

## The Risk of Cellulitis in Cirrhotic Patients: A Nationwide Population-Based Study in Taiwan

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**Background/Aims:** Cellulitis is a common infectious disease. However, the risk of cellulitis in cirrhotic patients is not well established, and whether liver cirrhosis is a risk factor for cellulitis remains unknown. This study evaluated the relationship between cellulitis and liver cirrhosis. **Methods:** The National Health Insurance Database, which was derived from the Taiwan National Health Insurance program, was used to identify patients. The study group consisted of 39,966 patients with liver cirrhosis, and the comparison group consisted of 39,701 randomly selected age- and sex-matched patients. **Results:** During the 3-year follow-up period, 2,674 (6.7%) patients with liver cirrhosis developed cellulitis, and 1,587 (4.0%) patients without liver cirrhosis developed cellulitis ( $p < 0.001$ ). Following a Cox's regression analysis adjusted for age, sex, and underlying medical disorders, the cirrhotic patients demonstrated a greater risk for the occurrence of cellulitis than the non-cirrhotic patients during the 3-year period (hazard ratio [HR], 1.66; 95% confidence interval [CI], 1.55 to 1.77;  $p < 0.001$ ). Additionally, cirrhotic patients with complications also had a greater risk for the occurrence of cellulitis than those patients without complications (HR, 1.23; 95% CI, 1.14 to 1.33;  $p < 0.001$ ). **Conclusions:** We conclude that cirrhotic patients have a greater risk of cellulitis than non-cirrhotic patients. (**Gut Liver 2012;6:482-485**)

**Key Words:** Cellulitis; Liver cirrhosis

### INTRODUCTION

Cellulitis is a common infectious disease. Cirrhotic patients are prone to infectious diseases due to their underlying immunocompromised status.<sup>1</sup> However, the risk of cellulitis in cirrhot-

ic patients has not been well established. To date, it is unknown whether liver cirrhosis is a risk factor for cellulitis. The purpose of our study was to determine whether cirrhosis is a predisposing factor of cellulitis, and identify the risk of cellulitis in complicated and non-complicated liver cirrhosis.

### MATERIALS AND METHODS

#### 1. Database and study sample

The secondary de-identified database used in this retrospective study was the Taiwan National Health Insurance (NHI) research database, which is joint database of the Taiwan NHI Bureau and National Health Research Institute. This database was used to identify all hospital discharges within Taiwan. The NHI program was developed in 1995 to collect information on all citizens residing in Taiwan, and by 2004, it included at least 95% of Taiwan's population. All researchers that use the NHI research database need to be approved by the National Health Research Institute, as well as agree to protect the privacy of patients. The present study was approved by the National Health Research Institute (approval no. 100101).

All patients discharged with a diagnosis of liver cirrhosis (ICD-9-CM code 571.5 or 571.2) from January 1, 2004 to December 31, 2004 were identified in the NHI research database. Only patients aged 30 years and older were included in the study. We excluded any patients with incomplete or missing basic data. A total of 39,966 cirrhotic patients without cellulitis at that admission were identified and enrolled into this study group. A comparison group composed of 39,701 sex- and age-matched (i.e., 30 to 44, 45 to 59, 60 to 74, and >75 years) patients were randomly selected from the same NHI research database. Each patient ( $n=79,667$ ) was individually followed up for

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3 years beginning from first hospitalization until the presence of cellulitis (ICD-9-CM codes 681 or 682). As in previous reports, complicated liver cirrhosis was defined as the presence of ascites, episodes of esophageal/gastric visceral bleeding, or hepatic encephalopathy.<sup>2-4</sup> Comorbidities were evaluated if the condition was noted at the time of initial hospital admission. Major and common systemic comorbid medical disorders, which may potentially affect the occurrence of cellulitis, were identified as confounding factors.

## 2. Statistical analysis

The SPSS statistical package (SPSS for Windows version 13.0; SPSS Inc., Chicago, IL, USA) was used to perform the statistical analyses. The Kaplan-Meier method with a log-rank test was used to evaluate the difference between the proportion of individuals that develop cellulitis in the liver cirrhosis and control groups during the 3-year follow-up period. The Cox proportional hazard regression was also used to compare the occurrence of cellulitis in the liver cirrhosis versus control patients, as well as in patients with complicated versus non-complicated cirrhosis. The hazard ratios (HRs) along with the 95% confidence intervals (CIs) were determined. A  $p < 0.05$  was considered statistically significant.

## RESULTS

Patients' characteristics and selected comorbid medical disorders at baseline are presented in Table 1. Of the 39,966 cirrhotic patients, the mean age was  $59.3 \pm 13.9$  years. Among all of the

**Table 1.** Demographic Characteristics and Comorbid Medical Disorders for the Cirrhotic Patients and Comparison Patients (n=81,538)

Characteristic	Cirrhotic patients (n=39,966)	Comparison patients (n=39,701)	p-value
Male	28,406 (71.1)	28,196 (71.0)	0.870
Age, yr			0.711
30-44	6,907 (17.3)	6,857 (17.3)	
45-59	12,774 (32.0)	12,725 (32.1)	
60-74	13,897 (34.8)	13,773 (34.7)	
>75	6,388 (16.0)	6,349 (16.0)	
Diabetes	7,803 (19.5)	6,888 (17.3)	<0.001
CRF	1,224 (3.1)	1,131 (2.8)	0.075
Connective tissue disease	58 (0.1)	74 (0.2)	0.164
Alcoholism	7,772 (19.4)	677 (1.7)	<0.001
Gout	753 (1.9)	989 (2.5)	<0.001
Heart failure	946 (2.4)	1,349 (3.4)	<0.001
HIV	15 (0)	20 (0.1)	0.403
Drug abuse	8 (0)	25 (0.1)	0.003

Data are presented as number (%).

CRF, chronic renal failure; HIV, human immunodeficiency virus.

79,667 patients, 4,261 patients (5.3%) developed cellulitis during the 3-year follow-up period. Cellulitis was developed in 2,674 patients with liver cirrhosis (6.7%), and 1,587 patients without liver cirrhosis (4.0%), respectively ( $p < 0.001$ ). The mean follow-up periods for patients with and without liver cirrhosis were 919 and 1,013 days, respectively. The mean duration between hospitalization and the onset of cellulitis was 426 days for cirrhotic patients compared with the 432 days in the reference group.

Since both diabetes mellitus (DM) and alcoholism are known risk factors for cellulitis and the incidences of DM and alcoholism were significantly higher in cirrhosis group than control group, we analyzing the occurrence of cellulitis in cirrhotic patients according to the presence of DM/alcoholism or not. During the 3-year follow-up period, the occurrence of cellulitis in the cirrhotic patients with DM, cirrhotic patients without DM, and control group were 8.3% (644/7,803), 6.3% (2,030/32,163), and 4.0% (1,587/39,701), respectively ( $p < 0.001$ ). The results in the cirrhotic patients with alcoholism, cirrhotic patients without alcoholism, and control group were 9.5% (735/7,772), 6.0% (1,939/32,194), and 4.0% (1,587/39,701), respectively ( $p < 0.001$ ).

The findings from the Cox regression analysis with a forward stepwise selection procedure based on the likelihood ratio are presented in Table 2. After adjusting for gender, age, chronic renal failure, diabetes, drug abuse, HIV infection, connective tissue disease, alcoholic status, and gout, the HR for cellulitis during the 3-year follow-up period was 1.66 (95% CI, 1.55 to 1.77;  $p < 0.001$ ). Furthermore, patients that were male (HR, 1.10; 95% CI, 1.02 to 1.18;  $p = 0.009$ ), and had connective tissue disease (HR, 2.16; 95% CI, 1.22 to 3.80;  $p = 0.008$ ), alcoholism (HR, 1.55; 95% CI, 1.42 to 1.68;  $p < 0.001$ ), diabetes (HR, 1.57; 95% CI, 1.47 to 1.68;  $p < 0.001$ ), heart failure (HR, 1.50; 95% CI, 1.28 to 1.76;  $p < 0.001$ ), or gout (HR, 1.79; 95% CI, 1.54 to 2.09;  $p < 0.001$ ) were at greater risk for developing cellulitis. The crude HR for the occurrence of cellulitis in complicated versus non-complicated liver cirrhosis was 1.30 (95% CI, 1.20 to 1.40;  $p < 0.001$ ). After adjusting for gender, age, and underlying medical disorders with a Cox regression analysis, the adjusted HR was 1.23 (95% CI, 1.14

**Table 2.** Adjusted Hazard Ratios for Cellulitis among the Patients during the 3-Year Follow-up Starting from the First Hospitalization

Variable	Occurrence of cellulitis		
	HR	95% CI	p-value
Liver cirrhosis	1.66	1.55-1.77	<0.001
Gender, male	1.10	1.02-1.18	0.009
Connective tissue disease	2.16	1.22-3.80	0.008
Alcoholism	1.55	1.42-1.68	<0.001
Gout	1.79	1.54-2.09	<0.001
Diabetes	1.57	1.47-1.68	<0.001
Heart failure	1.50	1.28-1.76	<0.001

HR, hazard ratio; CI, confidence interval.

**Table 3.** Crude and Adjusted HRs of Cellulitis among the 15,959 Complicated and 24,007 Non-Complicated Liver Cirrhosis Patients

Development of cellulitis	Non-complicated cirrhosis, No. (%)	Complicated cirrhosis, No. (%)	p-value
During follow-up period			
Presence	1,469 (6.1)	1,205 (7.6)	
Absence	22,538 (93.9)	14,754 (92.4)	
Crude HR (95% CI)	1	1.30 (1.20–1.40)	<0.001
Adjusted HR (95% CI)*	1	1.23 (1.14–1.33)	<0.001

HR, hazard ratio; CI, confidence interval.

\*Adjustments were made for patient's gender, age, diabetes mellitus, chronic renal failure, connective tissue disease, heart failure, gout, drug abuse, human immunodeficiency virus, and alcoholism.

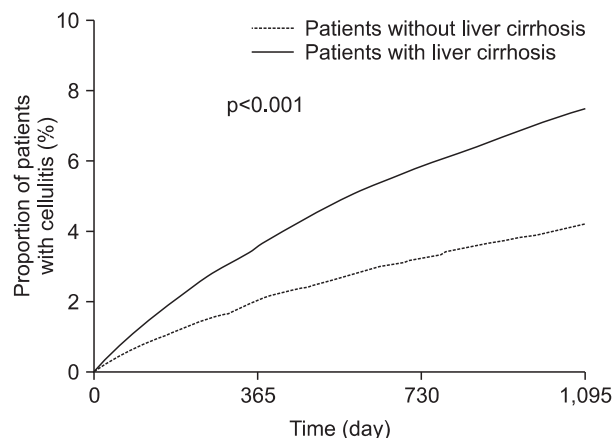
to 1.33;  $p < 0.001$ ), and the results were presented in Table 3.

The log-rank test indicated that cirrhotic patients had a significantly higher 3-year proportion of cellulitis than control patients ( $p < 0.001$ ). The results of the Kaplan-Meier survival analysis are presented in Fig. 1.

## DISCUSSION

Cellulitis is a common infectious disease in both the general population and cirrhotic patients. A recent study reported that cellulitis was present in 12.5% (10/80) of cirrhotic patients.<sup>5</sup> However, the real risk of cellulitis in cirrhotic patients compared to the general population is still unknown. To our best knowledge, this is the first report to directly compare the occurrence of cellulitis in cirrhotic versus non-cirrhotic patients. This is also the first study to identify the occurrence of cellulitis in complicated versus non-complicated liver cirrhosis.

The present study provided strong evidence for an increased risk of cellulitis in cirrhotic versus non-cirrhotic patients. Furthermore, an increased risk of cellulitis was noted in complicated versus non-complicated cirrhosis. Patients with liver cirrhosis usually have chronic edema in lower limbs, which may serve as the origin of bacterial infections.<sup>6</sup> Although gram-positive cocci are the most common type of bacteria in cellulitis of the general population, gram-negative bacilli (GNB) are increasing bacteria involved in the development of cellulitis in cirrhotic patients.<sup>6-9</sup> In one report, mortality rate of patients with GNB cellulitis was up to 56%.<sup>8</sup> In the general population, necrotizing fasciitis (NF) is the most severe form of soft tissue infections with a reported mortality rate of 34% (range, 6% to 76%).<sup>10</sup> A recent study in Taiwan reported a mortality rate of 17.0% for NF.<sup>11</sup> Similarly, in another study from Taiwan, the mortality rate in patients with NF was 15.2% (7/46).<sup>12</sup> However, NF results in greater mortality among cirrhotic patients. As reported by Cheng *et al.*,<sup>13</sup> the mortality from NF in cirrhotic patients was as high as 64.7% (11/17). Cellulitis is frequently indistinguishable from NF, as both conditions present with similar features upon initial presentation.<sup>14,15</sup>



**Fig. 1.** Time to hospitalization for cellulitis in patients with and without cirrhosis after a 3-year follow-up (2004 to 2007).

Furthermore, cellulitis in cirrhotic patients may be underestimated due to the frequently swelling of skin or soft tissue from hypoalbuminemia. Thus, primary health care providers should pay more attention to changes in skin erythematous and other clues/symptoms/signs of infection in cirrhotic patients, especially in those with a complicated status. Since cellulitis is a common infectious disease among in- and out-patients, clinicians should be informed about the higher occurrence of cellulitis in cirrhotic patients, especially in those with a complicated status. Given the difficulty of initially distinguishing cellulitis from NF, and the higher occurrence of cellulitis among cirrhotic patients, early detection of cellulitis and antibiotic treatment is needed for these immunocompromised patients.

Patients with underlying immunocompromised status or cardiovascular disease are at risk for the occurrence of cellulitis.<sup>16,17</sup> Our study findings corroborate these observations. Aside from the presence of liver cirrhosis, there was an increased risk of cellulitis noted among patients that were male, and had heart failure, gouty arthritis, and other immunocompromising conditions, such as diabetes, heavy alcohol use, and connective tissue disease (from increased steroid usage).

Using a nationwide population-based database, the present study found strong evidence for a greater occurrence of cellulitis among cirrhotic patients. However, there are several limitations that need to be addressed. First, the database we selected did not include all of the individuals' information. Certain factors that were not available and may contribute to the development of cellulitis include smoking, body weight, the dosage and duration of steroid use, and the amount of alcohol consumption. Therefore, to prevent potential bias in our findings, we selected and adjusted for related major and common medical comorbidities, such as alcoholism and connective tissue disease. Second, although the severity of liver cirrhosis is commonly classified according to the Child-Pugh score and model for end-stage liver disease, laboratory data, such as bilirubin, albumin, and prothrombin time, could not be obtained from the database used in

this study. Thus, patients were classified into complicated and non-complicated cirrhosis. However, patients with cirrhosis and major complications may actually be in a decompensated state. Otherwise, only in-patients were included in this study, and outpatients were not enrolled. This is a limitation of our study because hospital admission might not be necessary in the mild cirrhotic patients. Lastly, the exact etiology of liver cirrhosis was not identified in this national population-based study. However, the etiology of liver cirrhosis is well known to be related to hepatitis B or C virus in Taiwan.<sup>18,19</sup> Despite these limitations, our study is the most complete nationwide population-based study for identifying the risk of cellulitis among cirrhotic patients.

In summary, our study demonstrates that cirrhotic patients are at a greater risk for cellulitis, especially in those with complicated cirrhosis. Primary health care providers should pay more attention to the cirrhotic patients with skin erythematous change or any other symptoms and/or signs of infection.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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