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High Mortality of Cirrhotic Patients With End-Stage Renal Disease

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Abstract: Ascites, hepatic encephalopathy (HE), and esophageal variceal bleeding (EVB) are 3 major complications in patients with cirrhosis. Limited data exist with which to evaluate the long-term mortality of end-stage renal disease (ESRD) in cirrhotic patients with or without complications.

The National Health Insurance Database in Taiwan was used to identify patients with cirrhosis hospitalized between January 1, 2007, and December 31, 2007. The study group consisted of 1068 cirrhotic patients with ESRD, and the control group consisted of 10,680 randomly selected cirrhotic patients without baseline renal function impairment.

The overall 1-year and 3-year mortality rates were 48.5% and 73.1% in the ESRD group, and 32.9% and 55.6% in the control group, respectively. After adjusting for other comorbid disorders, the cirrhotic patients with ESRD showed a statistically significant increase in 3-year mortality (hazard ratio [HR], 1.65; $P < 0.001$). The HR for 3-year mortality of ESRD cirrhotic patients with recurrent complications was 1.98 ($P < 0.001$), compared to those with no recent or past complications. The HR of ESRD for 3-year mortality was 1.48 ($P < 0.001$) in cirrhotic patients with ascites, 1.67 ($P < 0.001$) in patients with EVB, and 1.19 ($P = 0.147$) in patients with HE.

ESRD increases the mortality rate in patients with cirrhosis. Recurrent complications can account for a 2-fold increase in the 3-year mortality of ESRD cirrhotic patients. ESRD has a smaller impact on the 3-year mortality of cirrhotic patients with HE compared to those with ascites or EVB.

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Abbreviations: ARF = acute renal failure, BNHI = National Health Insurance Bureau, CI = confidence interval, ESRD = end-stage renal disease, EVB = esophageal variceal bleeding, HCC = hepatocellular carcinoma, HE = hepatic encephalopathy, HR = hazard ratio, HRS = hepatorenal syndrome, ICD-9-CM = International Classification of Diseases∗ 9th Revision∗ Clinical Modification code, NHIRD = National Health Insurance Research Database, RFI = renal function impairment.

INTRODUCTION

End-stage renal disease (ESRD) is now recognized to be a growing public health problem.[1] Patients with ESRD have a defective T-cell-mediated immune system, related to excess premature ageing of the T-cell compartment caused by uremia.[2] This contributes to an increased vulnerability for infections, poor vaccination responses, a high risk for malignancies, and a high risk for atherosclerotic diseases. In addition, patients with ESRD suffer from a number of complex neurological complications, including vascular damage and cognitive dysfunction. In addition, they have an increased bleeding tendency related to uremic platelet dysfunction, intermittent heparin use in dialysis, and the use of antiplatelet agents and anticoagulants.[3] Maintenance dialysis for ESRD is one of the typical therapies for long-term vital organ replacement and can correct uremic syndrome.

Renal function impairment (RFI) confers a poor prognosis in cirrhotic patients with bacterial infections or with esophageal variceal bleeding (EVB).[4–7] ESRD is the most severe type of RFI. However, there are limited studies investigating the effect of ESRD on mortality in cirrhotic patients.[8] Ascites, hepatic encephalopathy (HE), and EVB are 3 major complications in cirrhosis.[9–11] The effects of these complications on mortality in cirrhotic patients with ESRD are also unknown. In order to enroll a large population of cirrhotic patients with ESRD, we used a nationwide population-based dataset. In this study we determined the effect of ESRD on the prognosis for patients with cirrhosis and also measured the effect of ESRD on mortality in patients with various complicating conditions.

PATIENTS AND METHODS

Database

Taiwan started the National Health Insurance Program (NHIP) in 1995. In Taiwan, the NHIP covers >98% of the population. The details of this program have been described in many studies.[12–14] In recent years, the National Health Research Institute (NHRI) and Taiwan National Health Insurance Bureau cooperated to establish the National Health Insurance research database (NHIRD). In Taiwan, the doctors can

apply a dataset from NHIRD for a clinical study. However, these clinical studies must be evaluated and approved by the NHRI in Taiwan.

We used a secondary de-identified dataset from NHIRD to perform this study, which had been approved by the Taiwan National Health Research Institute with application and agreement number 101516. The diagnostic coding information of the hospitalized patients was included in this dataset. However, all the identifying personal information was removed before analysis.

Otherwise, this study was approved by the Institutional Review Board of the Buddhist Dalin Tzu Chi Hospital, Chiayi, Taiwan (IRB B1010410). The review board waived the requirement for written informed consent from all patients.

Study Sample

The patients discharged with a diagnosis of cirrhosis (International Classification of Diseases, 9th Revision, Clinical Modification code 571.5, or 571.2 in the database) (ICD-9-CM) between January 1, 2007, and December 31, 2007, were enrolled in this study. The cirrhotic patients with ESRD were considered as the study group. Patients with ESRD were identified as those who required long-term dialysis before admission. In Taiwan, patients with long-term dialysis are given a certification to reduce their medical expenses. Cirrhotic patients without baseline RFI were selected randomly as the control group. Patients with RFI (including acute renal failure or chronic renal failure) were defined as those with the ICD-9-CM diagnosis codes of 580–588, 572.4, or another procedure code related to dialysis.[15] For patients with multiple hospitalization episodes during this period, only the first episode was included.

A total of 1068 cirrhotic patients with ESRD were enrolled in this study, and another 10,680 cirrhotic patients without RFI were selected as the control group. The following comorbid medical disorders were included: alcoholic-related disorders (ICD-9-CM codes 291, 303, 305.00–305.03, 571.0–571.3), hepatocellular carcinoma (HCC) (ICD-9-CM code 155.0), HE (ICD-9-CM code 572.2),[16] EVB (ICD-9-CM code 456.0, 456.20), or those who received an endoscopic procedure for variceal bleeding control (ICD-9 v3 procedure codes 42.33),[17] or ascites (ICD-9-CM code 789.5, or procedure code 54.91). HE, EVB, and ascites were defined as the major complications of liver cirrhosis in our study. *Recent* complications were defined as complications developed during hospitalization. *Past* complications were defined as complications developed within 10 years before hospitalization. For subgroup analysis, cirrhotic patients with ESRD were divided into 2 groups according to the presence or absence of recent complications, and these 2 groups were further divided into 2 groups each, based on the presence or absence of past complications.

Statistical Analyses

We used Student's *t* test to compare continuous variables, and the chi-square test to compare categorical variables. The Cox regression model was used to identify risk factors for mortality. We present hazard ratios (HR) along with the 95% confidence intervals (CI). Values of $P < 0.05$ were considered statistically significant. The Kaplan-Meier method with log-rank test was used for estimating the survival probabilities in cirrhotic patients with ESRD. Statistical analyses were performed using the SPSS statistical package (SPSS System for Windows, version 13.0).

RESULTS

Of the total 1068 cirrhotic patients with ESRD, 651 (61.0%) were men. The mean age of these patients was 62.6 ± 11.3 years. The overall 1-year and 3-year mortalities in the ESRD group were 48.5% and 73.1%, and those in the control group were 32.9% and 55.6%, respectively ($P < 0.001$). The demographic characteristics for the ESRD and control groups are shown in Table 1. The HRs of the predisposing factors for the 3-year mortality of cirrhotic patients were listed in Table 2. After adjusting for age, gender, and underlying medical comorbid disorders, patients with HCC (HR,1.90; 95% CI, 1.81–2.01; $P < 0.001$), advanced age (HR, 1.02; 95% CI, 1.02–1.02; $P < 0.001$), HE (HR, 1.84; 95% CI, 1.71–1.97; $P < 0.001$), male gender (HR, 1.17; 95% CI, 1.11–1.24; $P < 0.001$), ascites (HR, 2.08; 95% CI, 1.96–2.20; $P < 0.001$), EVB (HR, 1.24; 95% CI, 1.14–1.34; $P < 0.001$), alcohol-related cirrhosis (HR, 0.92; 95% CI, 0.86–0.99; $P = 0.034$), and ESRD (HR, 1.65; 95% CI, 1.53–1.78; $P < 0.001$) had 3-year mortality rates that differed significantly from patients in the control group. The Kaplan–Meier survival analysis for cirrhotic patients with ESRD and the control group in the 3-year follow-up period is shown in Figure 1.

The cirrhotic patients with ESRD were divided into 2 groups according to the presence or absence of recent complications, and each of those was further divided into 2 groups based on the presence or absence of past complications (see Figure 2). The flowchart in Figure 2 shows the 3-year mortality in each of these groups of cirrhotic patients with ESRD. In cirrhotic patients with ESRD, the 3-year overall mortality rates for patients with and without recent complications were 82.1% (261/318) and 69.3% (520/750), respectively. The HR of 3-year mortality for the recent complication group were 1.68 (95% CI, 1.44–1.96; $P < 0.001$), compared to patients without recent complications. The adjusted hazard ratios for cirrhotic patients with ESRD according to the complication status (recent or past) are shown in Table 3, and the Kaplan–Meier survival analysis is provided in Figure 3. The hazard ratio for 3-year mortality for the recurrent complication group (recent complication [+], past complication [+]) was 1.98 (95% CI, 1.61–2.43; $P < 0.001$), compared with the patients without any complications (recent complication [−], past complication [−]).

We also divided the ESRD group and control group according the presence of major complications (Table 4). In cirrhotic patients without major complications, the 3-year

TABLE 1. Demographic Characteristics of Cirrhotic Patients With and Without End-Stage Renal Disease

	ESRD (n = 1068)	Non-ESRD (n = 10,680)	*P* Value
Male, n (%)	651 (61.0)	7584 (71.0)	<0.001
Age, y	62.6 ± 11.3	59.2 ± 14.4	<0.001
HCC, n (%)	248 (23.2)	3389 (31.7)	<0.001
Hepatic encephalopathy, n (%)	99 (9.3)	1155 (10.8)	0.119
Ascites, n (%)	191 (17.9)	2067 (19.4)	0.245
Alcohol-related, n (%)	51 (4.8)	2379 (22.3)	<0.001
EVB, n (%)	65 (6.1)	1038 (9.7)	<0.001

ESRD = end-stage renal disease, EVB = esophageal variceal bleeding, HCC = hepatocellular carcinoma.

TABLE 2. Adjusted Hazard Ratios for Mortality in Cirrhotic Patients During the 3-Year Follow-Up Period Following First Hospitalization in 2007

Variable	Hazard Ratio	95% CI	*P* Value
Age	1.02	1.02–1.02	<0.001
Male	1.17	1.11–1.24	<0.001
Alcohol-related	0.92	0.86–0.99	0.034
Ascites	2.08	1.96–2.20	<0.001
Hepatic encephalopathy	1.84	1.71–1.97	<0.001
EVB	1.24	1.14–1.34	<0.001
HCC	1.90	1.81–2.01	<0.001
ESRD	1.65	1.53–1.78	<0.001

CI = confidence interval, ESRD = end-stage renal disease, EVB = esophageal variceal bleeding, HCC = hepatocellular carcinoma.

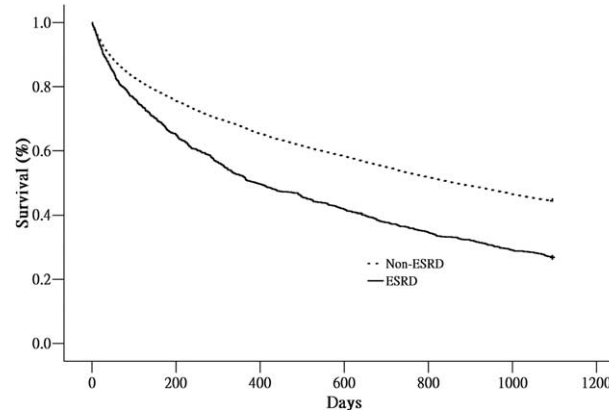

FIGURE 1. Kaplan–Meier survival analysis for cirrhotic patients in the 3-year follow-up period.

mortalities of ESRD and control groups were 69.3% and 49.9%, respectively. The adjusted HR of ESRD was 1.77 (95% CI, 1.66–1.89; $P < 0.001$). In cirrhotic patients with ascites, the 3-year mortalities of ESRD and control groups were 83.2% and 72.9%, respectively. The adjusted HR of ESRD was 1.48 (95% CI, 1.25–1.75; $P = 0.001$). In the cirrhotic patients with EVB, the 3-year mortalities of ESRD and control groups were 75.9% and 56.7%, respectively. The adjusted HR of ESRD was 1.67 (95% CI, 1.24–2.23; $P = 0.001$). In the cirrhotic patients with HE, the 3-year mortalities of ESRD and control groups were 82.8% and 71.6%, respectively, and the adjusted HR of ESRD was 1.19 (95% CI, 0.94–1.50; $P = 0.147$).

DISCUSSION

RFI contributes to a poor prognosis for cirrhotic patients, especially for those with acute renal failure (ARF) or hepatorenal syndrome (HRS).[18–21] However, cirrhotic patients with

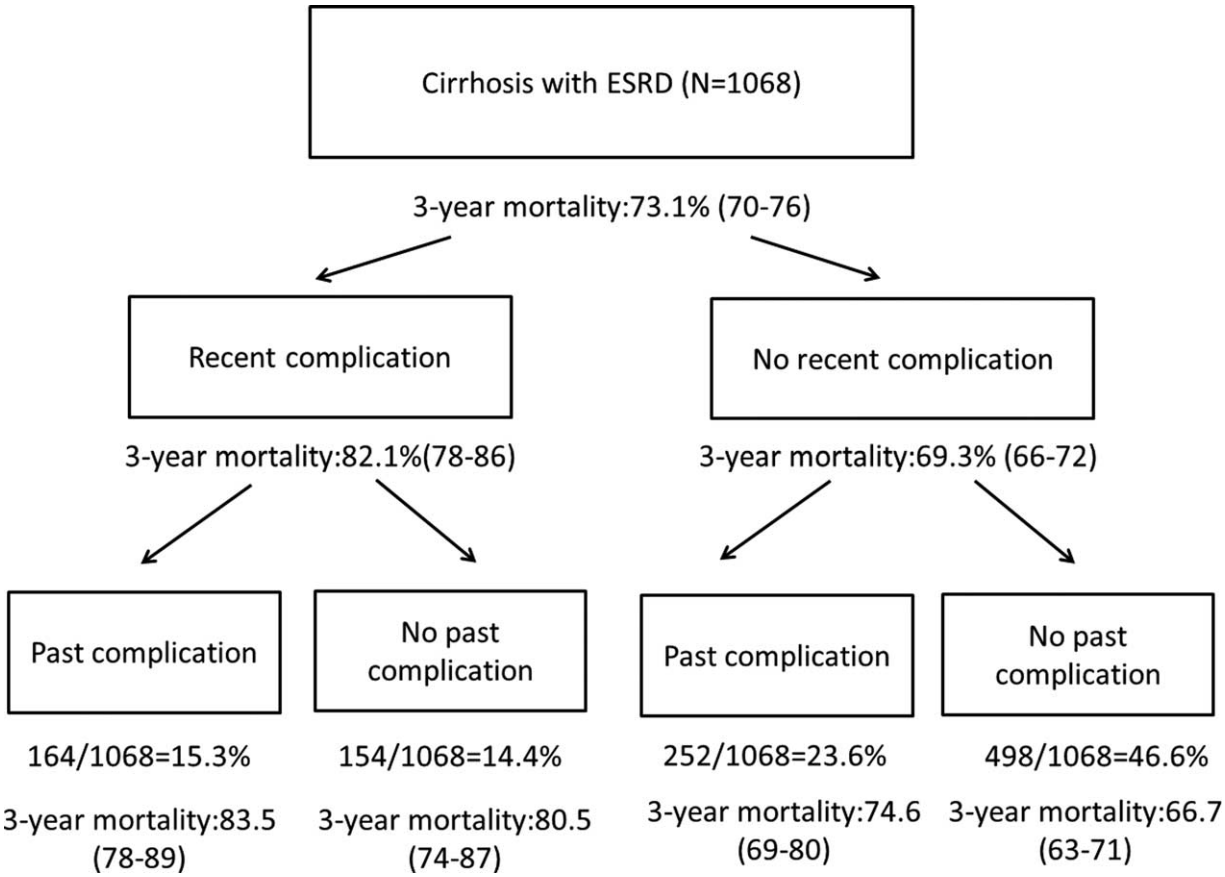

FIGURE 2. Flowchart for the 3-year mortality in cirrhotic patients with ESRD. ESRD = end-stage renal disease.

TABLE 3. Adjusted Hazard Ratios for Mortality in Cirrhotic Patients With End-Stage Renal Disease During the 3-Year Follow-Up Period According to Recent or Past Complication Status

Variable	Number	Hazard Ratio	95% CI	*P* Value
Complication status				
Recent (−), past (−)	498	Reference		
Recent (−), past (+)	252	1.34	1.12–1.61	<0.001
Recent (+), past (−)	154	1.76	1.42–2.17	<0.001
Recent (+), past (+)	164	1.98	1.61–2.43	<0.001

CI = confidence interval.

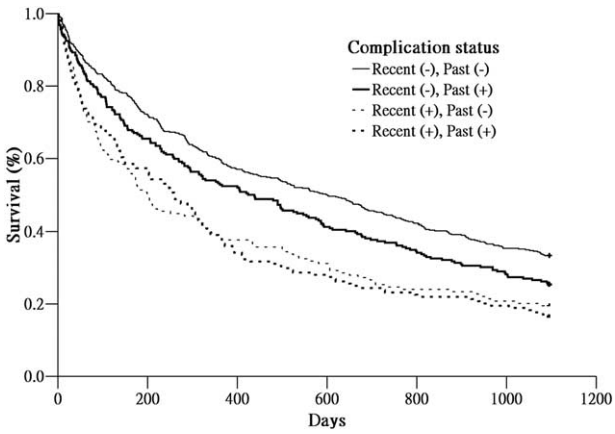

FIGURE 3. Kaplan–Meier survival analysis for cirrhotic patients with end-stage renal disease in the 3-year follow-up period according to the complication status.

ESRD are a specific group. Apart from undergoing regular dialysis, patients with cirrhosis and ESRD would not be identified as having HRS and acute renal failure during hospitalization. We were interested in understanding the effect of ESRD on mortality in the cirrhotic patients. Using a nationwide population-based database to enroll a large population, our study provides reliable and important information regarding cirrhotic patients with ESRD and reflects actual patient mortality in recent clinical practice.

Our study reveals that 3-year mortality in hospitalized cirrhotic patients with ESRD in 2007 was 73.1%. Cirrhotic patients with ESRD had 1.65 times increased 3-year mortality risk, compared to those without RFI. Liver cirrhosis and ESRD are both serious medical diseases associated with higher rates of mortality than in the general population. Uremia in ESRD can be corrected through dialysis, but ESRD still markedly increases mortality in cirrhotic patients, especially in those with recent complications. In another study, ESRD patients with cirrhosis had a 47% increased risk of death, compared to ESRD patients without cirrhosis.[8] Our study demonstrates the importance of ESRD in cirrhotic patients, and a concurrent diagnosis of cirrhosis and ESRD presents a high risk of mortality. Physicians should be aware of the importance of high mortality in these patients, especially in cirrhotic patients with recurrent complications.

In our study, we confirmed the effect of the timing of major complications on the 3-year mortality. As expected, concurrent major complications during hospitalization contributed to higher 3-year mortalities, and recurrent complications in ESRD cirrhotic patients during hospitalization contributed to the highest 3-year mortality risk, ~1.98 times greater than those without recent or past major complications. Interestingly, even for cirrhotic patients with ESRD who did not have major complications during their hospitalization, past major complications still increased their 3-year mortality.

The present study also identified the effect of ESRD on the 3-year mortality of cirrhotic patients with a variety of major complications. We found the effect of ESRD was greatest in cirrhotic patients without major complications, followed by those with EVB and those with ascites. In cirrhotic patients with HE, the effect of ESRD on the 3-year mortality was minimal. In our previous study, we also found that ESRD contributed the least to 3-year mortalities when compared to other types of renal failure, including HRS, ARF, and chronic kidney disease.[22] In HE patients, arterial ammonia concentration is correlated with the occurrence of cerebral herniation and increases in intracranial pressure.[23] We considered that the ammonia accumulation in cirrhotic patients with ESRD could be rescued through hemodialysis. This may be why ESRD has the least effect on 3-year mortality of cirrhotic patients with HE.

However, there were some limitations in this study. First, we could not evaluate the severity of cirrhosis from the diagnostic code. Usually, the severity of cirrhosis is based on the Mayo Clinic model for end-stage liver disease (MELD) score or Child-Pugh score. However, some laboratory data such as albumin, prothrombin time, or bilirubin was not available in our database. This is the intrinsic limitation in this kind of database study. Second, the causes of death also could not be identified in this study. Otherwise, the exact etiology of nonalcoholic liver cirrhosis could not be well identified in this study. However, the etiology of nonalcoholic liver cirrhosis is well established in the previous study.[24] Finally, the health complications existing before 1995 could not be identified because Taiwan National Health Insurance Program was

TABLE 4. Adjusted Hazard Ratios of ESRD for the 3-Year Mortalities of Cirrhotic Patients With Major Complications

Variable	Number (ESRD/Control)	Mortality (ESRD/Control)	HR (95% CI)	*P* Value
No complication	750/7125	69.3%/49.9%	1.77 (1.66–1.89)	<0.001
Ascites	191/2067	83.2%/72.9%	1.48 (1.25–1.75)	0.001
EVB	65/1038	76.9%/56.7%	1.67 (1.24–2.23)	0.001
HE	99/1155	82.8%/71.6%	1.19 (0.94–1.50)	0.147

CI = confidence interval, ESRD = end-stage renal disease, EVB = esophageal variceal bleeding, HE = hepatic encephalopathy, HR = hazard ratio.

established in 1995. However, we believe that there were only a few patients with complication before 1995 in our study due to the high mortality in complicated cirrhosis.

Despite these limitations, this nationwide population-based study identified the high long-term mortality risk in cirrhotic patients with ESRD. In summary, ESRD increases the mortality in cirrhotic patients. The existence of recent or past major complications in hospitalized cirrhotic patients with ESRD increases the 3-year mortality. However, ESRD contributed least effect on the 3-year mortality in cirrhotic patients with HE.

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