International Journal of Gerontology 9 (2015) 233–238

Contents lists available at ScienceDirect

International Journal of Gerontology

journal homepage: www.ijge-online.com

Original Article

Influence of Age on Critically Ill Patients with Cirrhosis☆

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A R T I C L E I N F O

Article history:
Received 4 January 2014
Received in revised form
11 March 2014
Accepted 1 October 2014
Available online 12 December 2015

Keywords:
critical care,
geriatric,
intensive care unit,
liver cirrhosis,
old age

S U M M A R Y

Background: The general prognosis of critically ill patients with cirrhosis is poor. We investigated the influence of age (< 65 years, 65–74 years, and ≥ 75 years) on the short- and medium-term outcomes of cirrhotic patients in the intensive-care-unit (ICU) setting.
Methods: This retrospective cohort study included 226 consecutive patients with liver cirrhosis who were admitted to the ICU. Clinical outcomes, including ICU mortality, in-hospital mortality, ventilator-free days, ICU days, ICU-free days, hospital days, and hospital-free days, were compared between the different age groups.
Results: The overall ICU mortality in patients aged < 65 years, 65–74 years, and ≥ 75 years was 29.4%, 20.0%, and 30.3%, respectively. For patients with compensated cirrhosis, age showed no significant correlation with mortality or clinical outcomes. For patients with decompensated cirrhosis, age ≥ 75 years was significantly correlated with in-hospital mortality, 6-month mortality, hospital days, and hospital-free days. After adjusting for sex, coronary artery disease, etiology of ICU admission, Acute Physiology and Chronic Health Evaluation II score, Model for End-Stage Liver Disease score, and mechanical ventilation, age ≥ 75 years remained significant for in-hospital mortality (hazard ratio 2.61, 95% confidence interval 1.27–5.39, $p = 0.009$) and 6-month mortality (hazard ratio 2.34, confidence interval 1.16–4.70, $p = 0.017$).
Conclusion: During ICU stays, old age does not have adverse effects on ICU mortality, ventilator-free days, ICU days, or ICU-free days in cirrhotic patients (either compensated or decompensated cirrhosis). After ICU discharge, age ≥ 75 years is an independent prognostic factor for in-hospital mortality and 6-month mortality in patients with decompensated cirrhosis.

1. Introduction

It has been suggested that intensive-care-unit (ICU) mortality rates are higher in the elderly than in younger patients[1]; however, several studies have also shown that it is not age per se, but other factors that predict mortality, including diagnosis, comorbidity, and premorbid cognitive and functional status[2–4]. Therefore, age alone should not be a criterion for admission and use of ICU resources[5].

Meanwhile, the incidence of liver cirrhosis is increasing exponentially[6]. Regardless of the reason for admission to an ICU, the presence of cirrhosis is independently associated with worse prognosis of critically ill patients[7]. Das et al[8] have shown that the occurrence of three nonhematologic organ-system failures after 3 days in patients with cirrhosis was associated with a mortality rate of almost 90%, and a 3-day trial of unrestrictive intensive care has been proposed for cirrhotic patients. Therefore, predicting the outcomes of critically ill patients with cirrhosis is important for medical decision-making and for providing prognostic advice to patients.

Studies have shown that, in elderly critically ill patients, the severity of acute illness is an even stronger predictor of mortality than age[9,10]. It has been suggested that the prognosis of cirrhotic patients during ICU stays is not related to the severity of liver

☆ Conflicts of interest: All contributing authors declare that they have no conflicts of interest.

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http://dx.doi.org/10.1016/j.ijge.2014.10.003

cirrhosis, but to the frequency of organ-system failure[11]. However, these results were not verified in an elderly age group. Therefore, we aimed to investigate the influence of age (< 65 years, 65–74 years, or ≥ 75 years) on short- and medium-term outcomes of cirrhotic patients in the ICU setting.

2. Materials and methods

2.1. Patients

The present retrospective study included consecutive adult patients with cirrhosis admitted to the medical ICU between August 2010 and April 2012. The study was performed according to the principles of the Declaration of Helsinki, and approved by the Ethics Committee of the Mackay Memorial Hospital, Taipei, Taiwan (Institutional Review Board number 12MMHIS017).

Of the 9000 ICU patient records, we reviewed those of 299 cirrhotic patients. The exclusion criteria were end-stage renal disease with renal replacement (10 cases), admission for surgical indications (25 cases), repeated ICU admissions during the study period (33 cases), and loss to follow-up during the study period (5 cases). A total of 226 patients met the inclusion criteria for entry into the study, and none of the study participants underwent liver transplantation.

2.2. Methods

The baseline characteristics of the participants included in the analysis were age, sex, etiology of liver disease, reasons for ICU admission, comorbidities, and Acute Physiology and Chronic Health Evaluation II (APACHE II) score. Laboratory data on liver function, Model for End-Stage Liver Disease score, Child–Pugh score, renal function, and electrolyte levels were also obtained upon admission to the ICU. The clinical mortality (ICU mortality, in-hospital mortality, and 6-month mortality) and outcomes [ventilator-free days (VFDs), ICU days, ICU-free days, hospital days, and hospital-free days] of patients aged < 65 years, 65–74 years, and ≥ 75 years were compared.

The patients were classified into compensated and decompensated cirrhosis groups. *Compensated cirrhosis* was defined as the absence of variceal bleeding, clinical hepatic encephalopathy, severe ascites, and hepatorenal syndrome on admission to the ICU.

VFDs were calculated as $(28 - x)$, where x was the number of days spent receiving mechanical ventilation. For example, VFD = 0 indicates patients who required mechanical ventilation for ≥ 28 days, or those who died before reaching 28 days on mechanical ventilation in the ICU. ICU-free days were calculated as $(30 - x)$, where x was the number of days spent in the ICU. ICU-free days = 0 indicated patients who died before 30 days, or stayed in the ICU for ≥ 30 days. Hospital-free days were calculated as $60 - x$, where x was the number of days spent in the hospital. Hospital-free days = 0 indicated patients who spent > 60 days in the hospital, or expired within 60 days during hospitalization.

2.3. Statistical analysis

Continuous variables were expressed as mean ± standard error of the mean unless otherwise stated. Analysis of variance (ANOVA) and Chi-square tests were used to assess differences in clinical outcomes in patients who were classified by age group. Cox proportional-hazard regression analysis and linear-regression analysis were used to investigate the association between parameters and clinical outcomes. All statistical analyses were performed using SPSS software (version 17.0; SPSS Inc., Chicago, IL, USA).

3. Results

The baseline demographic, clinical, and laboratory characteristics of the 226 enrolled patients are shown in Table 1. It should be noted that most cases of cirrhosis in patients aged < 65 years were related to alcohol consumption (68%), and most of these patients were men. These patients had more severe liver disease at ICU admission, represented by the high Child–Pugh score, total bilirubin, and international normalized ratio. Male sex is a risk factor for alcohol dependence and abuse in Taiwanese society. By contrast, most cases of cirrhosis in patients aged 65–74 years and ≥ 75 years were related to viral hepatitis.

ICU complications and clinical outcomes are listed in Table 2. A significantly higher proportion of cirrhosis-related complications (hepatic encephalopathy and gastrointestinal bleeding) was noted in patients aged < 65 years. For clinical outcomes, significant differences between age groups were noted in in-hospital mortality, 6-month mortality, and hospital-free days.

Portal hypertension is associated with some of the most severe complications of cirrhosis, including ascites and bleeding from gastroesophageal varices[12]. As portal pressure rises above 12 mmHg, the risk for gastroesophageal variceal hemorrhage increases dramatically[13]. Acute variceal bleeding in cirrhotic patients can be a dramatic event with severe gastrointestinal hemorrhage manifesting as hematemesis with or without melena, and commonly accompanied by hemodynamic instability, shock, and fall in hemoglobin[14]. Even with the current best medical care, mortality from variceal bleeding is still approximately 20%[15]. We analyzed the gastrointestinal-bleeding group into variceal bleeding and nonvariceal bleeding (Tables 1 and 2). We defined variceal bleeding according to the esophagogastroduodenoscopy result. *Active esophageal* or *gastric variceal bleeding* was defined as bleeding from an esophageal or gastric varix at the time of endoscopy, or the presence of large esophageal varices with blood in the stomach and no other recognizable cause of bleeding. 92 (86.7%) patients had variceal bleeding among 106 patients who were admitted to the ICU due to gastrointestinal bleeding. Variceal-bleeding patients were much more than nonvariceal-bleeding patients in the three different age groups. Younger patients with variceal bleeding (< 65 years old) were predominantly more than the elderly patients (> 65 years old) in the subgroup analysis of variceal-bleeding patients.

Table 3 shows the association between the different age groups and the clinical outcomes. Compared with patients aged < 65 years, those aged 65–74 years showed no significant correlation with mortality and clinical outcomes (regardless of compensated or decompensated cirrhosis). In patients with compensated cirrhosis, age ≥ 75 years did not have any significant correlation with mortality or outcomes. However, in patients with decompensated cirrhosis, age ≥ 75 years was significantly correlated with in-hospital mortality, 6-month mortality, hospital days, and hospital-free days (compared with patients aged < 65 years). Similar results were seen in the Kaplan–Meier survival curves. In this analysis, compared with patients aged < 65 years, those aged ≥ 75 years with decompensated cirrhosis had significant differences in the in-hospital and 6-month mortality (Figure 1). After adjusting for sex, coronary artery disease, etiology of ICU admission, APACHE II score, Model for End-Stage Liver Disease score, and mechanical ventilation, the significant correlation with in-hospital and 6-