ($P = 0.001$) than patients with stages 1 and 2 CKD. On the other hand, there were more male ($P = 0.000$) and HBV carrier rate ($P = 0.002$) in stages 1 and 2 than stages 4 and 5 CKD.

Comparison of liver biochemistry test

Patients with stages 4 and 5 CKD not only had lower serum albumin level ($P = 0.001$) and platelet count ($P = 0.037$), but also had longer prothrombin time ($P = 0.001$) than stages 1 and 2 CKD (Table 2).

Comparison of liver reserve

Patients with stages 4 and 5 CKD had higher incidences of advanced cirrhosis than stages 1 and 2 CKD (Table 3, $P = 0.002$).

Table 3 Liver cirrhosis classification, tumor staging, cause of mortality of patients with hepatocellular carcinoma stratified according to the stage of chronic kidney disease *n* (%)

Variable	Total (<i>n</i> = 440)	Stage 1 and 2 (<i>n</i> = 132)	Stage 3 (<i>n</i> = 263)	Stages 4 and 5 (<i>n</i> = 45)	<i>P</i> value
Liver cirrhosis classification (Child-Pugh score)					0.002
No	53 (12.0)	27 (20.5)	23 (8.7)	3 (6.7)	
Class A	236 (53.6)	67 (50.8)	151 (57.4)	18 (40.0)	
Class B	110 (25.0)	30 (22.7)	64 (24.3)	16 (35.6)	
Class C	41 (9.3)	8 (6.1)	25 (9.5)	8 (17.8)	
Tumor stage					0.001
Stage 1	213 (48.4)	60 (45.5)	133 (50.6)	20 (44.4)	
Stage 2	113 (25.7)	27 (20.5)	76 (28.9)	10 (22.2)	
Stage 3	84 (19.1)	40 (30.3)	36 (13.7)	8 (17.8)	
Stage 4	30 (6.8)	5 (3.8)	18 (6.8)	7 (15.6)	
Mortality	162 (36.9)	47 (35.6)	94 (35.9)	21 (46.7)	
Cause of mortality					0.050
Liver failure	27 (6.1)	10 (7.6)	16 (6.1)	1 (2.2)	
Tumor death	35 (8.0)	8 (6.1)	22 (8.4)	5 (11.1)	
Gastrointestinal bleeding	27 (6.1)	11 (8.3)	16 (6.1)	0 (0)	
Sepsis	69 (15.7)	18 (13.6)	36 (13.7)	15 (33.3)	
Others	5 (1.1)	1 (0.8)	4 (1.5)	0 (0)	

The *P* value represents comparison between patients with stages 4 and 5 and patients with stages 1 and 2.

Table 4 Cox regression analysis of mortality in patients with hepatocellular carcinoma and chronic kidney disease

Variable	Univariate analysis		Multivariate analysis	
	Odds ratio (95%CI)	<i>P</i> value	Odds ratio (95%CI)	<i>P</i> value
Chronic kidney disease stage	2.237 (1.376-3.636)	0.001	1.988 (1.012-3.906)	0.046
Liver cirrhosis stage	4.566 (2.331-8.929)	0.000	3.571 (1.590-8.000)	0.002
Tumor stage	3.509 (1.789-6.849)	0.000	2.169 (0.997-4.717)	0.051
Albumin, each increase of 1 mg/dL	0.503 (0.399-0.633)	0.000	0.657 (0.491-0.878)	0.005
Prolonged prothrombin time, each increase of 1 s	1.062 (1.036-1.089)	0.000	0.977 (0.942-1.013)	0.215

Comparison of tumor staging

Most of the HCCs were diagnosed in the early stages (Table 3). Patients with stages 4 and 5 CKD had higher proportions of advanced HCCs than stages 1 and 2 CKD ($P = 0.001$).

Comparison of mortality

At the end of analysis, 162 (36.9%) patients had died (Table 3). It was revealed that patients with stages 4 and 5 CKD suffered higher fatal septic complications than stages 1 and 2 CKD ($P = 0.050$). The one-, three-, and five-year survival rates were 86.2%, 71.3% and 55.9%, respectively (Figure 1). In addition, patients with stages 4 and 5 CKD suffered lower cumulative survival than stages 1 and 2 CKD (Figure 2, log-rank test, $\chi^2 = 11.764$, $P = 0.003$).

Mortality analysis

In a multivariate Cox regression model (Table 4), it was confirmed that CKD stage [odds ratio (OR) = 1.988, 95%CI: 1.012-3.906, $P = 0.046$], liver cirrhosis stage (OR = 3.571, 95%CI: 1.590-8.000, $P = 0.002$) and serum albumin level (OR = 0.657, 95%CI: 0.491-0.878, $P = 0.005$) were significant predictors for mortality.

DISCUSSION

The analytical data demonstrated that HCC patients with stages 4 and 5 CKD had inferior survival than stages 1 and 2 CKD. The reason is unclear but inferior liver reserve in this subgroup should be considered. In a large-scale study in Taiwan^[16], there was a higher risk for overall cancer mortality in CKD patients compared to non-CKD patients (adjusted hazard ratio 1.2). Moreover, CKD was associated with increased mortality from liver, kidney, and urinary tract cancers, with adjusted hazard ratios of 1.74, 3.3, and 7.3, respectively. Most importantly, patients with stage 4 CKD had poorer prognosis than the other groups^[16], but the reason was also unclear.

In the present study, patients with HCC were stratified according to the stage of CKD. Kaplan-Meier analysis revealed that patients with stages 4 and 5 CKD suffered lower cumulative survival than stages 1 and 2 CKD ($P = 0.003$). A multivariate Cox regression model confirmed that CKD stage ($P = 0.046$), liver cirrhosis stage ($P = 0.002$) and serum albumin level ($P = 0.005$) were significant predictors of mortality. Tumor stage was a significant predictor for mortality in the univariate model ($P = 0.000$), but not after multivariate analysis ($P = 0.051$).

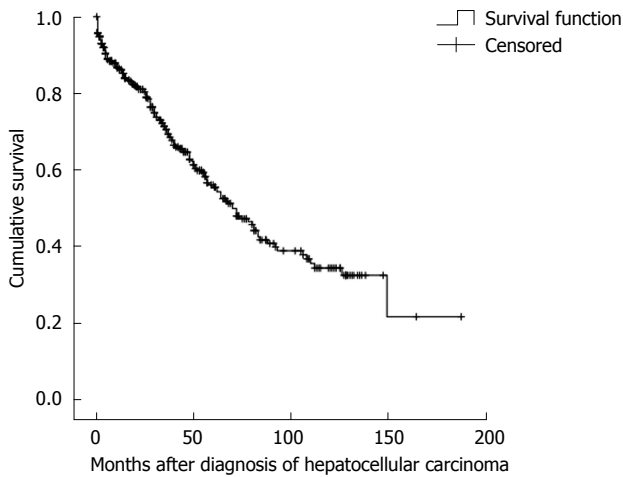


Figure 1 Kaplan-Meier survival analysis. The one-, three-, and five-year survival rate was 86.2%, 71.3% and 55.9%, respectively.

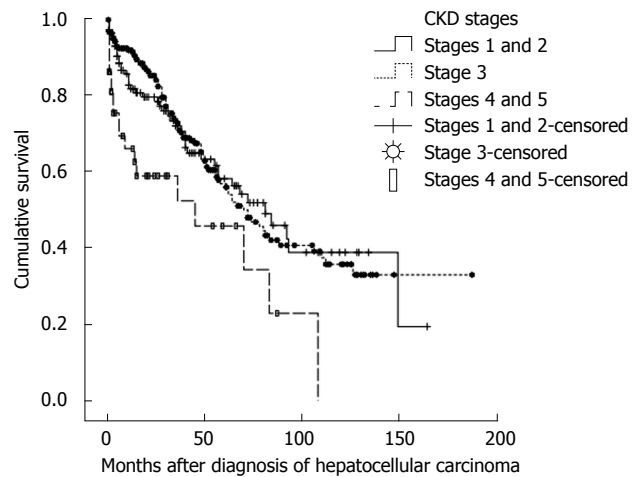


Figure 2 Survival analysis after stratification according to the stage of chronic kidney disease. Patients with stages 4 and 5 chronic kidney disease (CKD) suffered lower cumulative survival than stages 1 and 2 CKD (log-rank test, $\chi^2 = 11.764, P = 0.003$).

Previous study^[29] also reported that eGFR, as determined by MDRD equation, might provide better prognostic accuracy than the CKD-epidemiology collaboration equations independent of liver functional reserve and tumor staging, and is a more feasible renal surrogate for outcome prediction in patients with HCC and CKD stages 1-3 receiving TACE. Notably, the TNM classification did not accurately predict survival in HCC patients with CKD.

In this study, most HCC patients with CKD are male (74.8%). Moreover, there were more male in stages 1 and 2 than stages 4 and 5 CKD ($P = 0.000$). In 1981, Zevin *et al*^[30] reported a hemodialysis patient who developed HCC after long-term therapy with androgenic anabolic steroids. The tumor progressed very rapidly, with no evidence of regression despite discontinuation of the drug. The increased risk of malignancy in patients with chronic uremia and hemodialysis and the higher frequency of HCC associated with the use of anabolic steroids may explain the male predominance in CKD populations^[30]. Since CKD is associated with hypogonadism, the protective effect of estrogen on liver cancer may be reduced^[16]. Nevertheless, male predominance in HCC has been reported due to other than androgenic anabolic steroid use^[31].

In this study, hepatitis B, C and B and C co-infection virus were positive in 61.6%, 45.7% and 14.1% of the patients, respectively. Notably, there were more HCV ($P = 0.001$) in stages 4 and 5 CKD than stages 1 and 2 CKD, but more HBV ($P = 0.002$) in stages 1 and 2 than stages 4 and 5 CKD. Hence, the incidence of HBV (61.6%) is only a little higher than that of HCV (45.7%) in this study, although the national prevalence rates among adults in Taiwan is 1%-3% and 15%-20% for HCV and HBV, respectively^[32]. Notably, after implementation of national hepatitis B vaccination in Taiwan, the prevalence of HBsAg among persons younger than 15 years of age has decreased from 9.8% in 1984 to 0.7% in 1999^[33]. Higher incidences of HBV and HCV infection were noted in uremic patients, possibly because of cross-infection during hemodialysis. It was found that compared to those

who were negative for both markers, patients with both HBsAg and anti-HCV had increased incidence of chronicity^[34]. Earlier study^[35] also found that HCV infection, but not HBV infection, is significantly associated with prevalence and disease severity of CKD in chronic dialysis patients. However, another population-based study^[36] found no association between HCV and risk of development of CKD.

Very few data are available regarding the outcome of HCC in CKD populations. Nevertheless, previous evidences^[17-22] suggested that we should be more aggressive on the principle for management for HCC in CKD patients, because the prognosis was not different between patients with and without CKD. For example, Huo *et al*^[18] compared the survival of 172 HCC patients with and without CKD who underwent percutaneous injection therapy. After a mean follow-up period of 24 ± 9 mo, there was no significant survival difference in patients with and without CKD^[18]. Kondo *et al*^[19] also reported that radiofrequency ablation was a safe and effective option for small HCCs in ESRD patients undergoing chronic hemodialysis. Orii *et al*^[17] compared the outcomes of 17 patients with CKD who had undergone hepatectomy for HCC with 51 non-CKD patients subjected to hepatectomy for HCC. The operative and pathologic findings were comparable between the two groups. Post-operative circulatory insufficiency occurred more frequently in the CKD group ($P = 0.013$). Although the disease-free survival rates were comparable between the two groups, the overall survival rates were significantly lower in the CKD group than in the non-CKD group ($P = 0.031$). Orii *et al*^[17] therefore concluded that hepatectomy for HCC should be considered even for CKD patients if careful peri-operative management and suitable multi-disciplinary treatment for recurrent disease are provided. In the study by Yeh *et al*^[20], the outcomes of 26 ESRD-HCC patients who underwent hepatic resection were reviewed and compared to 1198

HCC patients without ESRD who underwent hepatic resection. There were more associated disease, more physical signs of anemia and post-operative complications, lower hemoglobin, platelet, and alpha-fetoprotein levels, elevated blood urea nitrogen and creatinine levels, smaller tumors, lower HBsAg positivity, higher HCV positivity, and longer hospital stays in the ESRD-HCC group compared to the HCC group. Nonetheless, the overall and disease-free survival rates were similar between the two groups^[20]. Cheng *et al.*^[21] also demonstrated that the operative morbidity and mortality between ESRD and non-ESRD groups were similar. The five-year disease-free survival rates for ESRD and non-ESRD groups were 35.0% and 34.2%, respectively ($P = 0.31$), while the five-year actual survival rates were 67.8% and 53.3%, respectively ($P = 0.54$). The study suggested that liver resection for HCC was justified in selected patients with ESRD^[21]. In the study by Sawada *et al.*^[22], 91 patients who underwent hepatectomy were retrospectively divided into two groups based on their creatinine clearance (Ccr) values: a group with Ccr values ≥ 50 to < 100 mL/min ($n = 77$) and a group with Ccr values of ≥ 20 but < 50 mL/min ($n = 14$). There were no statistically significant differences between the two groups in terms of intra-operative blood loss or intra-operative urine volume. The difference between the two groups in post-operative complications was not statistically significant. Thus, the team concluded that adequate indications, appropriate operative procedures, and peri-operative management might allow hepatectomy to be performed safely in patients with non-uremic minimal renal failure^[22].

In conclusion, our results showed that HCC patients with stages 4 and 5 CKD had inferior survival than stages 1 and 2 CKD, which might be explained by poorer liver reserve. Nevertheless, the retrospective nature of the study, the small patient population, and the short follow-up duration are limitations that warrant further investigations to validate the conclusion drawn here.

COMMENTS

Background

There is a paucity of data regarding outcomes of hepatocellular carcinomas (HCCs) in patients with chronic kidney disease (CKD), even though both hepatitis B virus and CKD are endemic in Taiwan.

Research frontiers

Previous reports found a strong evidence of increased cancer risk in patients with CKD, and the CKD was associated with malignancy and worse prognosis.

Innovations and breakthroughs

The authors analyzed the database of Chang Gung Memorial Hospital to examine the epidemiology of HCC in CKD populations in Taiwan. It was found that HCC patients with stages 4 and 5 CKD had inferior survival than stages 1 and 2 CKD. On the other hand, the TNM classification (or tumor stage) did not accurately predict survival in HCC patients with CKD.

Applications

The data is important to understand the outcome of HCC in CKD population in Taiwan, an area with highest prevalence and second highest incidence of end-stage renal disease in the world.

Terminology

HCC is the most common type of liver cancer. Most cases of HCC are secondary to either a viral hepatitis infection or cirrhosis. CKD is the slow loss of

kidney function over time. There are five stages of CKD, but kidney function is normal in stage 1, and minimally reduced in stage 2, moderately reduced in stage 3, severely reduced in stage 4, and very severely reduced (or called end-stage renal disease) in stage 5.

Peer review

The epidemiology of HCC in CKD population has not been extensively investigated. Therefore, this data is particularly important.

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