

The burden of cirrhosis and impact of universal coverage public health care system in Thailand: Nationwide study

Kittiyod Poovorawan,* Sombat Treeprasertsuk,** Kaewjai Thepsuthammarat,***
Polrat Wilairatana,* Bubpha Kitsahawong,**** Kamthorn Phaosawasdi****

* Department of Clinical Tropical Medicine, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand.

** Department of Medicine, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Bangkok, Thailand.

*** Clinical Epidemiology Unit, Faculty of Medicine, KhonKaen University, Thailand.

**** Vichaiyut Hospital and Medical Center, Thailand.

ABSTRACT

Background and rationale. Cirrhosis is responsible for significant health-care costs and morbidity. This study aims to evaluate the burden of illness associated with cirrhosis, its impact on the universal coverage public health care system in Thailand. **Material and methods.** We used data from the 2010 Nationwide Hospital Admission Data, the National Health Security Office (NHSO), Thailand. Their baseline characteristics, hospital costs, and outcomes were analyzed according to national health insurance categories including medical welfare scheme (MWFS), social security scheme (SSS) and civil servant medical benefit scheme (CSMBS). **Results.** 92,301 admissions were eligible for analysis. The mean age was 55 ± 12.8 years, and 63.3% of patients were above 50 years old. The majority of patients (79%) belonged to the MWFS group. The MWFS group incurred the lowest medical expense and had the shortest hospital stay compared to the SSS and CSMBS groups. Overall in-hospital mortality was 10.7%. Cirrhosis complications include bleeding esophageal varices, spontaneous bacterial peritonitis, hepatic encephalopathy, hepatorenal syndrome, and hepatocellular carcinoma. These complications significantly increased mortality rates compared to patients without complications (26 vs. 8.9%, $p < 0.001$). In-hospital mortality of patients with cirrhosis complications did not differ among the three national health insurance groups. Respiratory failure and septicemia were associated with the highest risk of death (HR 5.4; 95% CI: 4.8-5.9 and HR 5.2; 95% CI: 4.9-5.6 respectively; $P < 0.001$). **Conclusions.** Illness associated with cirrhosis is a significant public health problem in Thailand. Outcomes of cirrhosis complications did not differ between universal public health care coverage systems in Thailand.

Key words. Liver-related mortality. Cirrhosis complications. Health care reform. Population. Cost.

INTRODUCTION

Cirrhosis is the end-stage of every chronic liver disease. Its natural history is characterized by an asymptomatic phase followed by a rapidly progressive phase marked by the development of complications of portal hypertension and/or liver dysfunction.¹ Vari-

ous common chronic liver diseases such as alcohol consumption, metabolic syndromes related to overweight and obesity, viral hepatitis B and C have end results of liver cirrhosis and hepatocellular carcinoma.² Reviewed data in Europe demonstrated that cirrhosis-associated mortality is at least comparable with other diseases that are considered to be of major public health concern, such as breast cancer, colon cancer, chronic lung disease and renal diseases.³ Liver-related mortality has been underestimated during the past two decades in the United States and Brazil.^{4,5} There are nearly as many mortality cases attributed to complications of cirrhosis as there are to diabetes, and more than are attributable to kidney diseases.⁶ Cirrhosis is also responsible for significant health-care costs and morbidity, and

Correspondence and reprint request: Kittiyod Poovorawan, M.D., MSc.
Division of Gastroenterology and Liver Disease. Department of Clinical Tropical Medicine, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand.
Fax: + 662-3549-168
E-mail: kittiyod.poo@mahidol.ac.th

Manuscript received: February 23, 2015.

Manuscript accepted: April 05, 2015.

DOI: 10.5604/16652681.1171742

© 2019, Fundación Clínica Médica Sur, A.C. Published by Elsevier España S.L.U. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

the incidence of hospitalizations due to cirrhosis complications is increasing.⁷⁻⁹ Besides cirrhosis complications, various co-morbidities such as diabetes, cardiovascular disease, and chronic kidney disease also affect the prognosis of cirrhosis patients.¹⁰ A study in chronic hepatitis B patients in Thailand showed that the yearly cost of treatment for patients with end-stage liver disease including cirrhosis was five times higher than chronic liver disease without cirrhosis.¹¹ Previous reports of population-based prevalence rates of cirrhosis in Nakhon Nayok Province showed that standardized prevalence rates are 75.3 per 100,000, and prevalence is higher among males than females, particularly for alcoholic cirrhosis.¹²

Health-financing reforms in Southeast Asia have sought to reduce dependence on out-of-pocket payments, increase pooled health finance, and expand service use as steps towards universal coverage.¹³ Thailand developed a universal coverage public health care system in 2002.^{14,15} All citizens received individualized national insurance depending on work and public health classification to ensure basic health care services. Outcomes, economic burden, and the effect of the public health care system of cirrhosis in Thailand have not been well researched. We aim to evaluate the burden of illness associated with cirrhosis in Thailand and its effect on the national health insurance systems.

MATERIAL AND METHODS

Data sources

We analyzed cirrhosis data among hospitalized patients in Thailand from the 2010 Nationwide Hospital Admission Data, the National Health Security Office (NHSO), Thailand. Data consisted of inpatient information from three health insurance coverage schemes (Medical Welfare Scheme, MWFS, Social Security Scheme, SSS, and Civil Servant Medical Benefit Scheme, CSMBS), which covered 77% (MWFS), 10% (SSS), and 13% (CSMBS) of all admissions. All patients with cirrhosis diagnosis (ICD10-K74) aged at least 19 years old were included. Their baseline characteristics, hospital costs, and outcomes were analyzed according to national health insurance category.

Universal coverage public health care system

Thailand adopted a universal public health care system in 2002, which is comprised of three nation-

al health insurance categories –Civil Servant Medical Benefit Scheme (CSMBS), Social Security Scheme (SSS), and Medical Welfare Scheme (MWFS). CSMBS includes all civil servant officers with close family which individually reimburses medical expenses from the Controller General's Department. SSS includes all Thai employees who are registered to the National Social Security Fund. MWFS includes all the remaining Thai citizens in the national database, which can access public health services from public hospitals and private hospital registered with The National Health Security Office. All national health insurances cover basic healthcare services, however there are some differences between them. CSMBS covers some medications that are part of the National List of Essential Medicines, and liver transplant, whereas other schemes do not cover this. There are also some differences in hospital room fee reimbursement rules among these insurances.

In Thailand, government hospitals are classified into three levels, primary hospital is community hospital for primary healthcare, secondary hospital is a hospital for general healthcare, and tertiary hospital is a referral hospital for complicated diseases and specialized healthcare.

Statistical analysis

All statistical analyses were performed using SPSS version 13 (SPSS Inc., Chicago, IL). Continuous variables were compared between groups using unpaired t-test and one-way ANOVA. Categorical variables were compared between groups using χ^2 /Fisher's exact test. Multiple logistic regression analysis was used to adjust the odds ratio for the factors influencing mortality rate. The odds ratio and 95% CI of each factor are presented. $P < 0.05$ was considered statistically significant.

Ethical consideration

This study was done with approval from The Gastroenterological Association of Thailand in collaboration with The National Health Security Office, Thailand. The research protocol was approved by the Institutional Review Board, Faculty of Tropical Medicine, Mahidol University (MUTM 2014-056-01).

RESULTS

In the year 2010, Thailand's over 19-year-old population was 47.97 million, which accounted for 74%

of the country's population (64.7 million). The total number of adult inpatients was 3.87 million, who were admitted 4.86 million times, accounting for 71% of all inpatients. The diseases of digestive system were the third leading cause of hospitalization, which accounted for 379,532 admissions, or 10% of all admissions. Among admissions of digestive system, 92,301 admissions for cirrhosis (24.3%) were eligible for analysis.

The mean age of patients admitted with cirrhosis was 55 ± 12.8 years and 63.3% of patients were above 50 years old. The male to female ratio was 2:1, most patients were hospitalized in primary level hospitals, and in the central part of Thailand. The majority of patients (79%) belonged to the group of MWFS (Table 1).

The overall in-hospital mortality was 10.7%. Cirrhotic patients with complications including bleeding esophageal varices, spontaneous bacterial peritonitis, hepatic encephalopathy, hepatorenal syndrome, and hepatocellular carcinoma-related complications had significantly higher mortality rate than those patients without complications (26 vs. 8.9%, $p < 0.001$). The overall mean length of hospital stay was 5.8 days in cirrhosis patients. Longer durations, up to 8.6 days, were observed in patients with cirrhosis complications. Hepatorenal syndrome was the complication that caused the longest admission period, up to 10.2 days, and the highest mortality rate, up to 42.6% (Table 2).

Cirrhosis patients in the group of MWFS incurred the least medical expense compared to those in the

SSS and CSMBS groups – both for patients with and without complications. After categorizing according to cirrhosis complications including bleeding esophageal varices, spontaneous bacterial peritonitis, hepatic encephalopathy, hepatorenal syndrome and hepatocellular carcinoma-related complications, the MWFS group still incurred a significantly lower medical expense (Table 3).

Cirrhosis patients in the MWFS group had significantly shorter admission durations compared to the SSS and CSMBS groups, despite cirrhosis complications (Figure 1). In-hospital mortality of patients with cirrhosis complications did not differ among the three groups (Figure 2). Comorbidities and cirrhosis complications were significantly correlated with patient survival. Respiratory failure requiring continuous invasive mechanical ventilation for 96 consecutive hours or more, and septicemia were associated with the highest risk of death (HR 5.4; 95% CI: 4.8-5.9 and HR 5.2; 95% CI: 4.9-5.6 respectively; $P < 0.001$) (Table 4).

The etiology of liver cirrhosis was identified in 31,423/92,301 (34%) of cases. Out of these, the causes were identified as alcoholic liver disease in 73%, chronic hepatitis B in 14%, chronic hepatitis C in 12.6%, and non-alcoholic steatohepatitis (NASH) in $< 1\%$.

DISCUSSION

In 2010, cirrhosis accounted for 1.3 million deaths around the world, about 2% of global deaths.¹⁶

Table 1. Baseline characteristics, hospital level and geographic distribution of cases were classified according to their national health insurance.*

	Total (n = 92,301)	Medical Welfare Scheme (MWFS) (n = 72,985)	Civil Servant Medical Benefit Scheme (CSMBS) (n = 12,679)	Social Security Scheme (SSS) (n = 6,637)	P value
Age(years)	55.4 ± 12.8	54.9 ± 12.7	61.9 ± 12.5	47.4 ± 8.8	< 0.001
Male gender (%)	68.0	66.1	69.3	86.8	< 0.001
Hospital level (%)					
Primary	34.1	39.0	22.8	2.2	< 0.001
Secondary	25.0	25.9	23.4	18.6	< 0.001
Tertiary	32.9	29.8	53.7	27.0	< 0.001
Private	8.0	5.3	0.2	52.2	< 0.001
Region (%)					
Northern	24.0	25.5	19.5	15.9	< 0.001
Northeast	29.8	31.9	28.4	10.0	< 0.001
Central	38.2	34.7	42.0	69.9	< 0.001
Southern	7.9	7.9	10.1	4.3	< 0.001

* Plus-minus values are mean \pm SD for all comparisons.

Table 2. Baseline characteristic, duration of hospital stay, cost of hospitalization, and mortality rate classified according to complications directly related with cirrhosis.*

	Cirrhosis complications					
	Without complication (n = 82,652)	With cirrhosis complications† (n = 9,649)	Bleeding esophageal varices (n = 868)	Spontaneous bacterial peritonitis (n = 2,406)	Hepatic encephalopathy (n = 5,292)	Hepatorenal syndrome (n = 458)
Age (years)	55.3 ± 12.9	55.6 ± 12.3	53.5 ± 11.5	54.9 ± 12.4	55.5 ± 12.3	56.8 ± 12.1
Length of stay (days)	5.8 ± 7.7	8.6 ± 10.2	8.4 ± 9.9	8.6 ± 10.3	9.1 ± 10.9	10.2 ± 10.3
Hospital charge (baths)**	22,677 ± 65,990	41,937 ± 69,050	58,310 ± 87,746	35,310 ± 60,896	44,606 ± 71,001	58,134 ± 79,763
In-hospital mortality rate	8.9%	26%	19.7%	21.9%	32%	42.6%
						17.1%
						< 0.001

* Plus-minus values are mean ± SD for all comparisons. ** 1 US dollar = 32 baths (currency exchange). † Some patients had more than 1 complication. HCC: hepatocellular carcinoma.

Table 3. Medical expenses classified by cirrhosis complications and national health insurance.*

	Medical expense			
	Total (n = 92,301)	Medical Welfare Scheme (MWFS) (n = 72,985)	Civil Servant Medical Benefit Scheme (CSMBS) (n = 12,679)	Social Security Scheme (SSS) (n = 6,637)
Overall (n = 92,301)	24,691 ± 66,577	20,845 ± 62,781	38,795 ± 82,604	40,036 ± 66,998
With cirrhosis complications† (n = 9,649)	41,937 ± 69,050	35,119.3 ± 54,256.3	64,550.2 ± 107,373.8	67,661.0 ± 89,028.0
Bleeding esophageal varices (n = 868)	58,310 ± 87,746	52,104.7 ± 76,134.1	74,916.3 ± 117,425.2	76,644.3 ± 105,558.6
Spontaneous bacterial peritonitis (n = 2,406)	35,310 ± 60,896	29,034.7 ± 46,720.9	62,209.5 ± 104,787.0	55,747.9 ± 67,326.2
Hepatic encephalopathy (n = 5,292)	58,134 ± 79,763	37,787.1 ± 55,215.3	68,692.7 ± 114,138.6	75,349.4 ± 94,665.9
Hepatorenal syndrome (n = 458)	58,134 ± 79,763	36,429.4 ± 49,981.1	104,787.2 ± 102,096.5	129,973.2 ± 129,182.8
HCC related complications (n = 1,407)	40,056 ± 65,453	31,508.8 ± 51,778.7	62,101.0 ± 94,105.0	49,806.3 ± 60,332.4

* Plus-minus values are mean ± SD for all comparisons. † Some patients had more than 1 complication. HCC: hepatocellular carcinoma.

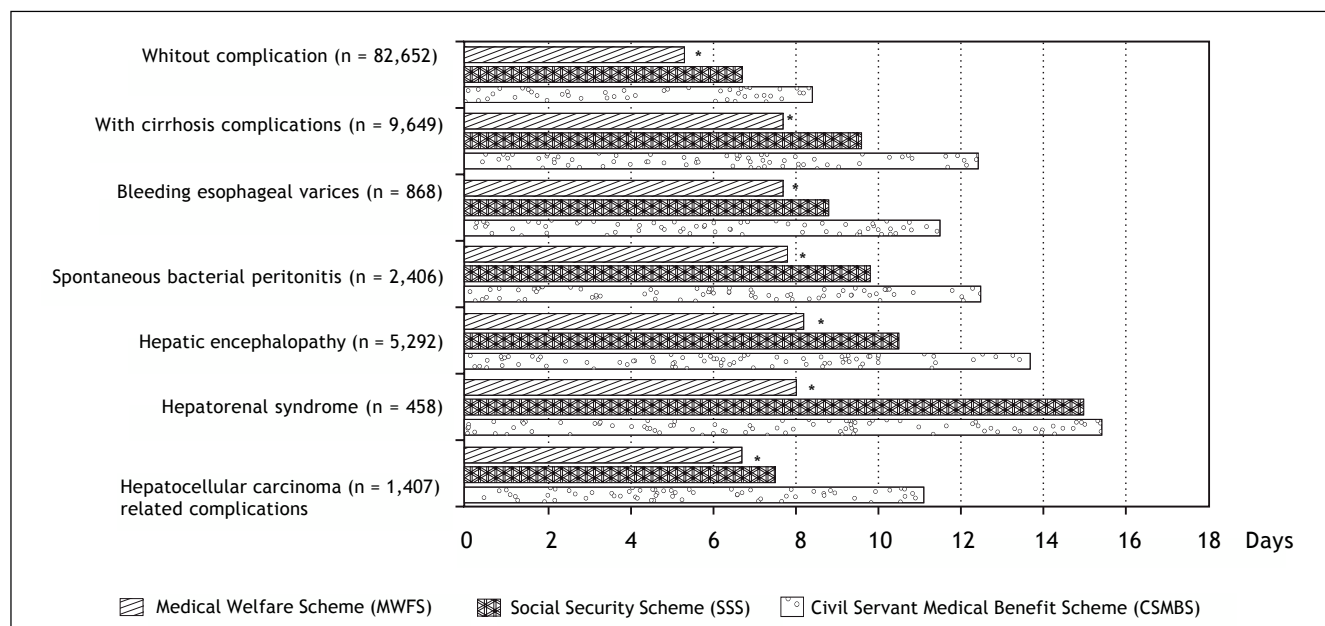


Figure 1. Length of hospitalization (days) classified by cirrhosis complications and national health insurance. * Statistically significance difference.

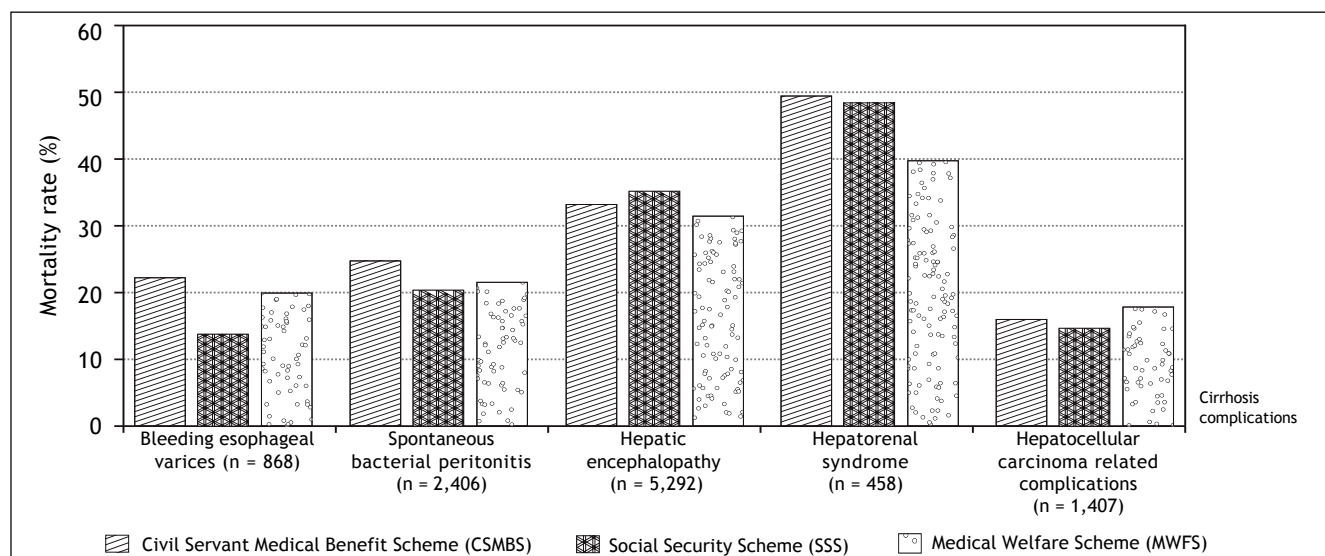


Figure 2. Mortality rate of cirrhosis complications classified according to national health insurance. * No statistically significance difference.

According to the National Center for Health Statistics (NCHS), chronic liver disease and cirrhosis is the 12th leading cause of death in the United States. The highest risk groups consist of persons aged 45 to 54 years and 55 to 64 years, where chronic liver disease and cirrhosis are the 4th and 7th leading cause of death.^{4,17}

Our data supports that liver cirrhosis is a public health problem in all areas and at every hospital

level in Thailand. Mortality rate of hospitalized liver cirrhosis patients in Thailand 2010 was 10.7%, compared to the overall mortality rate of inpatients of 4.4, 1.4 and 3.3% in CSMBS, SSS, and MWFS groups accordingly. In analysis of data from the National Health Security Office (NHSO), Thailand (2010), cirrhosis-related deaths was 20.5/100,000 persons which is comparable to estimated liver-related deaths in United State (25.7/100,000 persons

Table 4. Cirrhosis complications and co-morbidities associated with in-hospital mortality in patients hospitalized with liver cirrhosis.

Risk factors	Hazard ratio	95% CI	P value
Cirrhosis complications			
Bleeding esophageal varices	2.0	1.7, 2.4	< 0.001
Spontaneous bacterial peritonitis	1.8	1.6, 2.0	< 0.001
Hepatic encephalopathy	2.9	2.7, 3.1	< 0.001
Hepatorenal syndrome	4.1	3.3, 5.2	< 0.001
Hepatocellular carcinoma related complications	1.8	1.6, 2.1	< 0.001
Septicemia	5.2	4.9, 5.6	< 0.001
Diabetes mellitus	0.7	0.7, 0.8	< 0.001
Renal failure	2.9	2.7, 3.0	< 0.001
Ischemic heart diseases	1.4	1.2, 1.6	< 0.001
Continuous invasive mechanical ventilation for 96 consecutive hours or more	5.4	4.8, 5.9	< 0.001
Hemodialysis	1.8	1.5, 2.2	< 0.001

in 2008).⁴ Mortality rates of hospitalized cirrhosis patients range from 3.3 to 40% depended on severity of cirrhosis, complications, and co-morbidities.^{5,18,19} Cirrhosis complications significantly increase risk of death. According to our data, hepatorenal syndrome was the most fatal complication of cirrhosis, which might be due to decompensated liver disease and insufficient liver transplantation. We found that only 19 liver transplants have been done in this registry data, compare with more than 2,500 endoscopic interventions for bleeding esophageal varices. Our data were consistent with previous data, and show that infectious and renal complications in persons with cirrhosis directly impact clinical outcomes.^{20,21} These data support that morbidity and mortality due to cirrhosis and its complications are significant public health problems in Thailand.

Length of hospital stay and hospital expenses incurred were higher in SSS and CSMBs groups, compared with MWFS, however no statistically significant differences were found in mortality rates from the various cirrhosis complications.

Acute-on chronic liver failure (ACLF) is distinct from acute decompensation and has been significantly related to death in patients with cirrhosis.²² This study has limitations, since it is related to a retrospective survey, and non-specialized doctors are more prone to describe all morbid events in cirrhosis as decompensation. The absence of data description on ACLF does not mean that these cases are rare. Etiology of cirrhosis could only be determined in 34% of cases, and a better method to define etiology of cirrhosis in Thailand should be developed, since its treatment and prevention is essential for better patient care.

Base on this limited data, alcoholic liver disease might be one of the significant causes of liver cirrhosis consistent with previous report,²³ however out-patient data from the liver clinic in King Chulalongkorn Memorial hospital, Thailand, showed that chronic hepatitis B was the most common etiology (44.7%), followed by chronic hepatitis C (29.7%), alcoholic liver disease (14.8%), NASH (6.7%), and autoimmune hepatitis (4.1%) (unpublished data). These data suggest that most alcoholic patients did not access healthcare before admission from cirrhosis-related illness.

Alcohol consumption, viral hepatitis B and C, and metabolic syndromes related to overweight and obesity are the leading causes of cirrhosis and primary liver cancer.²⁴⁻²⁶ Prevention and treatment interventions in those conditions and risk factors are necessary to control further morbidities, mortality, and economic burden related to cirrhosis.

In conclusion, illness associated with cirrhosis is a significant public health problem in Thailand, with a mortality rate of up to 26% in hospitalized patients with decompensated forms of cirrhosis. Preventive measures are very important to reduce the burden of the disease in the future. Although differences among the three health care systems were found regarding medical expenses and admission periods, the outcomes of cirrhosis complications were similar for all of them.

ABBREVIATIONS

- **CI:** confidence interval.
- **CSMBs:** civil servant medical benefit scheme.
- **HCC:** hepatocellular carcinoma.
- **HR:** hazard ratio.

- **MWFS:** medical welfare scheme.
- **NASH:** non-alcoholic steatohepatitis.
- **NCHS:** National Center for Health Statistics.
- **NHSO:** National Health Security Office.
- **SSS:** social security scheme.

CONFLICTS OF INTEREST

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

FINANCIAL SUPPORT

This work was supported by the Gastroenterological Association of Thailand, The ICTM Grant of the Faculty of Tropical Medicine, Mahidol University, Thailand.

ACKNOWLEDGEMENTS

We would like to express our gratitude to the staff of the Office of Research Services and staffs at the Faculty of Tropical Medicine, Mahidol University, Faculty of Medicine, Chulalongkorn University, Clinical Epidemiology Unit, Faculty of Medicine, KhonKaen University, Vichaiyut Medical Center, and The National Health Security Office, Thailand.

REFERENCES

1. D'amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. *J Hepatol* 2006; 44: 217-31.
2. Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. *Gastroenterology* 2004; 127: S35-S50.
3. Blachier M, Leleu H, Peck-Radosavljevic M, Valla DC, Roudot-Thoraval F. The burden of liver disease in Europe: a review of available epidemiological data. *J Hepatol* 2013; 58: 593-608.
4. Asrani SK, Larson JJ, Yawn B, Therneau TM, Kim WR. Underestimation of liver-related mortality in the United States. *Gastroenterology* 2013; 145: 375-82.
5. Nader LA, De Mattos AA, Bastos GA. Burden of liver disease in Brazil. *Liver Int* 2014; 34: 844-9.
6. Kim WR, Brown RS, Jr., Terrault NA, El-Serag H. Burden of liver disease in the United States: summary of a workshop. *Hepatology* 2002; 36: 227-42.
7. Volk M L, Tocco R S, Bazick J, Rakoski M O, Lok A S. Hospital readmissions among patients with decompensated cirrhosis. *Am J Gastroenterol* 2012; 107: 247-52.
8. Nguyen GC, Segev DL, Thuluvath PJ. Nationwide increase in hospitalizations and hepatitis C among inpatients with cirrhosis and sequelae of portal hypertension. *Clin Gastroenterol Hepatol* 2007; 5: 1092-9.
9. Davalos Moscol M, Bustios Sanchez C. The burden of hepatic encephalopathy in Latin America. *Ann Hepatol* 2011; 10(Suppl. 2): S31-S35.
10. Jepsen P. Comorbidity in cirrhosis. *World J Gastroenterol* 2014; 20: 7223-30.
11. Yeekian C, Geratikornsupak N, Chumpongthong P, Tong-siri S, Dhitavat J, Phonrat B, Pitisuttithum P. Medical and economic burden of chronic hepatitis B patients at Queen Savang Vadhana Memorial Hospital. *J Med Assoc Thai* 2014; 97: 447-55.
12. Rattanamongkolgul S, Wongjitrat C, Puapankitcharoen P. Prevalence of cirrhosis registered in Nakhon Nayok, Thailand. *J Med Assoc Thai* 2010; 93(Suppl. 2): S87-S91.
13. Tangcharoensathien V, Patcharanarumol W, Ir P, Aljunid S M, Mukti A G, Akkhavong K, Banzon E, et al. Health-financing reforms in southeast Asia: challenges in achieving universal coverage. *Lancet* 2011; 377: 863-73.
14. Limwattananon S, Tangcharoensathien V, Tisayaticom K, Boonyapaisarncharoen T, Prakongsai P. Why has the Universal Coverage Scheme in Thailand achieved a pro-poor public subsidy for health care? *BMC Public Health* 2012; 12(Suppl. 1): S6.
15. Tangcharoensathien V, Pitayangsarit S, Patcharanarumol W, Prakongsai P, Sumalee H, Tosanguan J, Mills A. Promoting universal financial protection: how the Thai universal coverage scheme was designed to ensure equity. *Health Res Policy Syst* 2013; 11: 25.
16. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, Abraham J, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; 380: 2095-128.
17. Heron M. Deaths: leading causes for 2009. *Natl Vital Stat Rep* 2012; 61: 1-94.
18. Waddingham W, Cepkova M. PTU-139 Outcomes Of Patients With Liver Cirrhosis In A Non Liver-specialist Intensive Care Unit: Do Admission Lactate And Apache 2 Score Help Predict Successful Discharge? *Gut* 2014; 63(Suppl. 1): A99-A100.
19. Ratib S, Fleming K M, Crooks C J, Aithal G P, West J. 1 and 5 year survival estimates for people with cirrhosis of the liver in England, 1998-2009: a large population study. *J Hepatol* 2014; 60: 282-9.
20. Arvaniti V, D'amico G, Fede G, Manousou P, Tsochatzis E, Pleguezuelo M, Burroughs AK. Infections in patients with cirrhosis increase mortality four-fold and should be used in determining prognosis. *Gastroenterology* 2010; 139: 1246-56, 56 e1-5.
21. Fede G, D'amico G, Arvaniti V, Tsochatzis E, Germani G, Georgiadis D, Morabito A, et al. Renal failure and cirrhosis: a systematic review of mortality and prognosis. *J Hepatol* 2012; 56: 810-8.
22. Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, Durand F, 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.
23. Marinho RT, Duarte H, Gira J, Nunes J, Ferreira A, Velosa J. The burden of alcoholism in fifteen years of cirrhosis hospital admissions in Portugal. *Liver Int* 2014. Doi: 10.1111/liv.12569.
24. Venook AP, Papandreou C, Furuse J, De Guevara LL. The incidence and epidemiology of hepatocellular carcinoma: a global and regional perspective. *Oncologist* 2010; 15(Suppl. 4): 5-13.
25. Thong V D, Akkarathamrongsin S, Poovorawan K, Tangkijvanich P, Poovorawan Y. Hepatitis C virus genotype 6: virology, epidemiology, genetic variation and clinical implication. *World J Gastroenterol* 2014; 20: 2927-40.
26. Younossi Z M, Stepanova M, Afendy M, Fang Y, Younossi Y, Mir H, Srishord M. Changes in the prevalence of the most common causes of chronic liver diseases in the United States from 1988 to 2008. *Clin Gastroenterol Hepatol* 2011; 9: 524-30.