The effect of infections on the mortality of cirrhotic patients with hepatic encephalopathy

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SUMMARY

Cirrhotic patients are prone to having infections, which may aggravate hepatic encephalopathy (HE). However, the effect of infections on mortality in HE cirrhotic patients is not well described. The National Health Insurance Database, derived from the Taiwan National Health Insurance Programme, was used to identify 4150 adult HE cirrhotic patients hospitalized between 1 January 2004 and 31 December 2004. Nine hundred and eighty-five patients (23·7%) had one or more co-existing infections during their hospitalization. After Cox proportional hazard regression modelling adjusted by the patients' gender, age, and medical comorbidity disorders, the hazard ratios (HRs) in HE patients with infections for 30-day, 30- to 90-day, and 90-day to 1-year mortalities were 1·66 [95% confidence interval (CI) 1·42–1·94], 1·51 (95% CI 1·23–1·85) and 1·34 (95% CI 1·13–1·58), respectively. Compared to the non-infection group, the HRs of pneumonia, spontaneous bacterial peritonitis, urinary tract infection, sepsis without specific focus (SWSF), cellulitis, and biliary tract infection were 2·11, 1·48, 1·06, 2·21, 1·06, and 0·78, respectively, for 30-day mortality; 1·82, 1·22, 0·93, 2·24, 0·31, and 2·82, respectively, for 30- to 90-day mortality; and 2·03, 0·82, 1·24, 1·64, 1·14, and 0·60, respectively, for 90-day to 1-year mortality for HE cirrhotic patients. We conclude that infections increase the mortality of HE cirrhotic patients, especially pneumonia and SWSF.

Key words: Cirrhosis, hepatic encephalopathy, pneumonia, urinary tract infection, spontaneous bacterial peritonitis.

INTRODUCTION

Hepatic encephalopathy (HE) develops as cirrhosis progresses or as a result of portosystemic shunting, so that the liver cannot detoxify portal venous blood. Increased byproducts of gut flora such as ammonia and endotoxin in systemic circulation

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cause cognitive impairment and contribute to poor survival [1–5]. The incidence of HE ranges from 2% to 20% per year in decompensated cirrhotic patients, and the incidence of subclinical HE was reported to be about 40% in a cross-sectional study of Child–Pugh grade A cirrhosis [6–8].

Due to widespread derangements of immunity caused by cirrhosis, cirrhotic patients are prone to have bacterial infections [9]. In a previous report, infection episodes were reported in 40% of hospitalized cirrhotic patients [10]. Infections in cirrhotic patients are associated with decrease in hepatic functions and about a fourfold increase in mortality [11–13]. In addition, severe dehydration and increased nitrogenous substances caused by infectious diseases can aggravate the severity of HE [14].

However, the effect of infectious diseases on the mortality of HE cirrhotic patients is controversial. In a retrospective study including 333 HE cirrhotic patients, the patients with co-existing infections had higher mortality (46·5% *vs*. 22·7%, $P = 0·001$) [15]. In a prospective study including 100 patients with cirrhosis and grade 3/4 HE, admitted to a liver intensive-care unit, cultures were positive in 22/52 (42%) survivors and 19/48 (40%) non-survivors [2]. The former used spontaneous bacterial peritonitis, urinary tract infection, septicaemia, respiratory tract infection, and dermatological infection as infectious diseases, and the latter only used bacteraemia as infectious diseases. Both studies included a small population and did not adjust for possible confounding factors on the effect of infections on mortality. In this study, we used a nationwide population-based database to enrol a large population of hospitalized patients with chronic liver disease complicated by cirrhosis and HE, The aims of this study were (1) to investigate the effect of co-existing bacterial infections on mortality in hospitalized HE cirrhotic patients, and (2) to identify the effect of different infections on mortality in this population.

METHODS

Database

In 1995, Taiwan started the National Health Insurance (NHI) programme. Currently, the National Health Insurance Bureau (BNHI) covers more than 99% of the Taiwanese population. All medical records from all contracted medical institutions must be provided to the BNHI for medical payment. In accordance with the regulations governing the review of medical services, the BNHI reviews reimbursement claims filed by contracted medical institutions and screens the type, volume, quality and appropriateness of medical services provided under the NHI programme. These medical records are established as a database (the National Health Insurance Research Database; NHIRD), which is maintained by BNHI and NHRI. The dataset in this study is from this database, which includes all International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes of the hospitalized patients in Taiwan. The NHIRD research committee approved the use of this database to perform this study (agreement number 100101). The files from NHIRD did not include the patients' and their healthcare providers' private information.

Study population

In this retrospective study, we enrolled patients discharged between 1 January 2004 and 31 December 2004 with both diagnostic codes for cirrhosis (ICD-9-CM code 571·5 or 571·2) and HE (ICD-9-CM code 572·2). Because the aetiologies of cirrhosis were very different in young and adult cirrhotic patients, patients aged <30 years were excluded. Patients with biliary cirrhosis (ICD-9-CM code 571·6) also were excluded. Because patients receiving portosystemic shunts or transjugular intrahepatic portosystemic shunts were prone to have HE and had higher HE-associated mortality, they were excluded from this study. The patients with incomplete or missing basic data in the database were also excluded.

All enrolled HE cirrhotic patients were divided into two groups according to whether they had one or more co-existing infections reported during hospitalization. Because we could not identify microbiological information from this database, the patients receiving antibiotics (but not including antiviral agents) and having a diagnostic code for an infection during their hospitalization were considered as having a co-existing infection. The major infections included pneumonia (ICD-9-CM code 481–487) [16], sepsis (ICD-9-CM code 038, 020·0, 790·7 or 112·81) [17], urinary tract infection (UTI) (ICD-9-CM code 590·1, 595·0, 595·9 or 599·0) [18], biliary tract infection (BTI) (ICD-9-CM code 576·1, 575·0, 574·00, 574·01, 574·30, 574·31, 574·60, 574·61, 574·80, 574·81), empyema (ICD-9-CM code 510), cellulitis

(ICD-9-CM code 681 or 682), necrotizing fasciitis (ICD-9-CM code 728·86), central nervous system infection (including bacterial meningitis or brain abscess: ICD-9-CM code 324 or 320), septic arthritis (ICD-9-CM code 711), infective endocarditis (ICD-9-CM code 421), perianal abscess (ICD-9-CM code 566), liver abscess (ICD-9-CM code 572·0) and spontaneous bacterial peritonitis (SBP) (ICD-9-CM codes 567·2, 567·8 or 567·9) [19]. Patients with other diagnostic codes for secondary peritonitis, such as appendicitis, hollow organ or biliary tract perforation, ischaemic bowel disease, peritoneal dialysis catheter-related peritonitis, as well as those having an additional procedure code for abdominal surgery, were not included as having SBP. Patients with diagnostic codes for sepsis (ICD-9-CM code 038, 020·0, 790·7 or 112·81) without other diagnostic codes for an infectious focus were considered to have sepsis without specific focus (SWSF).

Because many factors affected the mortality of HE cirrhotic patients, the following medical disorders were investigated as possible confounding factors: alcoholism (ICD-9-CM codes 291, 303, 305·00–305·03, 571·0–571·3), hepatocellular carcinoma (HCC) (ICD-9-CM code 155·0), acute renal failure (ARF) (ICD-9-CM code 584, or 572·4), oesophageal variceal bleeding (OVB) (ICD-9-CM code 456·0, or 456·20), chronic renal failure (CRF) (ICD-9-CM code 585), peptic ulcer bleeding (PUB) (ICD-9-CM code 531–533), and ascites (ICD-9-CM code 789·5 or procedure code 54·91).

Statistical analysis

The SPSS statistical package (SPSS System for Windows, version 13.0, SPSS Inc., USA) was used to perform the analyses in this study. The χ^2 test or Fisher's exact test was used to compare categorical variables. One-way ANOVA was used to compare continuous variables. In order to identify risk factors for mortality, a proportional hazards Cox regression model was used to control for possible confounding factors. We present hazard ratios (HRs) with the 95% confidence intervals (CIs) using a significance level of $P < 0.05$. The starting point to evaluate the 30-day, 90-day, and 1-year mortalities in HE cirrhotic patients was the date of admission for enrolled hospitalizations. HRs for mortality were calculated for comparison between the groups with and without co-existing infection.

Table 1. *Demographic characteristics for hospitalized cirrhotic patients with hepatic encephalopathy and with or without co-existing infections (n = 4150)*

	Co-existing infection (n = 985)	No infection (n = 3165)	P value
Male, n (%)	653 (66·3)	2323 (73·4)	<0·001
Age, yr	58·4 ± 14·0	57·4 ± 13·7	0·052
HCC, n (%)	132 (13·4)	730 (23·1)	<0·001
OVB, n (%)	123 (12·5)	503 (15·9)	0·009
Ascites, n (%)	324 (32·9)	755 (23·9)	<0·001
CRF, n (%)	36 (3·7)	121 (3·8)	0·809
ARF, n (%)	34 (3·5)	132 (4·2)	0·315
Alcoholism, n (%)	253 (25·7)	883 (27·9)	0·174
PUB, n (%)	49 (5·0)	183 (5·8)	0·335

HCC, Hepatocellular carcinoma; OVB, oesophageal variceal bleeding; CRF, chronic renal failure; ARF, acute renal failure; PUB, peptic ulcer bleeding.

RESULTS

Patients' characteristics

A total of 4150 HE cirrhotic patients were enrolled in this study. Their mean age was 57·6 ± 13·8 years and 2976 (71·7%) patients were male. There were 985 (23·7%) patients with co-existing infections during their hospitalization. The demographic characteristics and comorbidities of the HE cirrhotic patients with and without infectious diseases are shown in Table 1. The infection group had significantly more patients of female gender and ascites. The non-infection group had significantly more patients of male gender, HCC, and OVB. Other factors, including PUB, alcoholism, ARF, CRF, and age were not significantly different between groups. The 30-day, 90-day and 1-year mortalities were 18·0%, 28·9%, and 46·5%, respectively, in the non-infection group, and 24·6%, 38·0%, and 57·6%, respectively, in the infection group.

Prognostic factors of 30-day, 30- to 90-day, and 90-day to 1-year mortalities

In a Cox proportional regression model, adjusted by age, gender and other confounding factors, including HCC, OVB, ascites, alcoholism, ARF, CRF and PUB, the HR of a co-existing infection on 30-day mortality was 1·66 (95% CI 1·32–1·94, $P < 0.001$). In order to evaluate the late effect of infection on

Table 2. *Prognostic factors of 30-day, 30- to 90-day, and 90-day to 1-year mortalities in hospitalized cirrhotic patients with hepatic encephalopathy*

| | 30-day mortality | | 30- to 90-day mortality | | 90-day to 1-year mortality | |
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Infection	1·66 (1·42–1·94)	<0·001*	1·51 (1·23–1·85)	<0·001*	1·34 (1·13–1·58)	0·001*
Age	1·01 (1·00–1·01)	0·028*	1·02 (1·01–1·03)	<0·001*	1·02 (1·01–1·02)	<0·001*
Male gender	1·37 (1·16–1·62)	<0·001*	1·21 (0·99–1·49)	0·070	1·06 (0·90–1·26)	0·478
HCC	2·24 (1·93–2·61)	<0·001*	3·21 (2·64–3·90)	<0·001*	1·69 (1·40–2·03)	<0·001*
OVB	1·59 (1·33–1·89)	<0·001*	1·28 (0·98–1·66)	0·067	0·98 (0·79–1·22)	0·855
Ascites	0·98 (0·84–1·14)	0·760	1·65 (1·37–2·00)	<0·001*	1·40 (1·19–1·64)	<0·001*
Alcoholism	0·66 (0·55–0·81)	<0·001*	0·70 (0·53–0·91)	0·009	0·86 (0·71–1·03)	0·105
ARF	3·61 (2·90–4·47)	<0·001*	2·92 (1·98–4·32)	<0·001*	1·49 (0·90–2·44)	0·118
CRF	0·77 (0·51–1·15)	0·196	2·09 (1·23–1·85)	<0·001*	1·94 (1·43–2·64)	<0·001*
PUB	0·94 (0·68–1·30)	0·715	1·33 (0·91–1·94)	0·142	0·953 (0·69–1·32)	0·769

HR, Hazard ratio; CI, confidence interval; HCC, hepatocellular carcinoma; OVB, oesophageal variceal bleeding; CRF, chronic renal failure; ARF, acute renal failure; PUB, peptic ulcer bleeding.
* $P < 0·05$.
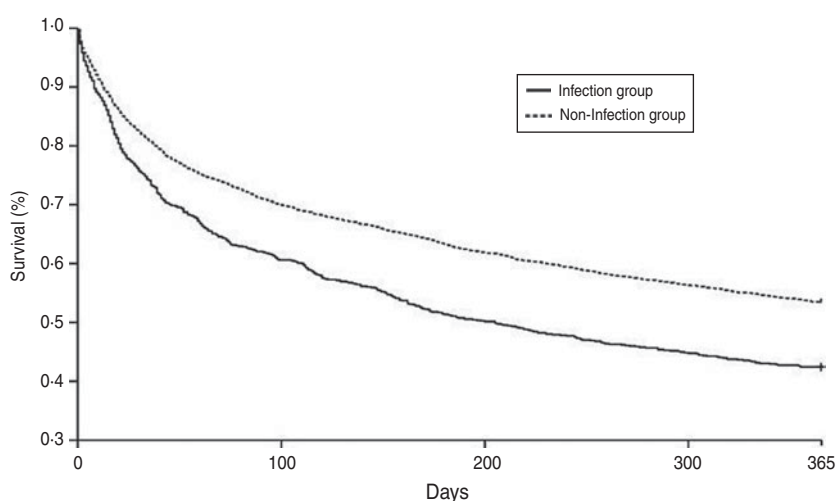
Fig. 1. Cumulative survival plot for hepatic encephalopathy cirrhotic patients with and without co-existing infections. After Cox regression modelling, adjusted by age, gender, and other confounding factors, the hazard ratios of infectious diseases for 30-day, 30- to 90-day, and 90-day to 1-year mortalities were 1·66 (95% CI 1·32–1·94, $P < 0·001$), 1·51 (95% CI 1·23–1·85, $P < 0·001$), and 1·34 (95% CI 1·13–1·58, $P < 0·001$), respectively.

mortality, we calculated the 90-day mortality of patients surviving >30 days and the 1-year mortality of patients surviving >90 days. The HRs of infection for 30- to 90-day and 90-day to 1-year mortalities were 1·51 (95% CI 1·23–1·85, $P < 0·001$), and 1·34 (95% CI 1·13–1·58, $P < 0·001$), respectively (Table 2). We found that the effect of infection on the mortality of HE cirrhotic patients was persistent but decreased over time. Figure 1 shows the cumulative survival plot for HE cirrhotic patients with and without co-existing infections.

The other significant risk factors for 30-day, 30- to 90-day, and 90-day to 1-year mortalities of HE cirrhotic patients are listed in Table 2. Age and HCC were consistent risk factors for mortality in HE cirrhotic patients. Male gender and OVB were risk factors for the 30-day mortality but not for 30- to 90-day and 90-day to 1-year mortalities. ARF was a risk factor for 30-day and 30- to 90-day mortalities, but not for 90-day to 1-year mortality. Alcoholism was negatively associated with mortality of HE cirrhotic patients.

Table 3. *The 30-day, 90-day and 1-year mortalities of different infections in hospitalized cirrhotic patients with hepatic encephalopathy*

Condition	Number (%)	30-day mortality (%)	90-day mortality (%)	1-year mortality (%)
Non-infection	3165 (76·3)	18·0	28·9	46·5
Infection	985 (23·7)	24·6	38·0	57·6
Pneumonia	146 (14·8)	33·6	47·3	69·2
UTI	239 (24·3)	15·5	25·1	48·3
SBP	167 (17·0)	23·4	38·3	54·5
SWSF	317 (32·2)	30·6	45·7	64·0
Cellulitis	39 (4·0)	12·8	15·4	38·5
BTI	23 (2·3)	13·0	39·4	47·8
Other	16 (1·6)	18·8	31·3	43·8
Dual infections	38 (3·9)	23·7	42·1	57·9

UTI, Urinary tract infection; SBP, spontaneous bacterial peritonitis; SWSF, sepsis without specific focus; BTI, biliary tract infection.

Table 4. *Adjusted hazard ratios of different infections on 30-day, 30- to 90-day, and 90-day to 1-year mortalities of cirrhotic patients with hepatic encephalopathy, compared to those without co-existing infections*

	30-day mortality HR (95% CI)	P value	30- to 90-day mortality HR (95% CI)	P value	90-day to 1-year mortality HR (95% CI)	P value
SBP	1·48 (1·07–2·05)	0·019*	1·22 (0·79–1·88)	0·375	0·82 (0·55–1·223)	0·339
Pneumonia	2·11 (1·57–2·83)	<0·001*	1·82 (1·15–2·87)	0·010*	2·03 (1·42–2·91)	<0·001*
UTI	1·06 (0·75–1·49)	0·761	0·93 (0·60–1·43)	0·737	1·24 (0·94–1·65)	0·129
SWSF	2·21 (1·78–2·75)	<0·001*	2·24 (1·65–3·05)	<0·001*	1·64 (1·25–2·16)	<0·001*
Cellulitis	1·06 (0·44–2·56)	0·899	0·31 (0·04–2·21)	0·243	1·14 (0·59–2·19)	0·707
BTI	0·78 (0·25–2·44)	0·673	2·82 (1·25–6·36)	0·012*	0·60 (0·15–2·41)	0·473

HR, Hazard ratio; CI, confidence interval; SBP, spontaneous bacterial peritonitis; SWSF, sepsis without specific focus; UTI, urinary tract infection; BTI, biliary tract infection.
* $P < 0.05$.

The demographic characteristics of cirrhotic patients with variable infections

In a total of 985 HE cirrhotic patients with infectious diseases, there were 146 (14·8%) patients with pneumonia, 239 (24·3%) patients with UTI, 167 (17·0%) patients with SBP, 317 (32·2%) patients with SWSF, 39 (4·0%) patients with cellulitis, 23 (2·3%) patients with BTI, while the remaining patients had other infectious diseases (1·6%) or dual infections (3·9%). The 30-day, 90-day, and 1-year mortalities of HE cirrhotic patients with different infections are given in Table 3.

The effects of different infections on mortality

After Cox proportional regression modelling adjusted for age, gender and other confounding factors, including HCC, OVB, ascites, alcoholism, ARF, CRF and PUB, the results of HRs of different infections on the mortality of HE cirrhotic patients are shown in Table 4. The HR of SWSF for 30-day mortality of HE cirrhotic patients was highest, followed by pneumonia and SBP. However, the HR of BTI for 30- to 90-day mortality was highest, followed by SWSF, and pneumonia. The HR of pneumonia for 90-day to 1-year mortality was highest, followed by SWSF. Figure 2 shows the cumulative survival plot for HE cirrhotic patients with different infections. We found that the effects of pneumonia and SWSF on the mortality of HE cirrhotic patients persisted over time.

DISCUSSION

In-patient mortality was about 15% in infected cirrhotic patients in a previous study [10]. When HE cirrhotic patients had co-existing infections, our
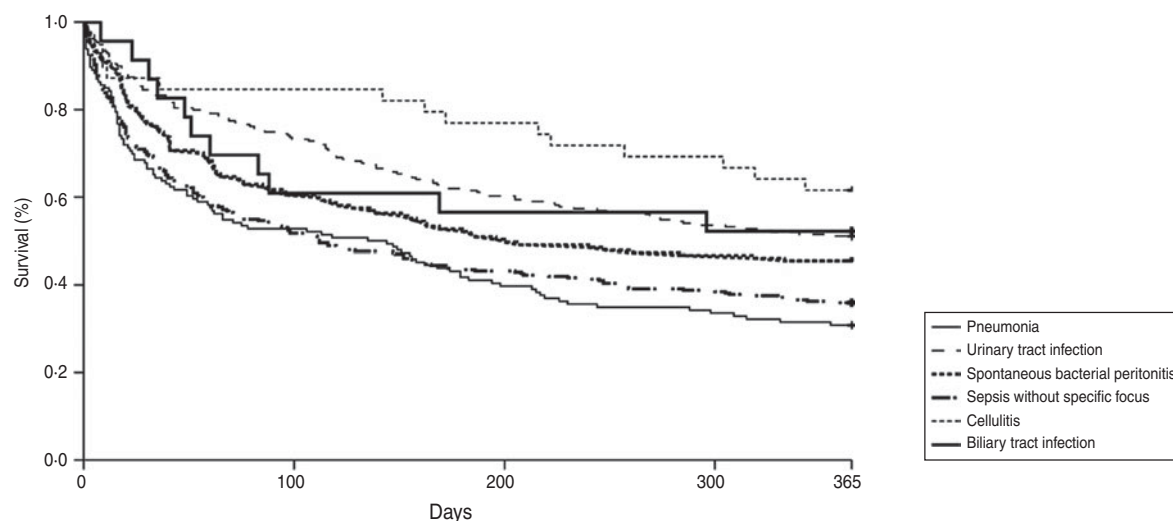
Fig. 2. Cumulative survival plot for hepatic encephalopathy cirrhotic patients with different infections. After Cox regression modelling, the hazard ratios (HRs) of pneumonia for 30-day, 30- to 90-day, and 90-day to 1-year mortalities were 2·11, 1·82, and 2·03, respectively; the HRs of urinary tract infections were 1·06, 0·93, and 1·24, respectively; the HRs of sepsis without specific focus were 2·21, 2·24, and 1·64, respectively; the HRs of spontaneous bacterial peritonitis were 1·48, 1·22, and 0·82, respectively; the HRs of cellulitis were 1·06, 0·31, and 1·14, respectively; and the HRs of biliary tract infection were 0·78, 2·82, and 0·60, respectively compared to the non-infection group.

study shows that their 30-day mortality was 24·6%, 90-day mortality 38%, and 1-year mortality 57·6%. After adjusting for other possible confounding factors for mortality, our study shows that co-existing infections increase mortality in hospitalized HE cirrhotic patients. We also found that the effect of different types of infection on mortality in HE cirrhotic patients was different.

In accord with previous studies, UTI and cellulitis had the lowest 30-day mortality in HE cirrhotic patients, and SWSF and pneumonia carried the highest 30-day mortality [15, 20]. The present study also shows that SWSF and pneumonia had a higher 90-day and 1-year mortality than other infections. Aspiration of gastric content to induce aspiration pneumonia is a severe complication in HE patients [21]. It can induce pulmonary inflammation, capillary leakage, and oxidative damage which cause acute lung injury [22, 23]. Besides acute effects, aspiration pneumonia can also cause permanent lung damage, which may contribute to the persistent effect of pneumonia on the mortality of HE cirrhotic patients [24–26].

Interestingly, BTI increased the HR for 30- to 90-day mortality, but not for early or late mortality. Biliary tract occlusion is the major cause of BTI. When BTI occurs, patients may require adequate drainage and antibiotics to prolong their survival. However, it is difficult for cirrhotic patients with

biliary tract occlusion to have the cause of occlusion removed due to the high risk of anesthesia and surgery. When drug-resistant pathogens emerge or a disease progresses, mortality is increased. That may be the reason why the 30- to 90-day mortality of HE cirrhotic patients with BTI was significantly increased.

The other predisposing factors for mortality of HE cirrhotic patients were age, male gender, HCC, OVB, non-alcoholic-related cirrhosis, and ARF. Of these, ARF was the most unfavourable prognostic factor for 30-day mortality. This result was compatible with a previous study [2]. ARF is an important marker for severity of disease and is associated with sepsis-related mortality [27, 28]. In addition, ARF can impair the renal function to clear ammonia and increase the susceptibility of aggravating brain oedema in HE cirrhotic patients [29, 30]. However, our study shows the effects of ARF are confined to early mortality, not late mortality. By contrast, CRF was associated with an increased risk of late but not early mortality.

Our study provides evidence that co-existing infections increase the risk of mortality in hospitalized HE cirrhotic patients; furthermore, the mortality risk varied by type of infection. Nonetheless, there are several limitations in our study. First, it was not possible to identify the Child–Pugh score according to the diagnostic ICD-9 codes in the database,

although the Child–Pugh score in HE cirrhotic patients was not shown to be associated with outcome in previous studies [2, 31]. Second, the aetiology for cirrhosis in Taiwan is known mostly to be related to chronic vial hepatitis, e.g. hepatitis B virus and hepatitis C virus [32]. However, the exact aetiology of liver cirrhosis could not be identified in this population-based study, even though there were 27% cirrhotic patients with a diagnostic code for alcoholism. Third, it was impossible to evaluate the grade of HE in this database. Finally, the database used in the present study could not provide microbiological data. Therefore, we were unable to discover the pathogens causing infection in HE cirrhotic patients. Despite these limitations, this study is the first complete nationwide population-based study to identify the relationship of infections and mortality in hospitalized HE cirrhotic patients. In conclusion, co-existing infections, particularly pneumonia and SWSF, increase the 30-day, 30- to 90-day, and 90-day to 1-year mortality risk of hospitalized HE cirrhotic patients.

ACKNOWLEDGEMENTS

DECLARATION OF INTEREST

None.

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