Observational Study

Medicine®

OPEN

# Alcohol use disorder increases the risk of necrotizing fasciitis

## A nationwide retrospective cohort study

Yong-Cheng Yii, MD[a,b], Vivian Chia-Rong Hsieh, PhD[c], Cheng-Li Lin, MSc[d,e], Yu-Chiao Wang, MSc[d,e], Wei-Kung Chen, MD[a,b,*]

**Abstract**

This nationwide retrospective cohort study determined the association between alcohol use disorder (AUD) and the risk of necrotizing fasciitis (NF).

This study used health insurance claims data of 52,212 in-patients with AUD and 208,848 controls randomly frequency-matched by age and sex at a 1:4 ratio. The AUD cohort included patients newly diagnosed with AUD between January 1, 2000 and December 31, 2008. The NF event occurrence was observed until December 31, 2011. We used the Kaplan–Meier method to present the cumulative incidence curve and Cox proportional hazard models to depict the risk of NF in patients with AUD.

The incidence of NF was 19.4 per 10,000 person-years in the AUD cohort, which was nearly 7.73-fold higher than that in the comparison cohort (2.54 per 10,000 person-years). After adjustment for age, sex, and comorbidities, the patients with AUD exhibited a 3.55-fold higher risk of NF than did the controls (hazard ratio [HR] = 3.55, 95% confidence interval [CI] = 3.00–4.20). Nevertheless, in the AUD groups without any comorbidity, patients with AUD exhibited a significant 15.2-fold higher risk of NF than did the comparison cohort (HR = 15.2, 95% CI = 10.9–21.3). Moreover, the adjusted HRs of NF risk with respect to the severity of AUD were 2.15 (95% CI = 1.76–2.62), 4.54 (95% CI = 3.67–5.62), and 10.7 (95% CI = 8.66–13.2) for mild, moderate, and severe AUD, respectively.

This study indicated that AUD should be considered an independent and significant risk factor for NF.

**Abbreviations:** aHR = adjusted hazard ratio, AUD = alcohol use disorder, CI = confidence interval, HR = hazard ratio, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, IRB = Institutional Review Board, NF = necrotizing fasciitis, NIH = National Health Insurance, SD = standard deviation.

**Keywords:** alcohol use disorder, necrotizing fasciitis, retrospective cohort study

*Editor: Dan Lipsker.*

*Conceptualization, investigation, and resources: Y-CY and W-KC. Methodology and software: C-LL, Y-CW, and W-KC. Validation, formal analysis, data curation, and writing (original draft preparation, review, and editing), and visualization: Y-CY, VC-RH, C-LL, Y-CW, and W-KC. Supervision, project administration, and funding acquisition: W-KC.*

*This study was supported in part by the Taiwan Ministry of Health and Welfare Clinical Trial and Research Center of Excellence (MOHW105-TDU-B-212-133019); China Medical University Hospital; Academia Sinica Taiwan Biobank Stroke Biosignature Project (BM10501010037); NRPB Stroke Clinical Trial Consortium (MOST 105-2325-B-039-003); Tseng-Lien Lin Foundation, Taichung, Taiwan; Taiwan Brain Disease Foundation, Taipei, Taiwan; Katsuzo and Kiyo Aoshima Memorial Funds, Japan; CMU under the Aim for Top University Plan of the Ministry of Education, Taiwan; Taipei Veterans General Hospital (V104C-108, V105C-085); and Ministry of Science and Technology, Taiwan (MOST 104-2314-B-075-012).*

*The authors have no conflicts of interest to disclose.*

*[a] Department of Emergency Medicine, China Medical University Hospital, [b] School of Medicine, College of Medicine, China Medical University, [c] Department of Health Services Administration, China Medical University, [d] College of Medicine, China Medical University, [e] Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan.*

*[*] Correspondence: Wei-Kung Chen, Department of Emergency, China Medical University Hospital, No. 2, Yuh-Der Road, Taichung 404, Taiwan (e-mail: ercwk@mail.cmuh.org.tw).*



*Medicine (2017) 96:32(e7509)*

*Received: 27 March 2017 / Received in final form: 19 June 2017 / Accepted: 20 June 2017*

*http://dx.doi.org/10.1097/MD.0000000000007509*

## 1. Introduction

Necrotizing fasciitis (NF), commonly known as the flesh-eating disease, is a rapidly progressing, synergistic bacterial infection of the fascia with a high mortality rate.[1] Hippocrates was the earliest to report NF as a description of a complication of erysipelas in the fifth century BC.[2]

The incidence of NF is estimated to be 0.04 to 0.4 per 10,000 person-years.[3–5] Although NF is not a common disease, it has a high mortality rate despite the advanced therapeutic methods developed in the past 3 decades; its overall mortality, as reported in 67 studies on NF including 3302 patients between 1980 and 2008, is 23.5%.[7] Another review article reported a mortality rate of 21.5% and an amputation rate of 15%.[8]

Reported risk factors of NF include age more than 50 years, peripheral vascular disease (PVD), diabetes mellitus, hypertension, ischemic heart disease (IHD), obesity, stroke, liver cirrhosis or chronic alcoholism, chronic renal failure, chronic obstructive pulmonary disease (COPD), cancer, trauma, steroid use, nonsteroidal anti-inflammatory drug use, and intravenous drug abuse.[6,8–13] Most review articles have suggested that diabetes mellitus is the most common comorbidity and risk factor in 44.5%,[8] 31%,[10] and 32%[11] of patients with NF, respectively. Among previous studies, few articles have identified alcohol use disorder (AUD) as a risk factor in 17%[10] and 6.1%[11] of patients with NF. Thus, AUD is considered a potential risk factor for NF; however, the association between AUD and NF has not been firmly established.

AUD is a major public health concern because it accounts for a considerable burden of disease globally. It is a chronic illness with a lifetime prevalence in approximately 20% of the general

population.[14] In 2014, the World Health Organization estimated that 5.1% of the global burden of disease and injury and 5.9% of all deaths worldwide are attributable to alcohol.[15] In addition, social costs attributable to alcohol represent 1.3% to 3.3% of the gross domestic product.[15] Alcohol consumption is associated with approximately more than 230 three-digit International Classification of Diseases (ICD)-10 codes.[16] Major alcohol-attributable conditions include tuberculosis, mouth, nasopharynx, other pharynx, and oropharynx cancer, esophageal cancer, colon and rectum cancer, liver cancer, breast cancer, diabetes mellitus, depressive disorders, epilepsy, hypertensive heart disease, IHD, stroke, dysrhythmias, lower respiratory infections, cirrhosis of the liver, preterm birth complications, fetal alcohol syndrome, pancreatitis, injuries, and violence.[17,18]

To date, few studies have explored the risk of NF in patients with a history of AUD. The relationship between NF and AUD should be investigated and clarified. We hypothesized that AUD increases the risk of NF. Thus, we conducted a nationwide retrospective cohort study in Taiwan to examine the association between AUD and NF development.

## 2. Patients and methods

### 2.1. Data source

The Taiwan National Health Insurance (NHI) program is a single-payer, compulsory health insurance program inaugurated in 1995 that currently covers almost all of the country's 23 million residents. For research and academic purposes, the national health insurance research database (NHIRD), containing the complete set of medical claims data from the Taiwan NHI, was established and is managed by the National Health Research Institutes (NHRI). The NHIRD comprises the beneficiary registry, outpatient and inpatient claims, prescription registry, and other medical claims-based information. The disease record system was established on the basis of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). This study collected each individual's disease history from inpatient files.

### 2.2. Study population

This study established 2 study cohorts, the AUD and non-AUD (control) cohorts. The AUD cohort comprised patients newly diagnosed with AUD (ICD-9-CM 303, 305.0, and V113) between January 1, 2000 and December 31, 2008, with the initial date of diagnosis considered the index date. The control cohort comprised individuals without AUD who were frequency-matched with the AUD cohort by age and sex at a 1:4 ratio. The index dates for control subjects were assigned the same dates as those of the matched cases. Both cohorts excluded individuals with a history of NF before the index date. Our outcome of interest was the event occurrence of NF (ICD-9-CM 728.86). The follow-up period for both cohorts started from the index date and ended on the occurrence of any of the following 3 conditions: withdrawal from the NHI program, an observed NF event, or December 31, 2011 (end of observation period).

The patients with AUD were further classified into 3 groups (mild, moderate, and severe) on the basis of the disease severity in tertiles. We hypothesized that severe AUD group has longer length of hospital stay. Therefore, we defined AUD severity as the ratio of the length of hospital stay because of AUD and the complete duration of the follow-up period.

Age, sex, and comorbidity were considered the confounding factors. The following comorbidities were included in the analysis: hypertension (ICD-9-CM 401–405), hyperlipidemia (ICD-9-CM: 272), diabetes (ICD-9-CM: 250), liver diseases (ICD-9-CM: 571), end-stage renal disease (ICD-9-CM: 585 from catastrophic illness registry), cancer (ICD-9-CM: 140–208 from catastrophic illness registry), IHD (ICD-9-CM: 410–414), stroke (ICD-9-CM: 430–438), COPD (ICD-9-CM: 491, 492, and 496), and PVD (ICD-9-CM: 443.9).

### 2.3. Data availability statement

All data and related metadata were deposited in an appropriate public repository in the NHRI. The data on the study population that were obtained from the NHIRD (http://nhird.nhri.org.tw/en/index.html) are maintained in the NHIRD (http://nhird.nhri.org.tw/). The NHRI is a nonprofit foundation established by the government. Only citizens of the Republic of China who fulfill the requirements of conducting research projects are eligible to apply for the NHIRD. The use of NHIRD is limited to research purposes only. Applicants must follow the Computer-Processed Personal Data Protection Law (http://www.winklerpartners.com/?p=987) and related regulations of National Health Insurance Administration and NHRI, and an agreement must be signed by the applicant and his/her supervisor upon application submission. All applications are reviewed for approval of data release.

### 2.4. Ethics statement

The NHIRD encrypts patient personal information to protect privacy and provides researchers with anonymous identification numbers associated with relevant claims information, including sex, date of birth, medical services received, and prescriptions. Therefore, patient consent is not required to access the NHIRD. This study was approved to fulfill the condition for exemption by the Institutional Review Board (IRB) of China Medical University (CMUH104-REC2-115). The IRB also specifically waived the consent requirement.

### 2.5. Statistical analysis

We analyzed the characteristics of the study population, including mean age, corresponding standard deviation (SD), and the number and proportion by sex and comorbidity. To assess the differences in the distribution, the mean age was assessed using the *t* test, whereas sex and comorbidity were examined using the chi-squared test. The incidence density of NF in the study groups was plotted against the occurrence of NF events represented using the length of follow-up duration in 10,000 person-years. Moreover, we presented the cumulative incidence curves for each study group by using the Kaplan–Meier method and examined the differences by using the log-rank test. To indicate the risk of NF between the AUD and comparison cohorts, the hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were estimated using univariate and multivariate Cox proportional hazard models. In addition, multiplicative interaction was assessed. We further analyzed the risk of NF in patients with AUD compared with individuals without AUD stratified by age, sex, comorbidity, and follow-up duration.

SAS 9.4 software (SAS Institute, Cary, NC) was used to perform all statistical analyses. R software (R Foundation for

**Table 1**

**Demographic risk factors and comorbidity history between the AUD and non-AUD groups.**

| | AUD | | | | |
|---|---|---|---|---|---|
| | No (N = 208,848) | | Yes (N = 52,212) | | |
| | n | % | n | % | *P* |
| Sex | | | | | .99 |
| Women | 20,560 | 9.84 | 5140 | 9.84 | |
| Men | 188,288 | 90.2 | 47,072 | 90.2 | |
| Age, y | | | | | .99 |
| <35 | 49,052 | 23.5 | 12,263 | 23.5 | |
| 35–65 | 145,292 | 69.6 | 36,323 | 69.6 | |
| ≥65 | 14,504 | 6.94 | 3626 | 6.94 | |
| Mean (SD)* | 44.3 (12.6) | | 44.3 (12.5) | | .51 |
| Comorbidity | | | | | |
| Hypertension | 22,659 | 10.8 | 14,864 | 28.5 | <.001 |
| Hyperlipidemia | 7605 | 3.64 | 9493 | 18.2 | <.001 |
| Diabetes | 13,639 | 6.53 | 12,528 | 24.0 | <.001 |
| IHD | 10,089 | 4.83 | 5407 | 10.4 | <.001 |
| Stroke | 9333 | 4.47 | 8358 | 16.0 | <.001 |
| COPD | 8358 | 4.00 | 5484 | 10.5 | <.001 |
| Live diseases | 8657 | 4.15 | 28,337 | 54.3 | <.001 |
| ESRD | 1418 | 0.68 | 414 | 0.79 | <.001 |
| Cancer | 9619 | 4.61 | 5621 | 10.8 | <.001 |
| PVD | 83 | 0.04 | 83 | 0.16 | <.001 |
| Mean of follow-up years (SD) | 7.21 (2.80) | | 5.81 (3.23) | | <.001 |

Chi-square test.

AUD = alcohol use disorder, COPD = chronic obstructive pulmonary disease, ESRD = end-stage kidney disease, IHD = ischemic heart disease, PVD = peripheral vascular disease, SD = standard deviation;

* Student *t* test.

Statistical computing, Vienna, Austria) was used for plotting the incidence curves. Statistical significance was set at <0.05 in 2-sided tests.

## 3. Results

Table 1 shows the demographic characteristics of the study population. This study enrolled 52,212 patients with AUD and 208,848 controls with a male predominance of 90%. No statistical difference in mean age between the AUD and comparison cohort was observed; the mean age was 44.3 years. The proportion of comorbidities was significantly higher in the AUD cohort than in the comparison cohort (all $P < .001$). The mean follow-up duration was 5.81 (SD: 3.23) and 7.21 (SD: 2.80) years in the AUD and comparison cohorts, respectively.

Table 2 shows the risk of NF between the AUD and comparison cohorts. In this study, 587 and 383 NF events were observed in the AUD and comparison cohorts, respectively. The incidence of NF was 19.4 per 10,000 person-years in the AUD cohort, which was nearly 7.73-fold higher than that of the comparison cohort (2.54 per 10,000 person-years). Moreover, Fig. 1 shows that the cumulative incidence curve of NF was significantly higher in patients with AUD than in comparisons (log-rank test, $P < .001$). After adjustment for age, sex, and comorbidities, patients with AUD exhibited a significant 3.55-fold higher risk of NF than did controls (HR = 3.55, 95% CI = 3.00–4.20). Female patients with AUD exhibited a 4.72-fold higher risk of NF than did female comparisons (HR = 4.72, 95% CI = 2.16–10.3); a 3.50-fold higher risk of NF was observed in male patients with AUD than in male comparisons (HR = 3.50, 95% CI = 2.94–4.16). Stratified by age, compared with controls, the HRs were 4.80 (95% CI = 2.93–7.85), 3.48 (95% CI = 2.86–4.24), and 2.23 (95% CI = 1.37–3.65) in patients with AUD in <35-, 35- to 65-, and ≥65-year age groups, respectively. In the study population with at least 1 comorbidity, patients with AUD exhibited only a 2.39-fold higher risk of NF than did the comparison cohort (HR = 2.39, 95% CI = 2.06–2.77); however, in the study population without any comorbidity, patients with AUD exhibited nearly 15.2-fold higher risk of NF than did the comparison cohort (HR = 15.2, 95% CI = 10.9–21.3).

Table 3 shows the risk of NF with respect to the severity of AUD. Relative to comparisons, the HRs of NF risk were 2.15 (95% CI = 1.76–2.62), 4.54 (95% CI = 3.67–5.62), and 10.7 (95% CI = 8.66–13.2) in patients with mild, moderate, and severe AUD, respectively. The risk of NF increased with the severity of AUD (*P* value for trend <.001).

Table 4 shows the risk of NF between patients with AUD and comparisons stratified by follow-up years. The results revealed that the NF risk was drastically higher in patients with AUD compared with comparisons at a follow-up time <1 year (HR = 13.9, 95% CI = 8.90–21.6). Compared with the comparisons, the HRs of NF risk were 3.89 (95% CI = 2.67–5.68), 2.18 (95% CI =

**Table 2**

**Risk of necrotizing fasciitis stratified by sex, age groups, and comorbidity (yes/no) between the AUD and non-AUD groups.**

| | AUD | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | No | | | Yes | | | Compared with non-AUD group | |
| Variables | Event | PY | Rate | Event | PY | Rate | Crude HR (95% CI) | Adjusted HR† (95% CI) |
| Overall | 383 | 1,506,389 | 2.54 | 587 | 303,413 | 19.4 | 7.73 (6.80–8.80)*** | 3.55 (3.00–4.20)*** |
| Sex | | | | | | | | |
| Women | 13 | 147,456 | 0.88 | 38 | 32,438 | 11.7 | 13.5 (7.21–25.4)*** | 4.72 (2.16–10.3)*** |
| Men | 370 | 1,358,933 | 2.72 | 549 | 270,975 | 20.3 | 7.56 (6.63–8.63)*** | 3.50 (2.94–4.16)*** |
| Age, y | | | | | | | | |
| <35 | 37 | 359,149 | 1.03 | 101 | 80,434 | 12.6 | 12.4 (8.52–18.1)*** | 4.80 (2.93–7.85)*** |
| 35–65 | 283 | 1,055,338 | 2.68 | 457 | 206,138 | 22.2 | 8.38 (7.22–9.73)*** | 3.48 (2.86–4.24)*** |
| ≥65 | 63 | 91,901 | 6.86 | 29 | 16,842 | 17.2 | 2.67 (1.72–4.15)*** | 2.23 (1.37–3.65)*** |
| Comorbidity | | | | | | | | |
| No | 75 | 1,199,453 | 0.63 | 65 | 79,523 | 8.17 | 13.1 (9.38–18.2)*** | 15.2 (10.9–21.3)*** |
| Yes | 308 | 306,936 | 10.0 | 522 | 223,890 | 23.3 | 2.38 (2.07–2.74)*** | 2.39 (2.06–2.77)*** |

AUD = alcohol use disorder, CI = confidence interval, HR = hazard ratio, PY = person-year; rate = incidence rate (per 10,000 person-years).

† Obtained by using the Cox proportional hazards model adjusted for age, sex, and comorbidities.

*** $P < .001$.

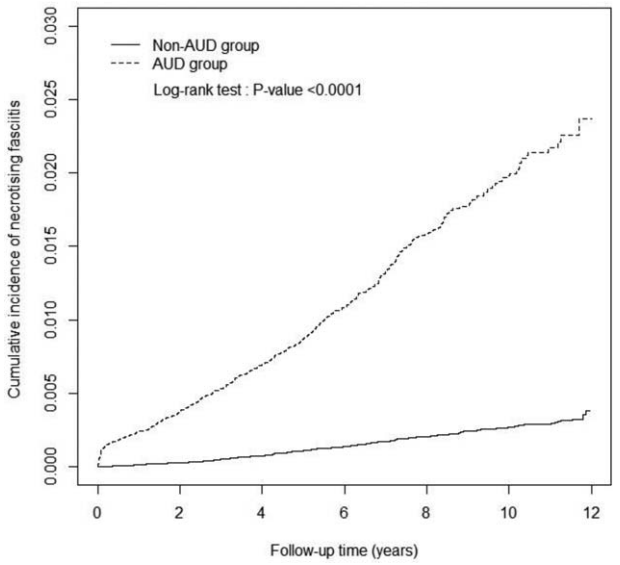


**Figure 1.** Cumulative incidence of necrotizing fasciitis between the alcohol use disorder (dashed line) and nonalcohol use disorder groups (solid line).

1.54–3.07), and 2.66 (95% CI = 2.04–3.47) in patients with AUD at a follow-up of 1 to 3, 3 to 5, and ≥ 5 years, respectively.

## 4. Discussion

NF is more prone to develop in immunocompromised patients with underlying medical conditions, and several studies have reported AUD as a risk factor.[6,8–13] However, some review articles have not reported AUD as a risk factor.[19–24] The concrete relationship between NF and AUD remains debatable. In our study, we found a strong positive association between AUD and NF. According to our review of relevant literature, the present study is the first to examine the risk of NF in patients with AUD by using a retrospective cohort design.

Previous studies have shown that NF is a rare life-threatening disease with a low incidence rate (0.04–0.4 per 10,000 person-years).[3–5] In our cohort study, we observed a substantially higher NF incidence rate of 2.54 and 19.4 per 10,000 person-years in the comparison and AUD cohorts, respectively. The AUD cohort exhibited a nearly 7.73-fold higher risk of NF than did the comparison cohort. After adjustment for age, sex, and comorbidities, the AUD cohort exhibited a 3.55-fold higher risk of NF than did the comparison cohort. These findings may indicate the rapid increase in the risk of NF in the recent decades, particularly in patients with AUD and underlying diseases. Because our cohort study design included hospitalized patients with AUD and had a longer follow-up period, the results are more accurate with relatively lesser underestimation of the incidence.

Alcohol consumption is known to contribute to increased deaths and illnesses and is causally related to more than 60 medical conditions.[25] Therefore, as expected, our study revealed that the AUD group had a significantly higher rate of comorbidities than did the comparison group (Table 1). In the study population with at least 1 comorbidity, patients with AUD exhibited a 2.39-fold higher risk of NF than did the comparison cohort (HR = 2.39, 95% CI = 2.06–2.77); however, in the study population with no comorbidity, patients with AUD exhibited nearly 15.2-fold higher risk of NF than did the comparison cohort (HR = 15.2, 95% CI = 10.9–21.3; Table 2). This finding of an evidently high risk is inconsistent with those of previous studies.[6,8–13,19–24] The most likely etiology is alcohol-related immunosuppression. Previous studies have proven that alcohol consumption, particularly chronic heavy drinking, affects all components of the immune system.[26–31] Chronic alcohol abuse reduces the number of peripheral T cells, disrupts the balance between various T-cell types, affects T-cell activation, impairs T-cell functioning, and increases T-cell apoptosis.[26,27,29,30] Furthermore, it reduces the number of B cells, reduces antigen-specific antibody responses, and alters B-cell development and maturation.[27,28,30,31] Consequently, alcoholics exhibit an increased susceptibility to diseases caused by viral[32–35] and bacterial infections,[36–40] thereby augmenting coincident disease progression leading to higher morbidity and mortality.

In addition, the impact of alcohol exposure on dermal wound healing has been studied before. The upregulated vimentin in injured muscles enhances the development of group A streptococci infection.[41–44] Other factors observed were poor compliance and increased injury risk in AUD groups. Systemic reviews have illustrated that acute alcohol intoxication was a significant risk factor for traumatic injury, and 41.0% of trauma recidivism was related to alcohol use.[45,46] This finding may cause skin injuries and further infection. In general, alcohol abusers are considered to have a low level of compliance with respect to seeking medical treatment,[47] which may lead to delay in treatment and disease progression. These factors may lead to an increase in NF occurrence.

Alcohol has a dose–response relationship with many disease outcomes, particularly in patients with heavy alcohol consumption.[48] We therefore examined the risk of NF stratified by the severity of AUD. We hypothesized that patients with heavier alcohol consumption have more severe AUD and have a longer duration of hospitalization. The risk of NF increased with the severity of AUD (*P* value for trend <.001; Table 3), which is consistent with findings of previous studies. Furthermore, we examined the incidence of NF between the AUD and non-AUD groups at various follow-up years. The AUD group exhibited a significantly higher risk of NF than did the non-AUD group at the <1 year follow-up (adjusted HR [aHR] = 13.9, 95% CI = 8.90–21.6). These findings indicated that AUD significantly increased the risk of NF.

Although the current medical advancement has reduced the mortality and morbidity of many diseases, treatment of NF remains a challenge. Once the NF is diagnosed, the current

**Table 3**

**Risk of necrotizing fasciitis stratified by severity of AUD compared with the non-AUD group.**

| Severity of AUD | N | Event | Rate | Adjusted HR† (95% CI) |
|---|---|---|---|---|
| Non-AUD group | 208,848 | 383 | 2.54 | 1.00 |
| AUD group | | | | |
| Mild ($T_1$) | 26,385 | 203 | 10.74 | 2.15 (1.76–2.62)*** |
| Moderate ($T_2$) | 14,233 | 181 | 24.11 | 4.54 (3.67–5.62)*** |
| Severe ($T_3$) | 11,594 | 203 | 51.7 | 10.7 (8.66–13.2)*** |
| *P* for trend | | | | <.001 |

AUD = alcohol use disorder; CI = confidence interval, HR = hazard ratio, rate = incidence rate (per 10,000 person-years), $T_1$ = first tertile, $T_2$ = second tertile, $T_3$ = third tertile, severity of alcoholism = (total length of hospital stay because of AUD during the follow-up duration)/(length of follow-up duration).

† Adjusted for age, sex, and comorbidities.

*** $P < .001$.

**Table 4**

**Incidence of necrotizing fasciitis between the AUD and non-AUD groups, stratified by follow-up year.**

| | AUD | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | No | | | Yes | | | Compared with non-AUD group | |
| Variables | Event | PY | Rate | Event | PY | Rate | Crude HR (95% CI) | Adjusted HR† (95% CI) |
| Follow time, y | | | | | | | | |
| <1 | 33 | 207,088 | 1.59 | 122 | 49,222 | 24.8 | 15.4 (10.5–22.6)*** | 13.9 (8.90–21.6)*** |
| 1–3 | 71 | 404,931 | 1.75 | 128 | 89,046 | 14.4 | 8.24 (6.17–11.0)*** | 3.89 (2.67–5.68)*** |
| 3–5 | 105 | 358,021 | 2.93 | 124 | 72,057 | 17.2 | 5.87 (4.53–7.61)*** | 2.18 (1.54–3.07)*** |
| ≥5 | 174 | 536,348 | 3.24 | 213 | 93,088 | 22.9 | 7.06 (5.78–8.62)*** | 2.66 (2.04–3.47)*** |

AUD = alcohol use disorder, CI = confidence interval, HR = hazard ratio, PY = person-year; rate = incidence rate (per 10,000 person-years).

† Obtained by using the Cox proportional hazards model adjusted for age, sex, and comorbidities.

*** $P < .001$.

recommendation is to refer patient to teaching hospital. Patient who is treated in teaching hospital has lower mortality rate than in community hospital.[46] Our study findings indicate that AUD significantly increases the risk of NF. In addition, alcohol consumption is known to contribute many major chronic diseases. Therefore, as a measure of preventive medicine, alcohol-related health policies should be developed to reduce the alcohol-attributable diseases and social burden.

### 4.1. Study limitations

Several limitations of our study should be considered. First, the retrospective design and the use of an administrative dataset with its associated limitations may have influenced the interpretation of our results. The NHIRD does not include detailed information on NF-related lifestyle factors, such as smoking history, accidental trauma history, obesity, medication use, and socioeconomic status. Therefore, we considered COPD as a comorbidity to substitute for smoking history. In addition, we adjusted for various potential NF-associated comorbidities, and AUD was consistently associated with NF development. Second, the accurate diagnosis of AUD remains a challenge. We identified hospitalizations with AUD based on specific ICD-9-CM codes to increase the accuracy. This may have led to bias because patients with AUD may have been hospitalized because of other simultaneously existing severe diseases. Thus, we cannot exclude possible misclassification. However, the NHI program currently covers more than 99% of the Taiwan population. Physicians or hospitals are liable to be heavily penalized if a peer review identifies chart findings inconsistent with coding. Miscoding is unlikely to have occurred systematically or incrementally over time. Therefore, the AUD diagnoses based on ICD-9 codes in this study were highly reliable. Finally, laboratory data on alcohol level, severity of AUD based on the criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders, and the amount of alcohol consumed or drinking pattern were not available, which may have influenced the results of our study to some extent.

## 5. Conclusion

According to our review of relevant literature, this population-based retrospective cohort study is the first to examine the relationship between NF and AUD. We conclude that AUD without comorbidity significantly increased the risk of NF (aHR = 15.2, 95% CI = 10.9–21.3). AUD should be considered an independent and significant risk factor for NF. The risk increased with the length of hospital stay because of AUD and within the first year of follow-up. Additional prospective clinical studies are needed to validate the casual association between NF and AUD.

## References


[1] Adant JP, Bluth F, Fissette J. Necrotizing fasciitis: a life-threatening infection. Acta Chir Belg 1998;98:102–6.

[2] Descamps V, Aitken J, Lee MG. Hippocrates on necrotising fasciitis. Lancet (Lond, Engl) 1994;344:556.

[3] Ellis Simonsen SM, van Orman ER, Hatch BE, et al. Cellulitis incidence in a defined population. Epidemiol Infect 2006;134:293–9.

[4] Tang WM, Ho PL, Fung KK, et al. Necrotising fasciitis of a limb. J Bone Joint Surg Br Vol 2001;83:709–14.

[5] Trent JT, Kirsner RS. Diagnosing necrotizing fasciitis. Adv Skin Wound Care 2002;15:135–8.

[6] Salcido RS. Necrotizing fasciitis: reviewing the causes and treatment strategies. Adv Skin Wound Care 2007;20:288–93.

[7] May AK. Skin and soft tissue infections. Surg Clin N Am 2009;89: 403–20.

[8] Goh T, Goh LG, Ang CH, et al. Early diagnosis of necrotizing fasciitis. Br J Surg 2014;101:e119–25.

[9] Headley AJ. Necrotizing soft tissue infections: a primary care review. Am Fam Physician 2003;68:323–8.

[10] Angoules AG, Kontakis G, Drakoulakis E, et al. Necrotising fasciitis of upper and lower limb: a systematic review. Injury 2007;38(suppl 5): S19–26.

[11] Das DK, Baker MG, Venugopal K. Risk factors, microbiological findings and outcomes of necrotizing fasciitis in New Zealand: a retrospective chart review. BMC Infect Dis 2012;12:348–58.

[12] El-Khani U, Nehme J, Darwish A, et al. Multifocal necrotising fasciitis: an overlooked entity? J Plast Reconstr Aesthet Surg 2012;65:501–12.

[13] Morgan MS. Diagnosis and management of necrotising fasciitis: a multiparametric approach. J Hosp Infect 2010;75:249–57.

[14] Slade T, Chiu WT, Glantz M, et al. A cross-national examination of differences in classification of lifetime alcohol use disorder between DSM-IV and DSM-5: findings from the world mental health survey. Alcohol Clin Exp Res 2016;40:1728–36.

[15] World Health OrganizationGlobal Status Report on Alcohol and Health. 2014;World Health Organization, 18. http://apps.who.int/iris/bitstream/10665/112736/1/9789240692763_eng.pdf?ua=1.

[16] Shield KD, Monteiro M, Roerecke M, et al. Alcohol consumption and burden of disease in the Americas in 2012: implications for alcohol policy. Rev Panam Salud Publica 2015;38:442–9.

[17] Corrao G, Bagnardi V, Zambon A, et al. A meta-analysis of alcohol consumption and the risk of 15 diseases. Prev Med 2004;38:613–9.

[18] Rehm J, Baliunas D, Borges GL, et al. The relation between different dimensions of alcohol consumption and burden of disease: an overview. Addiction (Abingdon, Engl) 2010;105:817–43.

[19] Chauhan A, Wigton MD, Palmer BA. Necrotizing fasciitis. J Hand Surg 2014;39:1598–601.

[20] Lancerotto LL. Necrotizing fasciitis: classification, diagnosis, and management. J Trauma Acute Care Surg 2012;72:560–6.

[21] Shimizu T, Tokuda Y. Necrotizing fasciitis. Intern Med (Tokyo, Japan) 2010;49:1051–7.

[22] Taviloglu K, Cabioglu N, Cagatay A, et al. Idiopathic necrotizing fasciitis: risk factors and strategies for management. Am Surg 2005;71: 315–20.

[23] Wang J-M, Lim H-K. Necrotizing fasciitis: eight-year experience and literature review. Braz J Infect Dis 2014;18:137–43.
[24] Zundel S, Lemaréchal A, Kaiser P, et al. Diagnosis and treatment of pediatric necrotizing fasciitis: a systematic review of the literature. Eur J Pediatr Surg 2017;27:127–37.
[25] Room R, Babor T, Rehm J. Alcohol and public health. Lancet 2005;365:519–30.
[26] Szabo G, Saha B. Alcohol's effect on host defense. Alcohol Res 2015;37:159–70.
[27] Pasala S, Barr T, Messaoudi I. Impact of alcohol abuse on the adaptive immune system. Alcohol Res 2015;37:185–97.
[28] Szabo G. Alcohol's contribution to compromised immunity. Alcohol Health Res World 1997;21:30–41.
[29] Cook RT. Alcohol abuse, alcoholism, and damage to the immune system —a review. Alcohol Clin Exp Res 1998;22:1927–42.
[30] Szabo G. Consequences of alcohol consumption on host defence. Alcohol Alcohol 1999;34:830–41.
[31] Molina PE, Happel KI, Zhang P, et al. Focus on: alcohol and the immune system. Alcohol Res Health 2010;33:97–108.
[32] Meyerholz DK, Edsen-Moore M, McGill J, et al. Chronic alcohol consumption increases the severity of murine influenza virus infections. J Immunol (Baltimore, MD: 1950) 2008;181:641–8.
[33] Lin CW, Lin CC, Mo LR, et al. Heavy alcohol consumption increases the incidence of hepatocellular carcinoma in hepatitis B virus-related cirrhosis. J Hepatol 2013;58:730–5.
[34] Molina PE, Bagby GJ, Nelson S. Biomedical consequences of alcohol use disorders in the HIV-infected host. Curr HIV Res 2014;12:265–75.
[35] Greenbaum A, Chaves SS, Perez A, et al. Heavy alcohol use as a risk factor for severe outcomes among adults hospitalized with laboratory-confirmed influenza, 2005–2012. Infection 2014;42:165–70.
[36] Rehm J, Samokhvalov AV, Neuman MG, et al. The association between alcohol use, alcohol use disorders and tuberculosis (TB). A systematic review. BMC Public Health 2009;9:450.
[37] Bhatty M, Pruett SB, Swiatlo E, et al. Alcohol abuse and *Streptococcus pneumoniae* infections: consideration of virulence factors and impaired immune responses. Alcohol (Fayetteville, NY) 2011;45: 523–39.
[38] Tamura DY, Moore EE, Partrick DA, et al. Clinically relevant concentrations of ethanol attenuate primed neutrophil bactericidal activity. J Trauma 1998;44:320–4.
[39] Boe DM, Nelson S, Zhang P, et al. Acute ethanol intoxication suppresses lung chemokine production following infection with *Streptococcus pneumoniae*. J Infect Dis 2001;184:1134–42.
[40] Parlet CP, Kavanaugh JS, Horswill AR, et al. Chronic ethanol feeding increases the severity of *Staphylococcus aureus* skin infections by altering local host defenses. J Leukoc Biol 2015;97:769–78.
[41] Lieber CS. Relationships between nutrition, alcohol use, and liver disease. Alcohol Res Health 2003;27:220–31.
[42] Ryle PR, Thomson AD. Nutrition and vitamins in alcoholism. Contemp Issues Clin Biochem 1984;1:188–224.
[43] Dhaliwal R, Heyland DK. Nutrition and infection in the intensive care unit: what does the evidence show? Curr Opin Critic Care 2005;11: 461–7.
[44] Parlet CP, Waldschmidt TJ, Schlueter AJ. Chronic ethanol feeding induces subset loss and hyporesponsiveness in skin T cells. Alcohol Clin Exp Res 2014;38:1356–64.
[45] Molina PE, Sulzer JK, Whitaker AM. Alcohol abuse and the injured host: dysregulation of counterregulatory mechanisms review. Shock (Augusta, Ga) 2013;39:240–9.
[46] Nunn J, Erdogan M, Green RS. The prevalence of alcohol-related trauma recidivism: a systematic review. Injury 2016;47:551–8.
[47] Sullivan JT, Naranjo CA, Sellers EM. Compliance among heavy alcohol users in clinical drug trials. J Subst Abuse 1988;1:183–94.
[48] Rehm J, Room R, Graham K, et al. The relationship of average volume of alcohol consumption and patterns of drinking to burden of disease: an overview. Addiction (Abingdon, Engl) 2003;98:1209–28.