

Risk factors and severity of acute liver injury in non-chronic liver disease and chronic liver disease patients

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Objectives To study factors related to acute liver injury and compare the severity and risk of those factors in patients with and without chronic liver disease.

Methods This cross-sectional study of 323 patients admitted to Somdejphrajaotaksin Maharaj Hospital between 1 January and 30 September 2019, analyzing data collected on the clinical background, signs and symptoms, and laboratory results of those patients.

Results Of the 323 patients in the study, 188 did not have chronic liver disease (58.2%) and 135 had chronic liver disease (41.8%). Risk factors for acute liver injury in the chronic liver disease group included bacterial infection (33.3%) and spontaneous bacterial peritonitis (4.4%), much significantly higher than the rates in the no chronic disease group. However, the risk factors excessive consumption of alcohol (30.3%) and dengue infection (11.2%) in the no chronic liver disease group were significantly higher than in the chronic disease group. Both groups had a high incidence of disease severity as well as a high incidence of complications and mortality, although the mortality rate was higher in the chronic liver disease group (15.0% vs. 6.9%).

Conclusions The types and frequencies of risk factors for acute liver injury in patients with chronic liver disease and those with no chronic liver disease groups are different. The incidence of bacterial infection and spontaneous bacterial peritonitis is higher in patients with chronic liver disease. The incidence of excessive alcohol consumption and dengue infection is much higher in patients without chronic liver disease. Both groups have high levels of disease severity, complications and mortality. Sepsis is the major cause of mortality, especially in patients with chronic liver disease. **Chiang Mai Medical Journal 2021;60(2):157-64. doi 10.12982/CMUMEDJ.2021.14**

Keywords: acute liver injury, chronic liver disease

Introduction

The term acute liver injury is used to describe a wide variety of conditions characterized by acute inflammation of the hepatic parenchyma and injury to hepatocytes resulting in elevated liver function lasting less than six months. Chronic liver disease refers to a liver disease condition associated with chronic inflammation or cirrhosis lasting more than six months where physical examination shows signs and symptoms of chronic

liver disease.

Acute liver injury is the one of the important problems in hepatic disease. Many factors can cause acute liver injury. If an acute liver injury is diagnosed and receives early treatment, acute liver failure, a leading cause of death, may be avoided (1). Many studies in Germany, South Korea and the United States have found that acute liver injury also affects severity of the illness and

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mortality rates (2-4). Causes of acute liver injury include drugs, viral infections, bacterial infections or sepsis, excessive alcohol consumption, gastrointestinal bleeding, fatty liver disease, autoimmune hepatitis and metabolic liver diseases (5-7).

Acute liver injury patients can be divided into two groups: patients with chronic liver disease and patients without chronic liver disease. Severe liver injury can cause acute liver failure. Patients with acute liver failure will be also more likely to have hepatic encephalopathy, jaundice and coagulopathy (6,7). Acute liver failure is a medical emergency condition with a high mortality rate. According to data from 858 hospitals in Thailand, the incidence of acute liver failure in patients was 62.9 cases per million population per year with a mortality rate within 30 days of 26.7% (1).

Somdejphrajaotaksin Maharaj Hospital in 2018 had 88 cases of acute liver injury and 4 cases of acute liver failure. Tests showed the chronic liver disease patients had more abnormality of a higher incidence of abnormal liver function and a higher mortality rate than patients without chronic liver disease.

The term acute liver injury is used to describe a wide variety of conditions and is characterized by acute inflammation of the hepatic parenchyma

or injury to hepatocytes resulting in elevated liver function lasting for less than six months. Chronic liver disease refers to a liver disease condition associated with chronic inflammation or cirrhosis lasting more than six months, in which physical examination can identify signs and symptoms of chronic liver disease.

Objectives

The objective of this research was to study differences in risk factors and severity of acute liver injury in patients with chronic liver disease and those without chronic liver disease. The results could assist in the development of guidelines for diagnosis and determination of the level of severity of acute liver injuries.

Methods

This cross-sectional study was conducted from January through September 2019 during which time data were collected from patients 15 years old or over at the Internal Medicine Department, Somdejphrajaotaksin Maharaj Hospital, Tak Province, Thailand. The inclusion criteria was patients with acute liver injury for less than 26 weeks. Exclusion criteria were advanced carcinoma, preg-

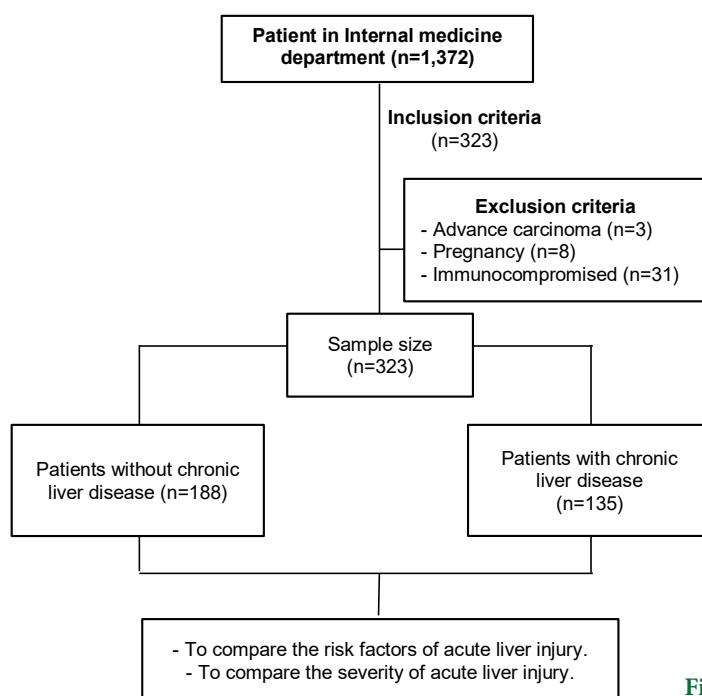


Figure 1. Conceptual framework

nancy, immunocompromised patients, patients with an uncontrolled disease and patients with multiple causes of acute liver disease. This study has been certified by the Human Ethics Committee at Somdejphrajaotaksin Maharaj Hospital, certification number 7/2019.

Information on patients included general characteristics, e.g., gender, age and underlying diseases, liver function test and other test results, records of treatment received, risk factors for acute liver injury and days of hospital stay until death. Chronic liver disease is defined as hepatitis for more than six months or cirrhosis. The sample size was calculated based on a review of previous studies. The current study had a larger sample size than other studies reviewed.

Data analysis included descriptive statistics (frequency, percentage, mean). Inferential statistical analysis with the chi-square test and Fisher's exact test were used to compare data and to identify relationships between risk factors and severity

of acute liver injury in patients without chronic liver disease and those with chronic liver disease. The confidence level was set at 95 percent and $p < 0.05$ were considered statistically significant.

Results

Of the 323 patients, most of whom were male, 188 patients did not have chronic liver disease (58.2%) and 135 patients had chronic liver disease (41.8%). Patients with chronic liver disease were significantly older and were also significantly more likely to have a history of blood transfusion than patients without chronic liver disease. Causes of chronic liver disease included chronic viral hepatitis B infection (3.6%), chronic viral hepatitis C infection (2.4%), alcoholic hepatitis (29.8%), nonalcoholic steatohepatitis (NASH) (29.8%), primary sclerosing cholangitis (2.4%) and non-alcoholic fatty liver disease (NAFLD) (32.0%). The majority of the chronic liver disease patients were Child-Pugh C (47.0%) (Table 1).

Table 1. Demographic data of patients without chronic liver disease and patients with chronic liver disease

Demographic data	Without chronic liver disease (n=188) n (%)	With Chronic liver disease (n=135) n (%)	p-value
Gender			0.419*
- Male	133 (70.7)	101 (74.8)	
Age (years)			< 0.05**
- < 18	4 (2.1)	0 (0.0)	
- 18-50	103 (54.8)	47 (34.8)	
- > 50	81 (43.1)	88 (65.2)	
Alcohol consumption	101 (53.7)	77 (57.0)	0.572*
History of blood transfusion	0 (0.0)	44 (32.6)	< 0.05*
History of chronic liver disease			
- Child-Pugh A	0 (0.0)	6 (11.8)	
- Child-Pugh B	0 (0.0)	21 (41.2)	
- Child-Pugh C	0 (0.0)	24 (47.0)	
Cause of chronic liver disease			
- HBV	0 (0.0)	3 (3.6)	
- HCV	0 (0.0)	2 (2.4)	
- Alcoholic hepatitis	0 (0.0)	25 (29.8)	
- NASH	0 (0.0)	25 (29.8)	
- Primary sclerosing cholangitis	0 (0.0)	2 (2.4)	
- NAFLD	0 (0.0)	27 (32.0)	

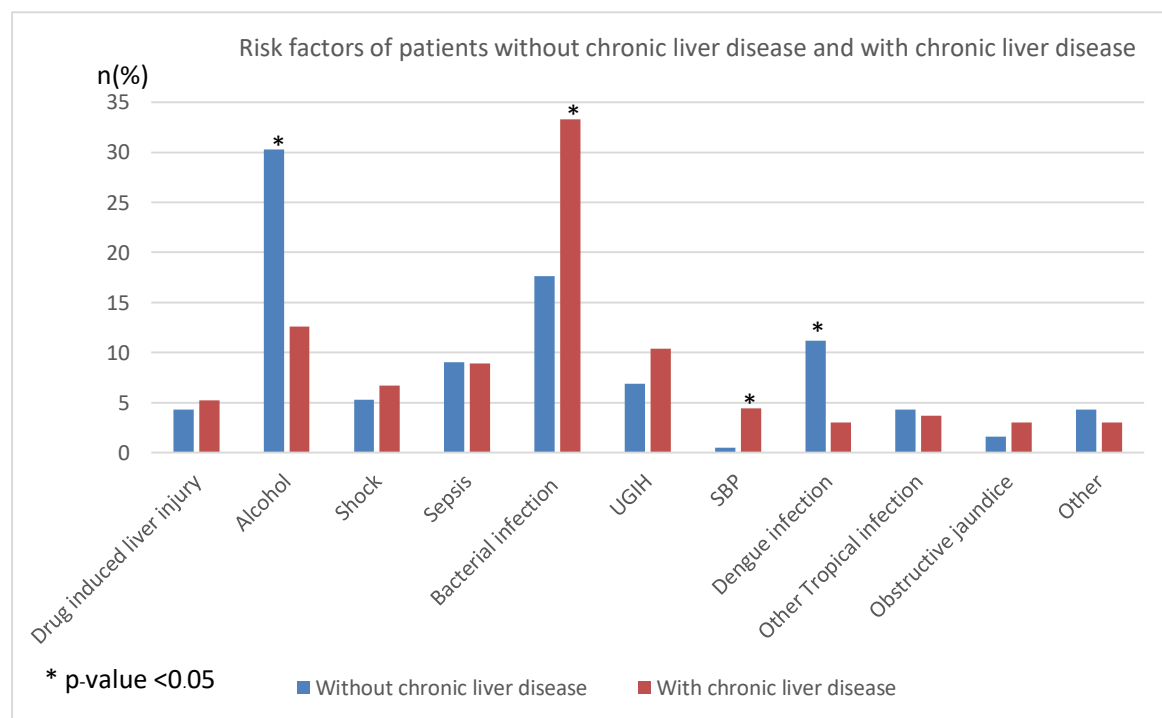
HBV, hepatitis B virus; HCV, hepatitis C virus; NASH, nonalcoholic steatohepatitis; NAFLD, nonalcoholic fatty liver disease

*Fisher exact test, **Chi-square test

Factors associated with acute liver injury in the study included drug-induced liver injury, excessive alcohol consumption, shock, sepsis, bacterial infection, upper gastrointestinal hemorrhage (UGIH), spontaneous bacterial peritonitis (SBP), dengue infection, tropical infections, and biliary tract obstruction (obstructive jaundice). Specific factors related to acute liver injury varied between the two groups, but the risk factors excessive alcohol consumption and dengue infection were higher risk factors for acute liver injury in patients without chronic liver disease than in those with chronic liver disease (30.3% vs 12.6% and 11.2% vs 3.0%, respectively). Spontaneous bacterial peritonitis (SBP) was found in only 0.5% of the group without chronic liver disease, but 4.4% of the group with chronic liver disease. The incidence of bacterial infection in the group without chronic liver disease was 17.6% compared to 33.3% in the group with chronic liver disease. Each of these differences was statistically significant (Graph 1).

Laboratory test results for increased levels of serum AST, ALT, total protein, PT, PTT and INR in patients without chronic liver disease and with chronic liver disease were not statistically significantly different. Differences which were statistically significant included total bilirubin, direct bilirubin, serum albumin and AST:ALT ratio. Patients with chronic liver disease had higher total bilirubin and direct bilirubin than patients without chronic liver disease, while total protein and serum albumin were lower in those patients. (Table 2)

Table 3 shows the severity of risk factors affecting each of the groups, including the high mortality rate in patients with sepsis. Chronic liver disease patients with sepsis had a higher rate of target organ failure (n=24), length day of time from stay until death longer hospital stay from admission to death (range=1-28 days) and higher number of deaths (n=13) than patients without chronic liver disease.



Graph 1. Risk factors of patients without chronic liver disease and those with chronic liver disease
UGIH, upper gastrointestinal hemorrhage; SBP, spontaneous bacterial peritonitis

*Fisher's exact test

Table 2. Laboratory data of patients without chronic liver disease and with chronic liver disease

Lab investigation	Without chronic liver disease (n=188) n (%)	With chronic liver disease (n=135) n (%)	p-value
AST			0.720**
< 3 ULN	82 (43.6)	55 (40.7)	
3-20 ULN	91 (48.4)	66 (48.9)	
> 20 ULN	15 (8.0)	14 (10.4)	
ALT			0.396**
< 3 ULN	110 (58.5)	89 (65.9)	
3-20 ULN	67 (35.6)	39 (28.9)	
> 20 ULN	11 (5.9)	7 (5.2)	
Total bilirubin			<0.05**
< 6	168 (98.2)	100 (82.0)	
6-12	2 (1.2)	13 (10.7)	
> 12	1 (0.6)	9 (7.4)	
Direct bilirubin (mg/dL)			<0.05*
< 0.4	78 (42.9)	24 (18.5)	
> 0.4	104 (57.1)	106 (81.5)	
Total protein (mg/dL)			0.166**
< 6.6	78 (41.5)	70 (51.9)	
6.6-8.3	91 (48.4)	52 (38.5)	
> 8.3	19 (10.1)	13 (9.6)	
Serum albumin (mg/dL)			<0.05**
< 2.8	11 (5.9)	79 (58.5)	
2.8-3.5	42 (22.3)	37 (27.4)	
> 3.5	135 (71.8)	19 (14.1)	
AST:ALT ratio			<0.05*
< 2	140 (74.5)	77 (57.0)	
> 2	48 (25.5)	58 (43.0)	
PT (sec.)			0.481*
< 22.5	64 (88.9)	67 (83.8)	
> 22.5	8 (11.1)	13 (16.2)	
PTT (sec.)			1.00*
> 57	69 (95.8)	76 (96.2)	
INR			0.239**
< 1.7	64 (88.9)	65 (81.2)	
1.7-2.3	4 (5.6)	4 (5.0)	
> 2.3	4 (5.6)	11 (7.9)	

AST, aspartate aminotransferase; ALT, alanine aminotransferase; PT, prothrombin Time; ULN, upper limit of normal; PTT, partial thromboplastin time; INR, International Normalized Ratio.

*Fisher exact test, **Chi-square test

Discussion

Risk factors for liver injury in patients without chronic liver disease and those with chronic liver disease at the Somdejphrajaotaksin Maharaj Hospital during the 9 month study period are

consistent with the research of Moreau et al. (8) and Maipang et al. (9) who discovered that the most influential risk factors for acute liver injury are bacterial infections, excessive consumption of alcohol, upper gastrointestinal hemorrhage and

Table 3. Comparison of organ failure and mortality in the without chronic liver disease group and the chronic liver disease group

Risk factors	Without chronic liver disease (n=188)				With chronic liver disease (n=135)			
	n	Target organ failure	Days of hospital stay until death	Deaths	n	Target organ failure	Days of hospital stay until death (days)	Deaths
- Drug induced liver injury	8	1	1	1	7	-	-	-
- Excessive Alcohol consumption	57	1	4	1	17	-	-	-
- Shock	10	3	1-4	3	9	7	2-10	3
- Sepsis	50	4	2-4	4	57	24	1-28	13
- UGIH	13	2	5	1	14	1-2	2-17	3
- SBP	1	-	-	-	6	3	2-4	2
- Dengue infection	21	1	-	-	4	-	-	-
- Tropical infection	8	-	-	-	5	2	-	-
-Obstructive jaundice	3	-	-	-	4	1	-	-
- Others	8	2	-	-	4	-	-	-

UGIH, Upper gastrointestinal hemorrhage; SBP, Spontaneous bacterial peritonitis

spontaneous bacterial peritonitis, risk factors that are commonly observed in Thailand.

Comparison of risk factors for both patients without chronic liver disease and those with chronic liver disease found that bacterial infection (33.3%) and spontaneous bacterial peritonitis (4.4%) were more common in chronic liver disease patients. This finding is consistent with reports that chronic liver disease patients are at high risk for infection due to an immunocompromised host (10). Excessive alcohol consumption (30.3%) and dengue infection (11.2%) were much more prevalent in the without chronic liver disease group. Both groups had high levels of severity as well as a high incidence of complications and high mortality rates; however, mortality was significantly higher in the chronic liver disease group.

This research did find an important risk factor that was higher than had been reported in previous studies: dengue infection. A potential reason for that difference is that Tak Province is located on the boarder of Thailand and Myanmar, an area where dengue is an important tropical infection. The findings of this study suggest that appropriate clinical practices, especially careful and close

monitoring, could reduce the incidence of complications in patients with chronic liver disease.

This study found that the highest mortality rate in both groups was due to sepsis, but that mortality was significantly higher for patients with chronic liver disease. Patients with chronic liver disease have an immunocompromised host, which makes them more susceptible to infection and can more easily lead to severe sepsis (10). This is a significant underlying factor in the high mortality rate found in patients with chronic liver disease. The findings from this study can be used in rural, general and tertiary hospitals to help reduce the incidence of complications of acute liver injury by careful and close monitoring, especially in patients with chronic liver disease.

Limitations of this study include the relatively short observation period and that the study was carried out in only one hospital, factors which compromise the generalizability of the findings. Extrapolation of the results of this study to other settings should be done with caution. Further research involving more patients and diverse settings is recommended.

Conclusions

The risk factors for acute liver injury in patients with chronic liver disease and patients without chronic liver disease are different. Bacterial infection and spontaneous bacterial peritonitis occur at a higher rate in chronic liver disease patients, but excessive alcohol consumption and dengue infection are much more frequent in patients without chronic liver disease. Both groups have high levels of severity as well as high rates of complications and mortality. Sepsis is the major cause of mortality in both groups, but particularly in chronic liver disease patients.

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None

Conflict of interest

The authors declare no conflicts of interest.

References

1. Thanapirom K, Treeprasertsuk S, Soonthornworasiri N, Poovorawan K, Chaiteerakij R, Komolmit P, et al. The incidence, etiologies, outcomes, and predictors of mortality of acute liver failure in Thailand: a population-base study. *BMC Gastroenterology*. 2019;19:18.
2. Arndt V, Brenner H, Rothenbacher D, Zschenderlein B, Fraisse E, Fliedner TM. Elevated liver enzyme activity in construction workers: prevalence and impact on early retirement and all-cause mortality. *Int Arch Occup Environ Health*. 1998;71:405-12.
3. Kim HC, Nam CM, Jee SH, Han KH, Oh DK, Suh I. Normal serum aminotransferase concentration and risk of mortality from liver diseases: prospective cohort study. *BMJ*. 2004;328:983.
4. Ruhl CE, Everhart JE. Elevated serum alanine aminotransferase and γ -glutamyltransferase and mortality in the United States population. *Gastroenterology*. 2009;136:477-85.
5. Kwo PY, Cohen SM, Lim JK. ACG clinical guideline: evaluation of abnormal liver chemistries. *American Journal of Gastroenterology*. 2017;112:18-35.
6. Bunchorntavakul C. Acute liver failure. *Thai Journal of Hepatology*. 2018;1:1-13.
7. Koch DG, Speiser JL, Durkalski V, Fontana RJ, Davern T, McGuire B, et al. The natural history of severe acute liver injury. *The American journal of gastroenterology*. 2017;112:1389-96.
8. Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology*. 2013;144:1426-37.
9. Maipang K, Potranun P, Chainuvati S, Nimanong S, Chotiyaputta W, Tanwandee T, et al. Validation of the prognostic models in acute-on-chronic liver failure precipitated by hepatic and extrahepatic insults. *PLOS ONE*. 2019;14:1-16.
10. Noor MT, Manoria P. Immune Dysfunction in Cirrhosis. *J Clin Transl Hepatol*. 2017;5:50-8.
11. Chumpu R, Khamsemanan N, Nattee C. The association between dengue incidences and provincial-level weather variables in Thailand from 2001 to 2014. *PLoS One*. 2019;14:e0226945.

ปัจจัยเสี่ยงและความรุนแรงของภาวะตับอักเสบเฉียบพลันระหว่างผู้ป่วยที่ไม่เป็นโรคตับเรื้อรัง และผู้ป่วยที่เป็นโรคตับเรื้อรัง

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วัตถุประสงค์ เพื่อศึกษาปัจจัยที่ทำให้เกิดภาวะตับอักเสบเฉียบพลัน และเปรียบเทียบความรุนแรงและปัจจัยเสี่ยงของภาวะตับอักเสบเฉียบพลันในกลุ่มผู้ป่วยที่ไม่มีโรคตับเรื้อรังและมีโรคตับเรื้อรัง

วิธีการ การศึกษารูปแบบ cross-sectional โรงพยาบาลสมเด็จพระเจ้าตากสินมหาราช ระหว่างวันที่ 1 มกราคม ถึงวันที่ 30 กันยายน พ.ศ. 2562 โดยเก็บข้อมูลอาการ อาการแสดงและผลการตรวจทางห้องปฏิบัติการ

ผลการศึกษา กลุ่มตัวอย่าง 323 คน เป็นกลุ่มผู้ป่วยที่ไม่เป็นโรคตับเรื้อรัง 188 ราย (ร้อยละ 58.2) และกลุ่มผู้ป่วยที่เป็นโรคตับเรื้อรัง 135 คน (ร้อยละ 41.8) เมื่อเปรียบเทียบระหว่างกลุ่มผู้ป่วยทั้ง 2 กลุ่ม พบว่า กลุ่มผู้ป่วยที่เป็นโรคตับเรื้อรังพบปัจจัยเสี่ยงที่ทำให้เกิดตับอักเสบเฉียบพลันได้แก่ภาวะติดเชื้อแบคทีเรีย (ร้อยละ 33.3) และภาวะเยื่อช่องท้องอักเสบจากการติดเชื้อแบคทีเรีย (ร้อยละ 4.4) ซึ่งมากกว่าอีกกลุ่ม อย่างไรก็ตามปัจจัยเสี่ยง การดื่มแอลกอฮอล์ (ร้อยละ 30.3) และติดเชื้อไวรัสตับอักเสบ (ร้อยละ 11.2) พบมากในผู้ป่วยที่ไม่เป็นโรคตับเรื้อรัง ในกลุ่มผู้ป่วยทั้งสองกลุ่มที่มีภาวะตับอักเสบเฉียบพลันมีความรุนแรงที่ทำให้เกิดภาวะแทรกซ้อน และอัตราการตายที่สูง โดยเฉพาะกลุ่มผู้ป่วยโรคตับเรื้อรังมีอัตราการตายที่สูงมากกว่า (ร้อยละ 15.0 เทียบกับ ร้อยละ 6.9)

สรุป ปัจจัยเสี่ยงของภาวะตับอักเสบเฉียบพลันในผู้ป่วยตับอักเสบเรื้อรังและผู้ป่วยที่ไม่เป็นตับอักเสบเรื้อรังมีความแตกต่างกัน อย่างไรก็ตาม การติดเชื้อแบคทีเรีย และภาวะเยื่อช่องท้องอักเสบจากการติดเชื้อแบคทีเรียเป็นสาเหตุที่พบได้มากในผู้ป่วยตับอักเสบเรื้อรัง แต่การดื่มแอลกอฮอล์และติดเชื้อไวรัสตับอักเสบเป็นสาเหตุที่พบมากในผู้ป่วยที่ไม่เป็นโรคตับเรื้อรัง ซึ่งผู้ป่วยทั้งสองกลุ่มที่มีความรุนแรงทำให้เกิดภาวะแทรกซ้อน และอัตราการตายที่สูง โดยเฉพาะภาวะติดเชื้อในกระแสเลือดเป็นปัจจัยหลักที่ทำให้ผู้ป่วยโรคตับเรื้อรังมีอัตราการตายสูง **เชียงใหม่เวชสาร 2564;60(2):157-64. doi 10.12982/ CMUMEDJ.2021.14**

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