

Liver cirrhosis as a real risk factor for necrotising fasciitis: a three-year population-based follow-up study

Tsung-Hsing Hung^{1,2}, MD, Chen-Chi Tsai^{2,3}, MD, Chih-Chun Tsai⁴, PhD, Chih-Wei Tseng^{1,2}, MD, Yu-Hsi Hsieh^{1,2}, MD

INTRODUCTION Necrotising fasciitis (NF) is often found in patients with diabetes mellitus, chronic renal failure, alcoholism, malignancy or liver cirrhosis. However, it remains unknown whether liver cirrhosis is an independent risk factor for the occurrence of NF. This study aimed to determine whether liver cirrhosis is an independent risk factor for the occurrence of NF, and to identify the relationship between severity of liver cirrhosis and occurrence of NF.

METHODS The National Health Insurance Research Database, maintained by Taiwan's National Health Insurance programme, was retrospectively analysed, and the hospitalisation data of 40,802 cirrhotic patients and 40,865 randomly selected, age- and gender-matched non-cirrhotic control patients was collected. The medical records of all patients were individually followed for a three-year period from the patients' first hospitalisation in 2004.

RESULTS During the three-year follow-up period, there were 299 (0.7%) cirrhotic patients with NF and 160 (0.4%) non-cirrhotic patients with NF. Cox regression analysis showed that liver cirrhosis was a risk factor for the occurrence of NF during the study period (hazard ratio 1.982; $p < 0.001$). Among cirrhotic patients, those with complicated liver cirrhosis had a higher risk for the occurrence of NF than patients with non-complicated liver cirrhosis (hazard ratio 1.320; $p = 0.028$).

CONCLUSION Cirrhotic patients had a higher risk for the occurrence of NF than non-cirrhotic patients, and the risk for NF was especially high among patients with complicated liver cirrhosis.

Keywords: cirrhosis, complicated liver cirrhosis, necrotising fasciitis

INTRODUCTION

Necrotising fasciitis (NF) is a type of soft tissue infection that spreads rapidly and progressively along the deep fascia. It is a life-threatening disease with a course that is often overwhelming in nature. Despite improved medical care, the mortality rate associated with NF remains between 12% and 34%.⁽¹⁻⁴⁾ Mortality is especially high among cirrhotic patients with NF, in whom rates have been reported to be nearly ninefold that among non-cirrhotic patients with NF.⁽¹⁻⁴⁾

Liver cirrhosis can weaken the intestinal-portal route barrier, which facilitates the entry of bacteria into the systemic circulation and renders patients prone to various infectious diseases such as spontaneous bacterial peritonitis, respiratory infections or urinary tract infections.^(5,6) Several reports have shown that liver cirrhosis is a common underlying disease in patients with NF.^(1-4,7,8) However, it remains unknown whether liver cirrhosis can increase the occurrence of NF.

The purpose of this study was twofold, namely to determine whether liver cirrhosis is an independent risk factor for the occurrence of NF, and to identify the relationship between severity of liver cirrhosis and occurrence of NF.

METHODS

This study was approved by the National Health Research Institutes (NHRI) in Taiwan. The National Health Insurance Research Database (NHIRD), established and maintained by the Bureau of National Health Insurance (BNHI), Taiwan, and

the NHRI, was used for the purpose of the present study. This database includes all data regarding hospitalised patients in Taiwan. The National Health Insurance (NHI) programme was established in 1995 and encompasses all citizens residing in Taiwan. The BNHI covers over 98% of Taiwan's population. Although researchers are welcome to use the NHIRD for their studies, the privacy of patients and healthcare providers is protected, as researchers using the database are required to submit their study protocols for evaluation by the NHRI.

In this retrospective study, hospitalised patients diagnosed with liver cirrhosis (in accordance with the International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] code 571.5 or 571.2 in the NHIRD) between 1 January 2004 and 31 December 2004 were included for analysis. Patients aged less than 30 years were excluded from the study, as the aetiologies of liver cirrhosis in such patients are often different from those of other cirrhotic patients. Patients with missing or incomplete medical data were also excluded.

As per Taiwan's NHI directives, cirrhotic patients with refractory ascites, episodes of oesophageal/gastric variceal bleeding or hepatic encephalopathy can obtain certification to reduce hospitalisation payments. Cirrhotic patients who availed such certification were identified from the database and categorised as those having complicated liver cirrhosis.

A total of 40,802 cirrhotic patients without baseline NF were enrolled in our study. Cirrhotic patients were stratified according to gender and age (age groups: 30–44 years; 45–59 years;

¹Division of Gastroenterology, Department of Medicine, Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Chiayi, ²School of Medicine, Tzu Chi University, Hualien, ³Division of Infectious Diseases, Department of Medicine, Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Chiayi, ⁴Department of Mathematics, Tamkang University, Tamsui, Taiwan

Correspondence: Dr Yu-Hsi Hsieh, Chief, Endoscopy Section, Division of Gastroenterology, Department of Medicine, Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, No 2, Minsheng Road, Dalin Township, Chiayi County 62247, Taiwan. hsieh.yuhsi@msa.hinet.net

60–74 years; > 75 years). Age- and gender-matched non-cirrhotic patients without baseline NF were also randomly selected from the database as the control group (n = 40,865). All patients (n = 81,667) were individually followed up for a three-year period, beginning with their first hospitalisation in 2004 until the diagnosis of NF (in accordance with ICD-9-CM codes 728.86), death, loss to follow-up or the end of study.

Time to development of NF was defined as the duration from the date selected for follow-up to the time of hospitalisation for NF. The medical comorbidities selected for the study were alcoholism (ICD-9-CM codes 291, 303, 305.00-305.03 and 571.0-571.3), diabetes mellitus (DM; ICD-9-CM code 250), chronic renal failure (CRF; ICD-9-CM code 585), solid organ transplantation (SOT; ICD-9-CM codes V42.0, V42.1 and V42.7), human immunodeficiency virus (HIV) infection (ICD-9-CM code 042), malignancy (ICD-9-CM code 140-208) and connective tissue disease (CTD; ICD-9-CM codes 710). Comorbidities were identified from the patients' hospitalisation records available prior to the end of follow-up. The term 'censored' was used to indicate patient death, patients lost to follow-up or the end of study.

Data was analysed using the Statistical Package for the Social Sciences for Windows version 13.0 (SPSS Inc, Chicago, IL, USA). Cox regression was used to model all factors associated with time to hospitalisation for NF. Age was entered into the Cox models as a continuous covariable using the following coding: 1 = 30–44 years; 2 = 45–59 years; 3 = 60–74 years; 4 = > 75 years. Potential confounding factors included in the analysis were DM, CRF, alcoholism, malignancy, age groups, SOT, gender, CTD and HIV infection. Hazard ratios (HRs) and 95% confidence intervals (CIs) were presented, with the significance level fixed at p-value ≤ 0.05. The R software for Windows (available at: <http://cran.r-project.org/bin/windows/base/>) was used to plot the estimated cumulative incidence curves and perform competing risk analysis.⁽⁹⁾

RESULTS

Table I shows the demographic characteristics and comorbidities of cirrhotic and non-cirrhotic patients enrolled in the study. A total of 81,667 patients were enrolled, and the mean age of the cohort was 59.3 ± 14.3 years. Among the 40,802 cirrhotic patients, 8,739 (21.4%) patients had complicated liver cirrhosis and 32,063 (78.6%) patients had non-complicated liver cirrhosis. During the three-year follow-up period, NF occurred in 299 (0.7%) cirrhotic patients and 160 (0.4%) non-cirrhotic patients. The distribution of many of the comorbidities was found to be significantly different between cirrhotic and non-cirrhotic patients.

Table II provides the results of Cox regression analysis of the various confounding factors for the occurrence of NF in all patients during the study. Significant positive correlation was found between the occurrence of NF and variables such as liver cirrhosis (HR 1.982; p < 0.001), DM (HR 2.978; p < 0.001), CRF (HR 1.615; p = 0.030) and alcoholism (HR 1.364; p = 0.018). Similarly, significant negative correlation was found between

Table I. Characteristics of cirrhotic and non-cirrhotic patients.

Variable	No. of patients (%)		p-value
	Cirrhotic (n = 40,802)	Non-cirrhotic (n = 40,865)	
Gender			0.925
Male	29,010 (71.1)	29,067 (71.1)	
Female	11,792 (28.9)	11,798 (28.9)	
Age group (yrs)			0.999
30–44	7,073 (17.3)	7,097 (17.4)	
45–59	13,069 (32.0)	13,098 (32.1)	
60–74	14,150 (34.7)	14,162 (34.7)	
> 75	6,510 (16.0)	6,508 (15.9)	
Comorbidities			
CTD	60 (0.1)	77 (0.2)	0.149
DM	8,010 (19.6)	7,168 (17.5)	< 0.001*
CRF	1,249 (3.1)	1,151 (2.8)	0.039*
Alcoholism	7,950 (19.5)	684 (1.7)	< 0.001*
SOT	129 (0.3)	77 (0.2)	< 0.001*
HIV infection	15 (0.0)	20 (0.0)	0.400
Malignancy	13,432 (32.9)	5,319 (13.0)	< 0.001*
Complicated liver cirrhosis			
Yes	8,739 (21.4)	0	-
No	32,063 (78.6)	0	-
Occurrence of NF	299 (0.7)	160 (0.4)	< 0.001*

*p ≤ 0.05 was considered statistically significant. CTD: connective tissue disease; CRF: chronic renal failure; DM: diabetes mellitus; HIV: human immunodeficiency virus; NF: necrotising fasciitis; SOT: solid organ transplantation

Table II. Cox regression analysis of confounding factors for the occurrence of necrotising fasciitis in cirrhotic and non-cirrhotic patients.

Variable	Hazard ratio (95% CI)	p-value
Liver cirrhosis	1.982 (1.609–2.441)	< 0.001†
Diabetes mellitus	2.978 (2.460–3.605)	< 0.001†
Chronic renal failure	1.615 (1.049–2.488)	0.030†
Alcoholism	1.364 (1.054–1.765)	0.018†
Malignancy	0.462 (0.340–0.627)	< 0.001†
Old age*	0.759 (0.679–0.848)	< 0.001†
SOT	0.740 (0.104–5.271)	0.763
Male gender	1.039 (0.829–1.303)	0.739
Connective tissue disease	3.288 (0.815–13.266)	0.094
HIV infection	6.246 (0.875–44.577)	0.068

*Old age was entered into the Cox regression models as a continuous covariable using the following coding: 1 = 30–44 years; 2 = 45–59 years; 3 = 60–74 years; 4 = > 75 years. †p ≤ 0.05 was considered statistically significant. CI: confidence interval; HIV: human immunodeficiency virus; SOT: solid organ transplantation

the occurrence of NF and variables such as old age (HR 0.759; p < 0.001) and malignancy (HR 0.462; p < 0.001).

Table III shows the demographic characteristics and comorbidities of patients with complicated and non-complicated cirrhosis. The distribution of many comorbidities and age groups were significantly different between cirrhotic patients with and without complicated liver cirrhosis. During the three-year follow-up period, NF occurred in 95 (1.1%) patients with complicated cirrhosis and 204 (0.6%) patients with non-complicated cirrhosis. As only 15 cirrhotic patients had HIV infection, HIV infection was not entered as a variable into the Cox regression model.

Table IV shows the results of Cox regression analysis of the various confounding factors for the occurrence of NF in cirrhotic patients during the study period. Significant positive correlation was found between the occurrence of NF and variables such as complicated liver cirrhosis (HR 1.320; $p = 0.028$), DM (HR 1.957; $p < 0.001$) and CTD (HR 4.996; $p = 0.025$). However, significant negative correlation was found between the occurrence of NF and variables such as old age (HR 0.642; $p < 0.001$) and malignancy (HR 0.416; $p < 0.001$).

Estimated cumulative incidence curves were constructed for time to hospitalisation for NF in cirrhotic ($n = 40,802$) and non-cirrhotic patients ($n = 40,865$) after the three-year follow-up (Fig. 1). Results of Gray's test for equality of cumulative incidence functions across groups showed that cumulative incidence curves for cirrhotic and non-cirrhotic patients were statistically different for the occurrence of NF.

DISCUSSION

The overall incidence of NF has been estimated to range between 0.24–0.4 per 100,000 adults.⁽¹⁰⁻¹²⁾ In a large survey of Canadian children, Eneli and Davies found that the incidence of NF caused by Group A streptococci was 0.21 per 100,000 children, while that of NF caused by non-Group A streptococci was 0.08 per 100,000 children.⁽¹³⁾ In the present study, we found that, in addition to the incidence of NF in cirrhotic patients (0.7%), the occurrence rate of NF in non-cirrhotic patients (0.4%) was also much higher than reported in the literature. This may partly be due to the fact that those enrolled in our study were all hospitalised patients who often already have comorbidities that contribute to their hospitalisation.

In Taiwan, liver cirrhosis in most adult patients is related to either the hepatitis B or hepatitis C virus.^(14,15) In our study, alcoholism accounted for liver cirrhosis in only 19.5% of cirrhotic patients, with liver cirrhosis in the remaining 80.5% of cirrhotic patients being related to viral hepatitis. Our findings suggest that alcoholism was not a key factor affecting the occurrence of NF in cirrhotic populations. We also found that liver cirrhosis itself could increase the risk of occurrence of NF. Other risk factors that were identified for the occurrence of NF in the present study included DM, CRF and alcoholism. Our results were compatible with the findings of earlier studies.^(4,8,16-20) However, to our knowledge, no previous cohort study in the literature has proven that liver cirrhosis is a risk factor for the occurrence of NF.

Earlier studies have suggested that NF was slightly more common in patients aged above 50 years^(10,20-23) and that malignancy was a contributing factor for NF due to impaired leucocyte function in such patients.^(18,24,25) Contrary to these studies, we found that malignancy and age groups were negatively correlated with the occurrence of NF during the three-year follow-up period. These findings may have been influenced by the fact that patient death was indicated as 'censored' in our study. Apart from patient deaths, hospitalised patients with malignancy or old age during the three-year follow-up period were also considered as censors. Such categorisation – when few episodes of NF are observed with a large number of censors – may have

Table III. Characteristics of all patients with complicated and non-complicated liver cirrhosis ($n = 40,802$).

Variable	No. of cirrhotic patients (%)		p-value
	Non-complicated ($n = 32,063$)	Complicated ($n = 8,739$)	
Gender			0.304
Male	22,758 (71.0)	6,252 (71.5)	
Female	9,305 (29.0)	2,487 (28.5)	
Age group (yrs)			< 0.001*
30–44	5,087 (15.9)	1,986 (22.7)	
45–59	9,611 (30.0)	3,458 (39.6)	
60–74	11,611 (36.2)	2,539 (29.1)	
> 75	5,754 (17.9)	756 (8.7)	
Comorbidities			
CTD	49 (0.2)	11 (0.1)	0.671
DM	6,163 (19.2)	1,847 (21.1)	< 0.001*
CRF	1,054 (3.3)	195 (2.2)	< 0.001*
Alcoholism	5,662 (17.7)	2,288 (26.2)	< 0.001*
SOT	74 (0.2)	55 (0.6)	< 0.001*
HIV infection	13 (0)	2 (0)	0.752
Malignancy	12,157 (37.9)	1,275 (14.6)	< 0.001*
Occurrence of NF	204 (0.6)	95 (1.1)	< 0.001*

* $p \leq 0.05$ was considered statistically significant. CTD: connective tissue disease; CRF: chronic renal failure; DM: diabetes mellitus; HIV: human immunodeficiency virus; NF: necrotising fasciitis; SOT: solid organ transplantation

Table IV. Cox regression analysis of confounding factors for the occurrence of necrotising fasciitis in patients with complicated and non-complicated liver cirrhosis.

Variable	Hazard ratio (95% CI)	p-value
Complicated liver cirrhosis*	1.320 (1.031–1.690)	0.028*
Diabetes mellitus	1.957 (1.527–2.508)	< 0.001*
Connective tissue disease	4.996 (1.225–20.371)	0.025*
Malignancy	0.416 (0.290–0.598)	< 0.001*
Old age†	0.642 (0.557–0.741)	< 0.001*
Alcoholism	1.137 (0.867–1.492)	0.354
Solid organ transplantation	0.893 (0.125–6.374)	0.910
Male gender	0.967 (0.725–1.290)	0.820
Chronic renal failure	1.133 (0.581–2.209)	0.713

*In comparison with non-complicated liver cirrhosis. †Old age was entered into the Cox regression models as a continuous covariable using the following coding: 1 = 30–44 years; 2 = 45–59 years; 3 = 60–74 years; 4 = > 75 years. * $p \leq 0.05$ was considered statistically significant. CI: confidence interval

given rise to some bias and caused an underestimation of the effect of age and malignancy on the occurrence of NF.

An antecedent traumatic wound, which may include trauma, intravenous or hypodermic injection, or surgery, has been suggested as a possible portal of entry for NF.^(26,27) However, studies have also found that most cirrhotic patients with NF do not have obvious lesions on the body surface that allow bacterial invasion.^(2,7,16) Monomicrobial NF is reported to be more common in cirrhotic patients,^(2,16) unlike patients with DM, in whom NF is reported to be mainly polymicrobial.^(2,16) Studies have also suggested that Gram-negative bacilli such as *Vibrio* spp., *Klebsiella* spp. and *Aeromonas* spp. are common causes of monomicrobial NF in cirrhotic patients, while *Streptococcus pyogenes* is commonly seen in patients with DM.^(2,7,16) These

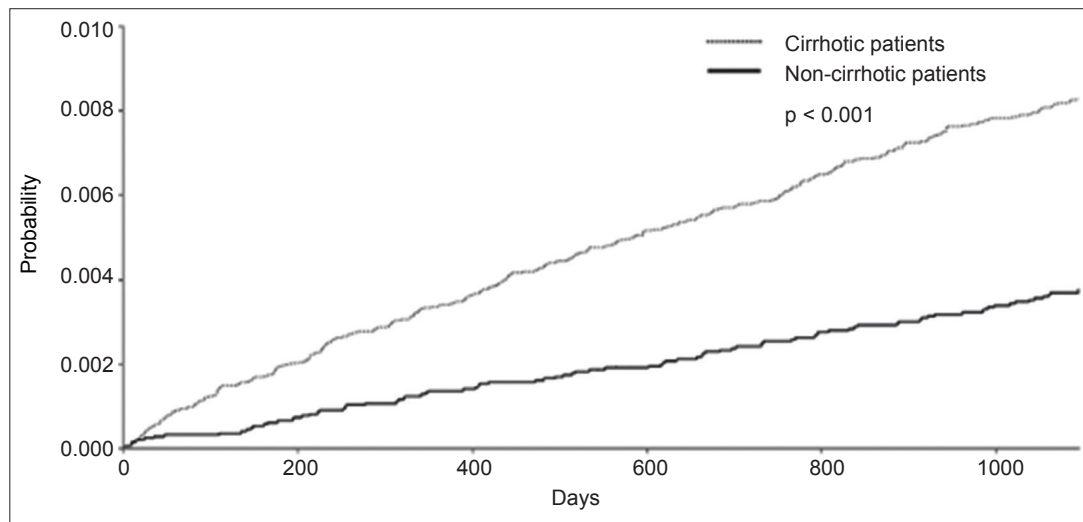


Fig. 1 Graph shows estimated cumulative incidence curves for time to hospitalisation for necrotising fasciitis in cirrhotic and non-cirrhotic patients.

findings suggest that the clinical setting of NF in cirrhotic patients is different from that in other debilitated individuals. A possible mechanism of NF in cirrhotic patients includes the seeding of bacteria in the oedematous soft tissue via the bloodstream through the intestinal portal route.^(2,7) Such aetiology may explain why the simultaneous involvement of two extremities is seen in 28% of cirrhotic patients with NF, with 58% of these patients having concurrent Gram-negative bacteraemia.⁽²⁾

In cirrhotic patients, intestinal bacterial overgrowth and increased intestinal permeability contribute to bacterial translocation from the intestines more easily than in normal hosts.⁽²⁸⁻³²⁾ The concomitant presence of impaired phagocytosis, poor opsonisation capacity, impaired reticuloendothelial system and low complement levels in cirrhotic patients⁽³³⁻³⁷⁾ makes them all the more prone to bacteraemia.⁽³⁸⁻⁴⁰⁾ Kuo et al reported that the frequencies of bacteraemia were positively correlated to the severity of liver cirrhosis.⁽⁴¹⁾ This might explain our finding that patients with liver cirrhosis had a higher occurrence of NF, and this was especially so among patients with complicated liver cirrhosis.

In our study, CTD was not a risk factor for the occurrence of NF in all patients, although it was a risk factor for the occurrence of NF in cirrhotic patients. This suggests that CTD and liver cirrhosis have a synergistic effect on the occurrence of NF. However, the immunosuppressive status caused by CTD or the immunosuppressive therapies usually prescribed for CTD is not a sufficient cause for bacterial blood stream infections leading to NF. This notwithstanding, the immunosuppressive effects of CTD may further weaken the immune status of cirrhotic patients, thus contributing to higher bacterial bloodstream infection and increased occurrence of NF in this cohort. Further extensive studies will be required to establish this association.

There were some limitations to our study. First, all selected patients were hospitalised patients and non-cirrhotic patients were selected as the control group in accordance with the diagnostic criteria outlined in the ICD-9-CM. This may have led to some bias, as patients who had liver cirrhosis but were not

diagnosed during hospitalisation would have been categorised as non-cirrhotic patients in our study. Next, laboratory data regarding bilirubin, albumin and prothrombin time could not be identified based on the ICD-9-CM coding from the database. Similarly, we could not evaluate the severity of liver cirrhosis based on the Child-Pugh score. Then, the database used in our study did not include complete information on individuals, such as the amount of alcohol consumed, or dosage and duration of steroid use. This may have somewhat influenced the results of our study. Furthermore, we could not discount the possibility of miscoding, or assess the validity of NF diagnosis in our database. Finally, the exact aetiology of liver cirrhosis was not identified in our national population-based study. However, despite its limitations, our study is the most complete nationwide population-based study to prove that liver cirrhosis is a risk factor for the occurrence of NF.

To summarise, we found that cirrhotic patients had a higher risk for the occurrence of NF than non-cirrhotic patients, and the risk for NF was especially high among patients with complicated liver cirrhosis. DM, CRF and alcoholism were risk factors for the occurrence of NF in both cirrhotic and non-cirrhotic patients, while CTD was a risk factor for NF in only cirrhotic patients. Old age and malignancy were negatively associated with NF. Future studies should aim to investigate and substantiate the associations noted in this study.

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