Original Article

ALBI grade in dialysis patients with hepatocellular carcinoma: prognostic impact and staging strategy

Shu-Yein Ho[1,2,3], Po-Hong Liu[3,4], Chia-Yang Hsu[3,5], Chih-Chieh Ko[3,6], Yi-Hsiang Huang[3,6,7], Chien-Wei Su[3,6], Cheng-Yuan Hsia[3,8], Rheun-Chuan Lee[3,9], Ming-Chih Hou[3,6], Teh-Ia Huo[2,3,10]

[1]Division of Gastroenterology and Hepatology, Min-Sheng General Hospital, Taoyuan, Taiwan; [2]Department of Medical Research, Taipei Veterans General Hospital, Taipei, Taiwan; [3]Faculty of Medicine, National Yang-Ming University School of Medicine, Taipei, Taiwan; [4]Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas, USA; [5]Division of Gastroenterology and Hepatology, University of Michigan, Ann Arbor, MI, USA; [6]Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan; [7]Institute of Clinical Medicine, National Yang-Ming University School of Medicine, Taipei, Taiwan; [8]Department of Surgery, Taipei Veterans General Hospital, Taipei, Taiwan; [9]Department of Radiology, Taipei Veterans General Hospital, Taipei, Taiwan; [10]Institute of Pharmacology, National Yang-Ming University School of Medicine, Taipei, Taiwan

Contributions: (I) Conception and design: YH Huang, CC Ko, RC Lee, MC Hou; (II) Administrative support: TI Huo; (III) Provision of study materials or patients: TI Huo; (IV) Collection and assembly of data: SY Ho; (V) Data analysis and interpretation: CY Hsu, PH Liu, CY Hsia, CW Su; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Teh-Ia Huo, MD. Professor of Medicine, Department of Medical Research, Taipei Veterans General Hospital, No. 201, Sec. 2, Shipai Rd., Taipei, Taiwan. Email: tihuo@vghtpe.gov.tw.

Background: Patients with hepatocellular carcinoma (HCC) may develop end-stage renal disease and receive dialysis, but the impact of dialysis on the prognosis is unclear. This study aimed to evaluate the outcome of dialysis HCC patients and the prognostic role of albumin-bilirubin (ALBI) grade in these patients.

Methods: Among the consecutive 3,794 HCC patients between 2002–2017, 43 patients undergoing dialysis, and 129 age, sex-matched controls were analyzed. Multivariate Cox hazards model was used to identify independent prognostic predictors.

Results: Dialysis patients had decreased overall survival when compared with non-dialysis patients (n=3,751) and matched controls (n=129; each P=0.004). Patients with ALBI grade 1 had the best survival in the pooled cohort of dialysis and matched controls (n=172). In the Cox model, total tumor volume >33 cm^3 [hazard ratio (HR): 6.763, P<0.001], presence of ascites (HR: 6.168, P<0.001), dialysis duration less than 24 months (HR: 3.144, P=0.006), diabetes-related dialysis (HR: 9.366, P=0.001) and non-curative treatments (HR: 9.220, P<0.001) were poor prognosis factors associated with increase mortality among dialysis patients. Of the 9 currently-used HCC staging systems, the CLIP score was the optimal cancer staging for dialysis patients.

Conclusions: Patients receiving dialysis had decreased overall survival compared with non-dialysis patients. Longer duration of dialysis, non-diabetes related dialysis, absence of ascites, and curative treatments were associated with improved survival in these patients. The ALBI grade is a feasible prognostic model to evaluate liver functional reserve, and the CLIP model is the best staging system for dialysis patients with HCC.

Keywords: Dialysis; hepatocellular carcinoma (HCC); albumin-bilirubin grade (ALBI grade)

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Introduction

Hepatocellular carcinoma (HCC) is the most common type of liver cancer and the fourth leading cause of cancer-related death globally with increasing incidence (1). The major risk factors for HCC are chronic viral hepatitis B and C (HBV, HCV), alcoholism and metabolic syndrome (2,3). HCC patients often coexist with liver cirrhosis which may predispose to renal insufficiency because of vasodilatation of splanchnic circulation, decreased effective blood volume, activation of vasoconstrictors and renal hypoperfusion (4).

Renal dysfunction occurs in about 25% of HCC patients (5). Previous studies showed that renal insufficiency was a negative prognostic predictor in HCC patients receiving surgical resection and transarterial chemoembolization (6,7). Of these patients, some could develop end-stage renal disease (ESRD) and require dialysis. Dialysis patients had an increased risk of uremia-related complications including cardiovascular events, chronic viral hepatitis, hypotension, and various microbial infections (8-10). Notably, 70–90% of HCC patients had renal dysfunction due to underlying chronic liver disease or cirrhosis, and various degrees of liver functional reserve are usually present in dialysis patients with HCC upon diagnosis.

The management of HCC depends on tumor burden and the severity of liver functional reserve. The Child-Turcotte-Pugh (CTP) score has been proposed to assess the degree of liver dysfunction. However, the CTP has its limitation because some parameters are based on arbitrarily defined cut-offs. Moreover, the interpretation of hepatic encephalopathy and ascites are subjective, and serum albumin and ascites are often inter-related. Alternatively, the model for end-stage liver disease (MELD) is an objective method, but its role is primarily for cirrhotic patients awaiting liver transplantation (11). Recently, the albumin-bilirubin (ALBI) grade, consisting of only serum albumin and bilirubin, was reported a simple and objective method to assess hepatic dysfunction. The feasibility of ALBI grade in HCC has been validated by several groups (12-15). However, the prognostic role of ALBI grade in HCC patients receiving dialysis has not been evaluated.

Multiple staging systems including Barcelona Clinic Liver Cancer (BCLC), Cancer of the Liver Italian Program (CLIP), Chinese University Prognostic Index (CUPI), Hong Kong Liver Cancer (HKLC), Japan Integrated Staging (JIS) system, Taipei Integrated Scoring (TIS) system, Tumor-Node-Metastasis (TNM) system, Okuda system, and Tokyo system, have been proposed for HCC (16,17). The prognostic accuracy of these staging systems in HCC patients receiving dialysis has not yet been determined. We aimed to assess the prognostic role of ALBI grade in dialysis HCC patients and determine the optimal staging system for this special patient group.

We present the study in accordance with the REMARK reporting checklist (available at http://dx.doi.org/10.21037/jgo-20-332).

Methods

Patients

During the 16-year period between 2002 to 2017, 3,794 HCC patients in our hospital were prospectively enrolled and retrospectively analyzed. Patients receiving maintenance dialysis were identified at the time of diagnosis based on medical charts. The baseline characteristics, including the underlying of liver disease, the degree of liver function reserve, serum biochemistries, tumor burden (size, number, vascular invasion, and distant metastasis), performance status, cancer stage, treatment, etiology of chronic kidney disease, duration, and forms of dialysis, were recorded upon diagnosis. Patients receiving dialysis for less than 3 months were excluded from this study. For analysis, dialysis patients were matched with patients without dialysis based on age and sex in a 1:3 ratio to specifically evaluate their outcome. The survival of patients was inspected every 3–4 months until death or dropout from the follow-up program.

Ethical statement

The study was approved by the Institutional Review Board of Taipei Veterans General Hospital (No. 2018-03-004CC) and complies with the standards of the Declaration of Helsinki (as revised in 2013) and current ethical guidelines. Informed consent was obtained before treatment.

Diagnosis and definition

The diagnosis of HCC was based on typical image finding according to current European Association for the Study of Liver (EASL) and American Association for the Study of Liver Diseases (AASLD) practice guidelines (1,2). Tumor invasion to branch or main portal vein, or inferior vena cava on CT scan or MRI was denoted as vascular invasion. Distant metastasis, such as lung, lymph node and bone, was confirmed by CT, MRI, or bone scan (18). Performance

status was assessed by using the Eastern Cooperative Oncology Group (ECOG) performance scale (19). The calculation of total tumor volume (TTV) was previously described (20). The equation of model for end-stage liver disease (MELD) score was provided in our previous study (21). The ALBI score was calculated according to the following equation = 0.66 × $\log_{10}$bilirubin (μmol/L) – 0.085 × albumin (g/L). ALBI grades were classified into three groups: ALBI grade 1 (score ≤–2.60), ALBI grade 2 (score >–2.60 and ≤–1.39) and ALBI grade 3 (score >–1.39) (12,14). The equation of estimated glomerular filtration rate (eGFR) was calculated based on the modification of diet in renal disease (MDRD) formula (22). The underlying etiology of chronic kidney disease was classified as diabetes nephropathy and non-diabetes cause such as hypertension, renal artery stenosis, and chronic glomerulonephritis. The forms of dialysis included hemodialysis and peritoneal dialysis.

Treatments

Patients were discussed in the multidisciplinary board conference of Taipei Veterans General Hospital for diagnosis and treatment guidance. The risks and benefits of therapeutic information were explained to each patient. Shared decisions were made by the patients and physicians after individual counseling. Informed consent was obtained before treatment. The procedure of surgical resection, radiofrequency ablation (RFA), and transarterial chemoembolization (TACE) has been prescribed in our previous study. (23). Surgical resection, local ablation therapy, and liver transplantation were collectively defined as curative treatments, and TACE, chemo- or targeted therapy, and other treatments were classified as non-curative treatments.

Statistic analysis

All statistical analyses were performed by using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY, USA). The Kaplan-Meier analysis with the log-rank test was used to evaluate in univariate survival analysis. Multivariate Cox proportional hazards model was used to identify the independent prognostic predictors and adjusted hazard ratio (HR). Corrected Akaike information criterion (AICc) was obtained to reveal how staging system correlated with patient survival. Homogeneity was measured by χ^2 test to evaluate the differences in survival among patients in the same stage within each system. A P value of less than 0.05 was considered statistically significant.

Results

Baseline characteristics

Table 1 shows the comparison of baseline information of all study patients, matched control, and dialysis patients. The mean age of dialysis patients was 62 years, and the majority (65%) of patients were male. HCV (30%) and HBV (28%) were the main cause of chronic liver disease in dialysis patients. Dialysis patients had higher percentage of dual HBV and HCV (9%) infection compared with other two cohorts. The dialysis group had a significant lower albumin level (P=0.028 and 0.042, respectively), higher bilirubin level (P=0.005 and 0.009, respectively), higher creatinine level (P<0.001), lower eGFR level (P<0.001), lower serum α-fetoprotein (AFP) level (P<0.001), larger TTV (P<0.001) compared with other two cohorts. Dialysis patients had a worse performance status compared with non-dialysis and matched controls (P=0.017 and 0.018, respectively). Dialysis patients had higher MELD scores when compared with other two cohorts (all P<0.001). The presence of ascites was also higher in dialysis patients compared with other two cohorts (P<0.001 and P=0.008 respectively). Otherwise, there was no significant difference in vascular invasion, distant metastasis, treatment, BCLC staging and CLIP score between dialysis patients and the other two cohorts.

Comparison of overall survival between dialysis and non-dialysis patients

The median survival of dialysis patients, non-dialysis patients, and matched controls were 16 [95% confidence interval (CI): 8.6–23.4] months, 28 (95% CI: 25.6–30.3) months, and 38 (95% CI: 25–51) months, respectively. Dialysis HCC patients had increased risk of mortality compared with non-dialysis patients (P=0.004, *Figure 1A*), and matched controls (P=0.004, *Figure 1B*). The survival probabilities at 1, 3 and 5 years were 55%, 33% and 14% in dialysis patients, 66%, 45%, 34% in non-dialysis patients, and 68%, 51%, 36% in matched controls, respectively. Among patients receiving dialysis, 36 (84%) patients died during the study period. The cause of death was classified as hepatic-related and non-hepatic related. Eighteen (50%) of patients died of hepatic cause (tumor progression, hepatic failure) and others died of non-hepatic causes (sepsis and others).

Table 1 Comparison of baseline characteristics of dialysis (n=43), non-dialysis (n=3,751) and age, sex-matched controls (n=129) HCC patients

Variables	Dialysis patients	Non-dialysis patients	P	Matched-control	P
Numbers	43	3,751		129	
Age (years, mean ± SD)	62±12	65±13	0.211	62±12	0.980
Male/female, n (%)	28 (65)/15 (35)	2,867 (76)/884 (24)	0.103	84 (65)/45 (35)	1.000
Etiologies of liver disease, n (%)			0.068		0.100
HBV	12 (28)	1,501 (40)		56 (43)	
HCV, n (%)	13 (30)	811(22)		33 (26)	
HBV + HCV, n (%)	4 (9)	131 (4)		3 (2)	
Others, n (%)	14 (33)	1,308 (34)		37 (29)	
Laboratory values (mean ± SD)					
Albumin (g/L)	3.4±0.7	3.7±0.6	0.028	3.7±0.7	0.042
Bilirubin (mg/dL)	2.7±6.5	1.5±2.7	0.005	1.2±1.1	0.009
ALT (IU/L)	68±104	70±91	0.892	76±108	0.687
Creatinine (mg/dL)	8.3±2.5	1.1±0.6	<0.001	1.1±0.6	<0.001
Sodium (mmol/L)	137±4	138±4	0.016	139±4	0.022
INR of PT	1.1±0.2	1.1±0.3	0.737	1.1±0.2	0.909
Platelet (1,000 μL/L)	154±99	170±96	0.261	170±106	0.386
AFP (ng/mL), median [IQR]	10 [4–139]	45 [8–826]	<0.001	51 [9–764]	<0.001
eGFR (mL/min/1.73 m^2)	6.9±3.0	76±30	<0.001	77±32	<0.001
Tumor nodules (single/multiple), n (%)	29 (67)/14 (33)	2,408 (64)/1,343 (36)	0.659	83 (64)/46 (36)	0.712
Tumor size, mean ±SD	6.22±4.5	6.03±4.5	0.750	6.6±4.8	0.458
Tumor size >3 cm, n (%)	28 (65)	2419 (65)	0.932	84 (65)	1.000
TTV, median [IQR]	65 [10–609]	47 [9–381]	<0.001	7 [33–280]	0.001
Vascular invasion or metastasis, n (%)	10 (23)	1,028 (28)	0.531	32 (25)	0.838
Ascites, n (%)	19 (44)	842 (23)	0.001	30 (23)	0.008
DM, n (%)	13 (30)	959 (26)	0.486	31 (24)	0.420
CTP class (A/B/C), n (%)	27/12/4 (63/28/9)	2,760/819/172 (74/21/5)	0.110	92/34/3 (71/27/3)	0.121
CTP score (mean ± SD)	6.6±1.8	6.0±1.5	0.023	6.1±1.5	0.068
MELD (<8/8–14/ 14–20/>20), n (%)	0/0/11/23 (0/0/24/76)	1,590/1,708/330/123 (42/46/8/3)	<0.001	57/57/13/2 (44/44/10/2)	<0.001
ALBI grade (1/2/3), n (%)	14/21/8 (33/49/18)	1,430/1,949/372 (38/52/10)	0.062	58/60/11 (45/47/8)	0.053
Performance status (0/1/2/3–4), n (%)	18/10/9/6 (51/17/15/14)	2,208/770/422/351 (60/21/11/10)	0.018	85/20/14/10 (66/15/11/8)	0.017
BCLC (0/A/B/C/D), n (%)	2/10/3/21/7 (5/23/7/49/16)	293/922/637/1,483/416 (8/25/17/40/10)	0.282	15/32/24/47/11 (12/28/1/36/9)	0.112

Table 1 (*continued*)

Table 1 (*continued*)

Variables	Dialysis patients	Non-dialysis patients	P	Matched-control	P
CLIP (0/1/2/3/4/5/6), n (%)	14/16/8/6/1/2/1 (32/26/19/14/2/5/2)	1,199/987/560/433/353/179/40 (32/26/15/12/9/5/1)	0.741	40/36/20/12/16/5/0 (31/28/16/9/12/4/0)	0.293
Treatment			0.374		0.449
Surgical resection	8 (19)	1,099 (29)		37 (29)	
Liver transplantation	0	20 (1)		1 (1)	
Percutaneous ablation	8(19)	672 (18)		16 (12)	
TACE	13 (30)	1,021 (27)		45 (35)	
Chemotherapy or target therapy	2 (5)	301 (8)		8 (6)	
Others	12 (28)	638 (17)		22 (17)	
Curative/non-curative treatments	16/27 (38/62)	1,791/1,960 (48/52)	0.219	70/102 (40/60)	0.720

ALBI, albumin-bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AFP, α-fetoprotein; CTP, Child-Turcotte-Pugh; DM, diabetes mellitus; INR of PT, international normalized ration of prothrombin time; MELD, model of end-stage liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus; TACE, transarterial chemoembolization; SD, standard deviation.

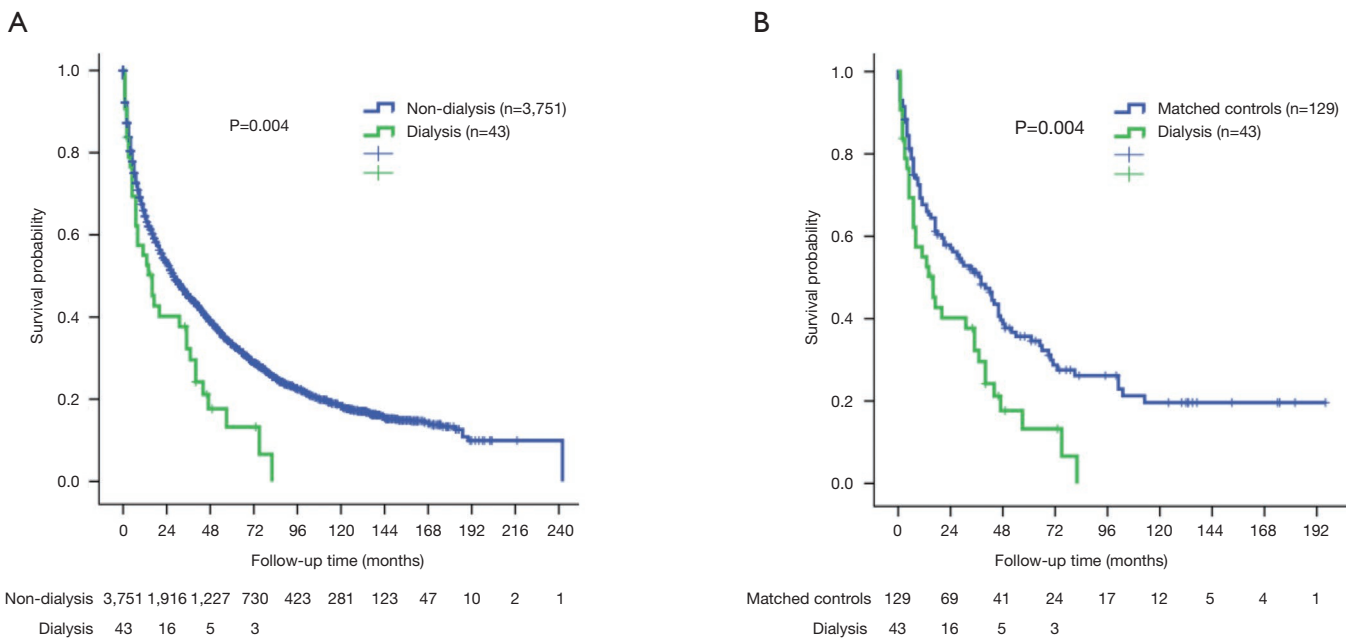

Figure 1 Comparison of survival distribution (A) between dialysis patients and non-dialysis patients with HCC [dialysis patients had a worse survival than non-dialysis patients (P=0.004)] and (B) between dialysis patients and age, sex matched controls [dialysis patients still had a worse survival (P=0.004)].

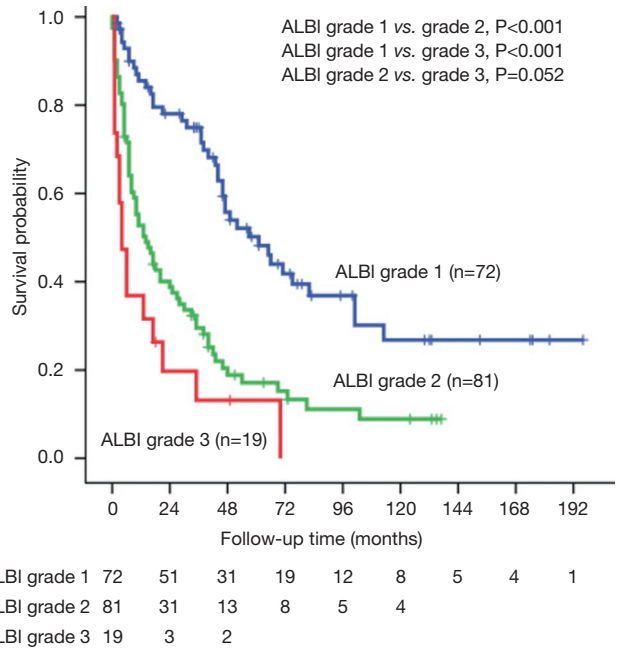

Figure 2 Survival distribution of dialysis and age, sex matched controls stratified by the ALBI grade. ALBI grade 1 patients had the best survival in comparison with other two groups (P<0.001). ALBI, albumin-bilirubin.

Long-term survival of dialysis patients and matched controls stratified by ALBI grade

For the 172 (dialysis and matched controls) patients, the median survival was 61 (95% CI: 40.4–81.6) months for ALBI grade 1, 14 (95% CI: 7.2–20.8) months for ALBI grade 2, and 4 (95% CI: 0.8–7.2) months for ALBI grade 3 (*Figure 2*). There was significant survival difference between ALBI grade 1 *vs.* grade 2 (P<0.001), ALBI grade 1 *vs.* grade 3 (P<0.001), but not between ALBI grade 2 *vs.* grade 3 (P=0.052). The 1-, 3- and 5-year survival rates were 86%, 75% and 50% for ALBI grade 1, 53%, 29% and 17% for ALBI grade 2, and 11%, 8% and 0% for ALBI grade 3 patients, respectively (*Figure 2*).

Long-term survival of dialysis patients stratified by ALBI grade

The median survival was 44 (95% CI: 34.2–53.7) months for ALBI grade 1, 8 (95% CI: 2–14) months for grade 2, and 1 month for grade 3 patients. There was significant survival difference between ALBI grade 1 *vs.* grade 2 (P=0.002) and ALBI grade 1 *vs.* grade 3 (P=0.008), but not between ALBI grade 2 *vs.* grade 3 (P=0.317) patients. The 1-, 3- and 5-year survival rates were 93%, 76%, 24% for ALBI grade 1, 43%, 14% and 9% for grade 2, and 25%, 13% and 0% for grade 3 patients, respectively (*Figure 3*).

Univariate and multivariate survival analysis of dialysis patients and matched controls

In univariate analysis of the pooled cohort of dialysis patients and matched controls, lower serum albumin level (P<0.001), higher serum bilirubin level (P=0.027), higher serum ALT level (P=0.005), prolonged INR of PT (P<0.001), higher AFP level (P<0.001), larger TTV (P<0.001), vascular invasion (P<0.001), distant metastasis (P<0.001), ascites (P<0.001), receiving dialysis (P<0.001), poor performance status (P<0.001), higher ALBI grade (P<0.001) and non-curative treatments (P<0.001) were associated with an increased risk of mortality.

Multivariate Cox proportional hazards model was used to identify the independent prognostic factors. Serum albumin level and serum bilirubin were not analyzed in the multivariate analysis due to inter-related with ALBI grade. Multivariate analysis revealed that TTV >33 cm^3 (HR: 1.677, 95% CI: 1.100–2.557, P=0.016), distant metastasis (HR: 2.673, 95% CI: 1.320–5.412, P=0.006), ascites (HR: 1.675, 95% CI: 1.106–2.534, P=0.015), dialysis (HR: 1.751, 95% CI: 1.165–2.630, P=0.007), ALBI grade 2 (HR: 2.001, 95% CI: 1.363–3.164, P=0.001), ALBI grade 3 (HR: 1.962, 95% CI: 1.054–3.652, P=0.034), and non-curative treatments (HR: 2.416, 95% CI: 1.554–3.755, P<0.001) were associated with increased risk of mortality in this pooled cohort (*Table 2*).

Multivariate survival analysis of dialysis patients

Of the 43 patients receiving maintenance dialysis, 42 received hemodialysis and 1 received peritoneal dialysis. The median duration of dialysis before the diagnosis of HCC was 36 months (range, 3–167 months). Among dialysis patients, 13 (30%) of patients had diabetes-related chronic kidney disease. Significant survival differences were found for lower serum albumin level (P<0.001), higher serum bilirubin level (P=0.020), higher serum ALT level (P=0.024), prolonged INR of PT (P=0.004), larger TTV (P=0.019), vascular invasion (P<0.001), distant metastasis (P<0.001), ascites (P<0.001), shorter duration of hemodialysis before the diagnosis of HCC (P=0.03), diabetes-related cause of dialysis (P=0.012), performance

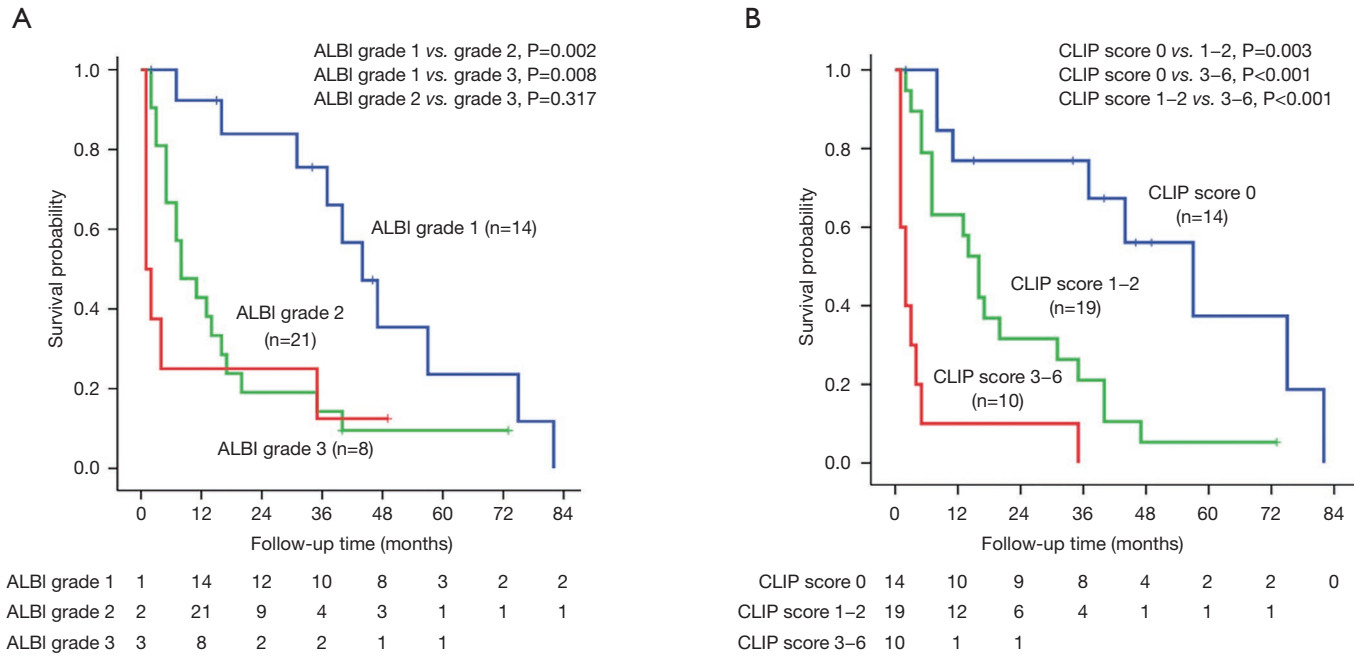

Figure 3 Survival stratification by ALBI grade and CLIP score. (A) Survival distribution of dialysis patients with HCC stratified by the ALBI grade. ALBI grade 1 patients had the best survival in comparison with other two groups. (B) Survival distribution of dialysis patients with HCC to the CLIP score. There was significant survival difference between CLIP score 0 *vs.* scores 1–2 (P=0.03), score 0 *vs.* scores 3–6 (P<0.001), and scores 1–2 *vs.* scores 3–6 (P<0.001). ALBI, albumin-bilirubin.

status 1 (P=0.022), performance status 2-3 (P=0.004), ALBI grade 2 (P=0.005), ALBI grade 3 (P<0.001) and non-curative treatments (P<0.001) in the univariate analysis.

The Cox multivariate analysis revealed TTV >33 cm^3 (HR: 6.763, 95% CI: 2.503–18.270, P<0.001), ascites (HR: 6.168, 95% CI: 2.371–16.403, P<0.001), dialysis duration less than 24 months before diagnosis (HR: 3.144, 95% CI: 1.388–7.122, P=0.006), diabetes-related cause of dialysis (HR: 9.366, 95% CI: 3.320–26.424, P=0.001) and non-curative treatments (HR: 9.220, 95% CI: 3.090–27.510, P<0.001) as poor prognostic factors of adverse outcome in dialysis patients (*Table 3*).

Overall survival analysis according to ALBI grade

There was no overall survival difference between dialysis and non-dialysis patients stratified for ALBI grade 1, 2 and 3 (*Figure 4*, all P>0.05).

Performance of HCC staging systems for dialysis patients

Among the currently proposed HCC staging systems, the CLIP system offered the lowest AICc value and the highest homogeneity, suggesting that CLIP may better discriminate survival in dialysis patients (*Table 4*). Further analysis showed that there was significant survival difference between CLIP score 0 *vs.* scores 1–2 (P=0.003), score 0 *vs.* scores 3–6 (P<0.001) and scores 1–2 *vs.* scores 3–6 (P<0.001) (*Figure 3B*, P<0.001).

Discussion

Over the 3,794 HCC patients identified between 2002–2017, only 43 (1.1%) patients had ESRD receiving maintenance dialysis. We specifically investigated and compared their long-term survival with non-dialysis patients. We found that patients receiving dialysis had a significantly decreased overall survival compared with non-dialysis patients. Notably, the ALBI grade can well discriminate the survival difference in the combined cohort of dialysis patients with age and sex-matched controls. We also demonstrate that the CLIP staging system may provide better prognostic accuracy for this specific patient group in comparison with other currently used staging systems.

Table 2 Univariate and multivariate survival analysis in 43 dialysis and 129 non-dialysis age, sex matched control patients

Overall survival	Number	Univariate analysis			Multivariate analysis		
		1-year survival (%)	3-year survival (%)	P	HR	95% CI	P
Age (≤60/>60 years)	80/92	71/53	59/41	0.803			
Sex (male/female)	112/60	62/69	45/48	0.292			
HBsAg (negative/positive)	83/89	62/67	39/53	0.141			
Anti-HCV (negative/positive)	109/63	62/70	48/44	0.513			
Albumin level (≥3.5/<3.5 g/dL)	104/68	79/42	64/20	<0.001			
Bilirubin level (≤1.1/>1.1 mg/dL)	121/51	71/49	51/34	0.027			
ALT (≤40/>40 IU/L)	77/95	70/61	53/41	0.005			
Platelet (≥150,000/<150,000/μL)	79/93	58/70	42/50	0.366			
INR of PT (≤1.1/>1.1)	109/63	72/52	55/30	<0.001			
AFP (≤20/>20 ng/mL)	72/100	73/58	59/37	0.005			
TTV (≤33/>33 cm^3)	80/92	82/49	69/26	<0.001	1.852	1.201–2.856	0.005
Vascular invasion (no/yes)	135/37	73/34	55/15	<0.001			
Distant metastasis (no/yes)	161/11	68/11	49/0	<0.001	2.673	1.320–5.412	0.006
Ascites (no/yes)	123/49	75/38	57/21	<0.001	1.608	1.061–2.439	0.025
Dialysis (no/yes)	129/43	68/55	55/33	0.005	1.713	1.140–2.573	0.010
Performance status							
0	103	77	63				
1	53	49	26	<0.001			
2–4	16	38	13	<0.001			
ALBI grade							
Grade 1	72	86	75		1		
Grade 2	81	53	29	<0.001	2.077	1.362–3.168	0.001
Grade 3	19	37	13	<0.001	2.371	1.235–4.550	0.009
Curative/noncurative treatments, n (%)	70/102	91/47	75/27	<0.001	2.263	1.449–3.535	<0.001

The forepart of the parentheses was set as the reference group in the univariate and multivariate analysis. AFP, α-fetoprotein; ALBI, albumin-bilirubin; ALT, alanine aminotransferase; anti-HCV, antibody against hepatitis C virus; HBsAg, hepatitis B virus surface antigen; INR of PT, international normalized ratio of prothrombin time.

Patients with HCC could develop ESRD during their disease course, but only a minority of these patients were receiving dialysis therapy at the time of diagnosis. Previous studies reported comparable survival rates between dialysis and non-dialysis patients with HCC (5,24). By contrast, another study from Japan revealed that patients receiving dialysis had lower survival rate compared with non-dialysis patients (25). Therefore, the prognosis of HCC patients with dialysis was highly debated. In this study, we confirmed that dialysis patients had a poor long-term survival compared with non-dialysis patients, with 71% increased risk of mortality identified in the multivariate model.

When compared with non-dialysis patients at baseline, patients receiving dialysis had lower serum albumin level, higher serum bilirubin level and higher rate of ascites formation, indicating poor liver functional reserve. In

Table 3 Univariate and multivariate survival analysis in dialysis HCC patients (n=43)

Overall survival	Number	Univariate analysis			Multivariate analysis		
		1-year survival (%)	3-year survival (%)	P	HR	95% CI	P
Age (≤60/>60 years)	20/23	64/48	41/26	0.847			
Sex (male/female)	28/15	54/59	32/34	0.330			
HBsAg (negative/positive)	25/18	59/50	28/39	0.936			
Anti-HCV (negative/positive)	24/19	45/68	36/29	0.593			
Albumin level (≥3.5/<3.5 g/dL)	22/21	81/29	61/5	<0.001			
Bilirubin level (≤1.1/>1.1 mg/dL)	34/9	64/22	39/11	0.020			
ALT (≤40/>40 IU/L)	23/20	64/45	45/20	0.024			
Platelet (≥150,000/<150,000/μL)	18/25	54/56	36/31	0.388			
INR of PT (≤1.1/>1.1)	32/11	65/27	45/0	0.004			
AFP (≤20/>20 ng/mL)	27/16	59/48	39/21	0.168			
TTV (≤33/>33 cm^3)	19/24	74/40	52/16	0.019	6.763	2.503–18.270	0.001
Vascular invasion (no/yes)	35/8	59/38	41/0	<0.001			
Distant metastasis (no/yes)	39/4	61/0	36/0	<0.001			
Ascites (no/yes)	24/19	75/30	53/6	0.001	6.168	2.371–16.403	<0.001
Duration of dialysis (>24/≤24 months)	15/28	67/33	41/19	0.030	3.144	1.388–7.122	0.006
Cause of dialysis (non-DM/DM)	30/13	66/31	40/15	0.012	9.366	3.320–26.424	<0.001
Performance status							
0	18	67	61				
1	19	51	17	0.022			
2–4	6	33	0	0.004			
ALBI grade							
Grade 1	14	93	76				
Grade 2	21	43	14	0.010			
Grade 3	8	25	13	0.005			
Curative/non-curative treatments	16/27	94/33	72/11	<0.001	9.220	3.090–27.510	<0.001

The forepart of the parentheses was set as the reference group in the univariate and multivariate analysis. AFP, α-fetoprotein; ALBI, albumin-bilirubin; ALT, alanine aminotransferase; anti-HCV, antibody against hepatitis C virus; HBsAg, hepatitis B virus surface antigen; INR of PT, international normalized ratio of prothrombin time.

addition, dialysis patients more frequently had poor performance status and advanced cancer stage. These characteristics may decrease the likelihood to receive aggressive treatment associated with unfavorable long-term survival in dialysis patients.

The degree of liver functional reserve is a crucial prognostic predictor in the management of HCC. The CTP classification and the MELD score have been used to predict the outcome in cirrhotic patients. However, about 20% of HCC did not have cirrhosis at the time of diagnosis. Furthermore, the value of creatinine in the MELD equation was set at 4 mg/dL in dialysis patients, and this

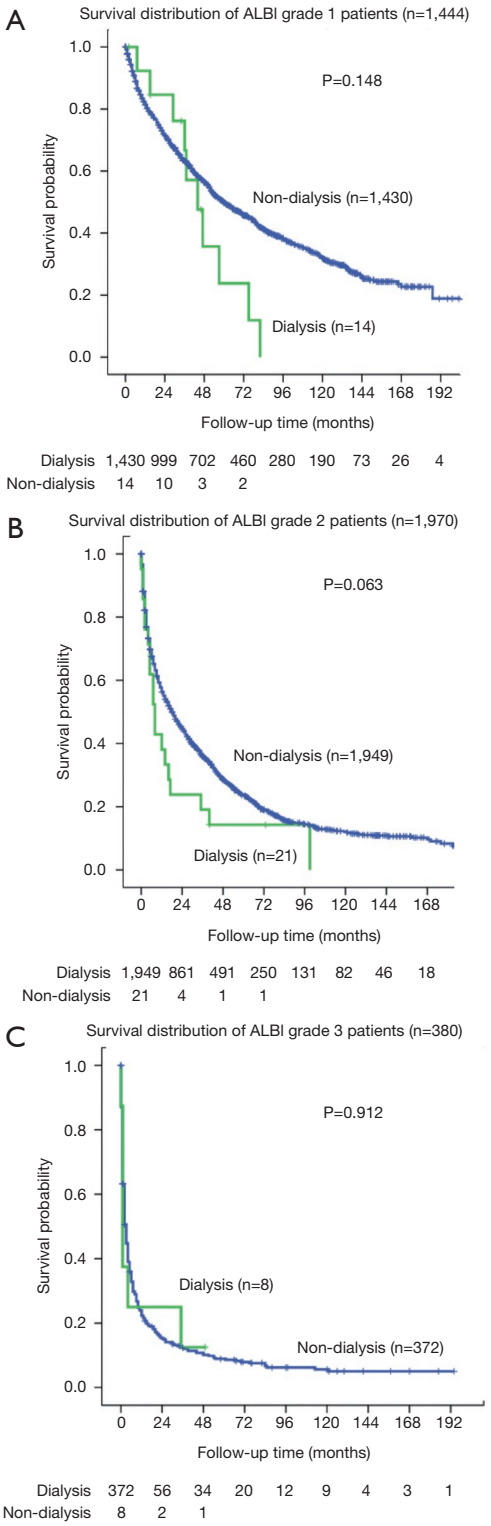

Figure 4 Comparison of survival between dialysis and non-dialysis patients according to ALBI grade. There were no significant survival differences between dialysis and non-dialysis patients stratified for ALBI grade 1 (A), grade 2 (B) and grade 3 (C).

Table 4 Prognostic performance of different staging systems in dialysis patients with HCC (n=43)

Staging system	Homogeneity (Wald χ^2)	AICc
BCLC	18.712	195.407
CLIP	32.025	182.095
CUPI	2.464	192.310
HKLC	20.790	183.897
JIS	25.704	188.416
Okuda	9.086	205.033
TNM	8.139	205.981
Tokyo	20.930	193.190
TIS	17.388	196.731

BCLC, Barcelona Clinic of Liver Cancer; CLIP, Cancer of the Liver Italian Program; CUPI, Chinese University Prognostic Index; HKLC, Hong Kong Liver Cancer; JIS, Japan Integrated Scoring; TNM, tumor-node-metastasis; TIS, Taipei Integrated Scoring system.

score is considered less reliable in these patients. Therefore, the predictive accuracy of these two models to assess liver dysfunction in chronic liver disease or mild cirrhosis has been challenged. More recently, the application of ALBI grade to evaluate liver functions in HCC was proposed, but its prognostic role in dialysis patients with HCC is unclear. Our results confirm that patients with ALBI grade can well discriminate survival difference among HCC patients with dialysis and matched controls. Notably, patients with ALBI grade 2 and grade 3 had 2.1- and 2.4-fold increased risk of mortality, respectively, compared with patients ALBI grade 1 in multivariate analysis. Alternatively, in the analysis for solely dialysis patients, ALBI grade was not an independent prognostic predictor. Rather, tumor burden, treatment strategy, and the cause of dialysis prevailed and determined the survival of these patients.

Among the cohort of dialysis and age, sex-matched controls, TTV, distant metastasis, ascites, patients receiving dialysis, ALBI grade, and treatment strategy were identified as independent predictors of poor survival. We also evaluated the prognostic determinants in solely dialysis patients with HCC and found that larger TTV, ascites, duration of dialysis ≤24 months, diabetes-related cause of dialysis, and non-curative treatments were associated with decreased long-term survival. These results were largely consistent with previous studies (24-26). Notably, those with shorter duration of dialysis were associated with poor

outcome. The possible explanation is that the development of ESRD may be directly related to advanced cirrhosis resulting in decreased survival in these patients. The cause of dialysis related to DM is another predictor of poor outcome compared with those with non-diabetes related dialysis. The exact mechanism remains unclear; however, in accordance with previous studies, DM was regarded as a predictor of poor survival in dialysis HCC patients (26-28).

Ascites formation is a hallmark of portal hypertension. Previous study revealed that the presence of ascites was not only related to advanced cirrhosis but may also predispose to tumor progression. Our data consistently showed that ascites was associated with 6.2-fold increased risk of death compared with those without ascites (7,29).

Treatment strategy is usually the single most important factor to predict survival for HCC (2). Patients receiving curative treatments had significantly better 1- and 3-year survival compared with those undergoing non-curative treatments in the cohort of dialysis patients and matched controls. In this study, about 38% of dialysis patients with HCC received curative treatments which were associated with significantly improved outcome. These results imply that curative treatments can be safely performed in dialysis patients with well-preserved liver function and good performance status (30), and to improve overall survival in HCC patients receiving dialysis.

Dialysis patients are associated with increased risk of HBV and HCV infection transmitted primarily through the dialysis environment. A previous study reported that hemodialysis patients had at higher risk of early HCV infection which may in turn progress to liver cirrhosis and HCC (31). Consistent with this finding, our results showed that HCV infection was more common in dialysis patients compared with non-dialysis patients. Additionally, patients receiving hemodialysis are characterized by a higher prevalence of dual HBV/HCV infection, suggesting the importance of virus screening in these patients.

Multiple staging systems have been suggested for HCC. However, the best staging system specifically for dialysis patients with HCC is undetermined. Our findings suggest that the CLIP score, which had the lowest AICc and highest homogeneity compared with other staging systems, had a better prognostic performance to discriminate survival in dialysis patient with HCC.

Liver dysfunction in the setting of liver cirrhosis or HCC is associated with high mortality due to the accumulation of protein-bound metabolites, such as bilirubin which is not removed by conventional hemodialysis. Alternatively, albumin levels are lower in dialysis patients than among the general population and are a powerful predictor of mortality. Albumin levels are mainly controlled by the rate of albumin synthesis that is in turn affected by the nutritional status. In dialysis patients, hypoalbuminemia is a strong predictor of poor outcome (32). Given the fact that dialysis itself could not alter these levels, the clinical impact of dialysis in terms of prognostic prediction is probably in multiple ways. Still, our results suggest that ALBI grade can serve as a prognostic marker in dialysis patients.

This study has some potential shortcomings. First, this is a single-center study from Asian-Pacific region. HBV is the predominant etiology of HCC and the results require external validation from other search groups where different etiologies prevail. Second, the vast majority of dialysis patients received hemodialysis and only one patient received peritoneal dialysis. The assessment between hemodialysis and peritoneal dialysis would be difficult. Third, some patients did not fully comply with treatment recommendations according to the BCLC system. The anti-cancer treatments were mainly decided by the multidisciplinary HCC board in our hospital. Lastly, dialysis patients are a heterogeneous group that could contain inherent biases in comparison with other patient groups. Although the Cox multivariate analysis is used to adjust the confounders, there still could be potentially uncontrolled factors in data interpretation.

Conclusions

In conclusions, dialysis patients with HCC had decreased overall survival compared with non-dialysis patients. The duration of hemodialysis, ascites, tumor burden, distant metastasis, and treatment strategy were associated with long-term outcome of HCC patients receiving dialysis. The ALBI grade is a feasible model to evaluate the severity of liver injury in dialysis patients with HCC, and the CLIP score can better stage their long-term prognosis.

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Footnote

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