Original Article

Palliative Care for End-Stage Cirrhotic Patients in Intensive Care Units

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A R T I C L E   I N F O

S U M M A R Y

Background: The majority of patients suffering from end-stage liver disease (ESLD) experience a predictable decline in quality of life and physical function, as well as significant psychological distress. They are frequently hospitalized and are relatively less likely to be referred to palliative care. This study aims to elucidate whether patients with terminal disease receive appropriate management.
Methods: We retrospectively reviewed 236 patients with liver cirrhosis who were hospitalized in the intensive care unit between August 2013 and July 2015 in Taitung Mackay Memorial Hospital, Taiwan. The basic patients' information, laboratory results, prognosis, medical cost are collected. We further calculate the number of invasive medical procedure or life-sustaining therapy of end-stage patients before death.
Results: The overall in-hospital mortality rate was 35.2%. We subdivided patients into higher severity and lower severity groups. Several factors were not statistically different between the two categories, including sex, cirrhosis etiology, length of hospital stay, and hospital cost. In the higher severity group, 61.9% patients died during hospitalization. Among these patients, 68.9% DNR consent was given by a surrogate decision-maker within the 24 hours prior to death. Even among those with terminal disease status, many received life-support management in the pre-dying period.
Conclusion: Many end-stage cirrhotic patients received inappropriate life-support intervention during hospitalization, even during the pre-dying period. Identification of markers that can reliably predict prognosis in patients with cirrhosis and early introduction of adequate palliative care prior to the terminal disease phase may help to improve physical and psychological outcomes.

1. Introduction

Cirrhosis is associated with significant morbidities. End-stage liver disease (ESLD) frequently causes complications such as ascites, encephalopathy, jaundice, and gastrointestinal hemorrhage. Liver transplantation is the only means of curative management. However, only a small proportion of ESLD patients have the opportunity for liver transplantation. Most patients suffering from ESLD experience a predictable decline in quality of life, reduced physical function, and significant psychological distress.[1–3] They are frequently hospitalized with hepatic or non-hepatic complications.[4] Patients and their families often suffer substantial physical, psychological, and economic burdens. Ideally, a combination of palliative care and potentially life-sustaining therapy can improve quality of life and length of survival. When life-sustaining therapy is no longer an adequate option, further end-of-life care may be required.[5]

There is an increased awareness that advanced life-prolonging treatments for terminal cancer patients may not be beneficial. Hospice care and do-not-resuscitate (DNR) orders are frequently applied to patients with malignancy to improve quality of life and dignity. However, end-stage cirrhotic patients are comparatively less likely to be referred to hospice care.[6,7] A significant proportion of admissions to intensive care units (ICU) for ESLD patients result from a lack of awareness of the natural course of the disease and a lack of discussion about end-of-life care.[8] These patients and their families rarely received adequate psychological, emotional, social, and spiritual support. Several severity scoring systems have been applied to patients with cirrhosis and critical illness, such as Child-Pugh score, Model for End-stage Liver Disease (MELD) score,[9] and Acute Physiology And Chronic Health Evaluation II (APACHE II) score.[10] However, there remain no standard guidelines for monitoring critical ESLD patients to facilitate palliative management. Due to the lack of a clear cut-off point for the "terminal stage" in ESLD patients, palliative care is often initiated only when death is believed to be imminent. There is a requirement for physicians and policy-makers to clarify the number of people expected to require palliative care and strategies to introduce appropriate management at an earlier stage to reduce distress to patients and families.

In this study, we attempted to address the following questions:
1. Had ESLD patients in the ICU previously received sufficient palliative information and appropriate care?
2. In current clinical practice, how often did ESLD patients receive invasive interventions, life-support management, or palliative

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care when terminal or in the pre-dying period?

2. Materials and methods

2.1. Patients and information

We retrospectively reviewed cirrhotic patients who were hospitalized in the ICU between August 2013 and July 2015 in Taitung Mackay Memorial Hospital, Taiwan. Patients over the age of 20 years with a history of liver cirrhosis (as diagnosed by abdominal echogram or computed tomography, with evidence of at least one of following: splenomegaly, esophageal/gastric varices, ascites, jaundice, or hepatic encephalopathy) were included. The exclusion criteria were any history of malignancy, or hospitalization exclusively for surgical problems such as trauma or fracture. Patients who received liver transplantation were also excluded. The patient records and information were anonymized and de-identified prior to analysis. The following baseline information was collected: patients' age, sex, incidence of viral hepatitis, alcohol use, DNR history, length of hospital stay, and medical costs during hospitalization.

This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of MacKay Memorial Hospital, number 16MMHIS077.

2.2. Data collection and analysis

A flowchart depicting the study design is shown (Fig. 1). Upon admission of patients to the ICU, the following data were collected: initial vital signs, laboratory results, complete MELD score, Child-Pugh score, and APACHE II score. Until now, there was lack a consistency for using a best scoring system to predict the mortality rate of ICU patients with underlying cirrhosis.[11,12] We compared the ability of several scoring systems to predict mortality in ICU cirrhotic patients. MELD was initially created to predict survival after elective placement of transjugular intrahepatic portosystemic shunts.[13] The model was subsequently validated as a predictor of survival in patients with liver disease[14] and became the basis for prioritization of liver transplantation.[9,15] Along with Child-Pugh score, MELD is one of the most widely employed tools in clinical practice and study design. Although myriad articles have attempted to create new or modified scoring systems, or to compare existing ones, they have produced conflicting results.[9,16–21] Moreover, APACHE II is the most

commonly used scoring system for medical ICU patients.[10,22] Therefore, we evaluated the effectiveness of all three methods in our study. We used receiver operating characteristic (ROC) curve analysis to assess the performance of each scoring system in predicting in-hospital mortality. This analysis enabled us to select the most reliable predictor. We also calculated the Youden index[23] to define the optimal cut-off point to maximize the clinical sensitivity and specificity of the scoring method. We used this cut-off point as a criterion for classifying patients according to severity.

Patients were therefore divided into those with higher severity and lower severity disease status. Several characteristics were compared between the two groups. Finally, we attempted to determine whether terminal patients received appropriate management. We selected several inappropriate life-support procedures for analysis, as below: cardiac message, vasopressor or inotropic agent usage, central vein catheter usage, blood transfusion, mechanical ventilation, renal replacement therapy, and antibiotics usage. We further compared the frequency with which end-stage cirrhotic patients of different severities received invasive medical procedures, life-sustaining therapy, and palliative care prior to death.

2.3. Statistical analysis

Data are presented as n (%) or mean ± standard deviation. The statistical significance of the continuous data was determined using the Student's t-test and the significance of the differences between the categorical variables was determined using the chi-square test. ROC curve analysis was used to assess the predictive power of different scoring systems for mortality and to identify a cutoff point. Statistical analyses were performed using SPSS software, version 22 (IBM SPSS Statistics, Armonk, NY). All statistical analyses were defined as two-sided hypothesis with a significance level of $p < 0.05$.

3. Results

3.1. Overall patients' characteristics

A total of 236 cirrhotic patients (male: 76.7%; mean age: 54.9) who had been admitted to the ICU were included. The general characteristics are shown (Table 1). On average, patients were at a relatively late stage of liver disease (mean MELD score: 21.34) and the
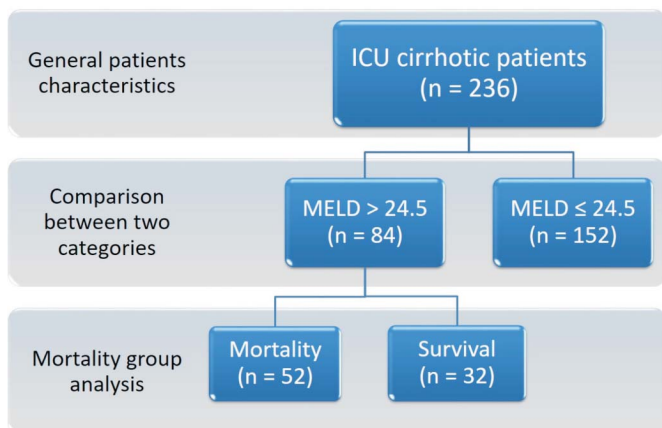

Fig 1. Flowchart of study design. First, we retrospectively reviewed 236 cirrhotic patients who were hospitalized in the intensive care unit (ICU). We divided these patients into two severity categories according to Model for End-stage Liver Disease (MELD) score. Several characteristics were compared between the two groups. We then attempted to elucidate whether those patients with terminal disease received appropriate management.

Table 1
General characteristics of cirrhotic patients in ICU (n = 236)

Male gender	181 (76.7)
Age (years)	54.85 ± 14.50
Hospital stay (days)	16.72 ± 15.16
ICU stay (days)	6.90 ± 8.71
MELD score	21.34 ± 9.28
Child-Pugh score	9.2 ± 2.12
APACHE II	22.17 ± 8.97
DNR code history	6 (2.5)
Mortality	83 (35.2)
Cirrhosis etiology	
HBV	27 (11.4)
HCV	27 (11.4)
HBV + HCV	3 (1.3)
Alcohol	92 (39.0)
Alcohol + HBV	25 (10.6)
Alcohol + HCV	10 (4.2)
Alcohol + HBV + HCV	2 (0.8)

Data are presented as number (percentage) or mean ± standard deviation. ICU, intensive care unit; MELD, Model for End-stage Liver Disease; APACHE II, acute physiology and chronic health evaluation II; DNR, do not resuscitate.

overall in-hospital mortality rate was 35.2%. Mean medical cost per patient during hospitalization was about US$ 6063. Despite patients being aware of the history of cirrhosis and their relatively late stage disease status, only 2.5% had given DNR consent prior to admission.

3.2. Severity of patients

The ROC curve analysis (Fig. 2) demonstrated that MELD, Child-Pugh, and APACHE II score were all effective tools for predicting in-hospital mortality, with p value 0.000. The area under the curve is greatest using MELD score, so we selected this system to assess patients' severity in our study. The ROC curve showed a MELD score cut-off point of 24.5. We therefore divided patients into higher severity (MELD > 24.5, n = 84) and lower severity (MELD ≤ 24.5, n = 152) groups (Table 2). Many factors including sex, cirrhosis etiology, length of stay, and hospital cost were not statistically different be-
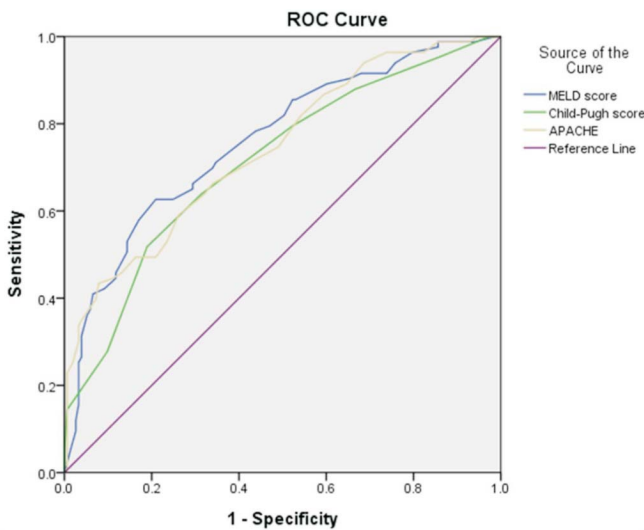
Score	Area under the curve	Significance	95% confidence interval	
			Lower bound	Upper bound
MELD	0.761	0.000	0.696	0.825
Child-Pugh	0.713	0.000	0.644	0.782
APACHE	0.742	0.000	0.675	0.808

Fig 2. The predictors of mortality of cirrhotic patients. Receiver operating characteristic (ROC) curve analysis of the capacity of three scoring systems to predict in-hospital mortality: Child-Pugh score, Model for End-stage Liver Disease (MELD) score, and Acute Physiology And Chronic Health Evaluation II (APACHE II) score. The area under the curve is greatest for MELD score.

Table 2
Patients information analysis between two categories (sorted by MELD score when patients arrival in ICU)

	MELD > 24.5 (n = 84)	MELD ≤ 24.5 (n = 152)	p value
Male sex	69 (82.1)	112 (73.7)	0.14
Indigenous	11 (13.1)	33 (21.7)	0.10
Age	49.75 ± 12.63	57.67 ± 14.73	< 0.001
Alcoholism	34 (40.5)	73 (48.0)	0.27
Hospital stay (days)	15.58 ± 15.24	18.95 ± 15.02	0.10
ICU stay (days)	6.60 ± 8.80	7.07 ± 8.68	0.69
DNR signed during hospitalization	47 (56.0)	40 (26.3)	< 0.001
Mortality	52 (61.9)	31 (20.4)	< 0.001
Medical cost (US dollars)	6011 ± 6597	6092 ± 5126	0.92

Data are presented as number (percentage) or mean ± standard deviation. MELD, Model for End-stage Liver Disease; ICU, intensive care unit; DNR, do not resuscitate.

tween the two categories. However, lower age and a greater incidence of DNR confirmation during hospitalization were both associated with higher severity (both $p < 0.05$).

3.3. Did they receive appropriate palliative care?

A total of 52 patients with MELD score > 24.5 on day of admission died during hospitalization. Among these patients, a DNR order was applied in 86.5% patients, in many cases (68.9%) consented to by Surrogate Decision-Makers (SDMs) within the 24 hours prior to death. Even in the case of terminal disease status, many still received significant life-support management in the pre-dying period (Fig. 3) without appropriate palliative care.

4. Discussion

4.1. Severity of cirrhotic patients in ICU

Because of the lack of a "terminal phase" in ESLD, palliative care is often initiated only when death is perceived as being imminent. Cirrhotic patients who have an estimated survival of six months or less may be eligible for hospice care, particularly if they are not candidates for transplantation. A systematic review summarizes the data on clinical indicators of 6-month mortality among patients with advanced noncancer illnesses; cirrhotic patients with MELD score > 21 (or Child-Pugh score > 12) or hospitalized cirrhotic patients with MELD score > 18 (or Child-Pugh > 10) had a median survival of 6 months or less and systematic reviews have found very few interventions that improve survival.[24] In our study, we compared the capacity of three severity scoring systems to predict the mortality rate in ICU cirrhotic patients: MELD, Child-Pugh, and APACHE II score. ROC curve analysis demonstrated that all three methods were reliable predictors of in-hospital mortality. MELD proved the most effective discrimination tool in our study population and a MELD score of 24.5 was set as the cut-off point for high disease severity. Comparison of higher (MELD > 24.5) and lower (MELD ≤ 24.5) severity groups has the potential to increase understanding of patients' epidemiological characteristics. No significant association was found between severity and sex, race, cirrhotic etiologies, length of hospital stay, or medical cost. Interestingly, patients in high MELD score group were significant younger in our study. We are unable to offer an explanation for this association, but it may result in reduced probability of DNR consent prior to hospitalization. An
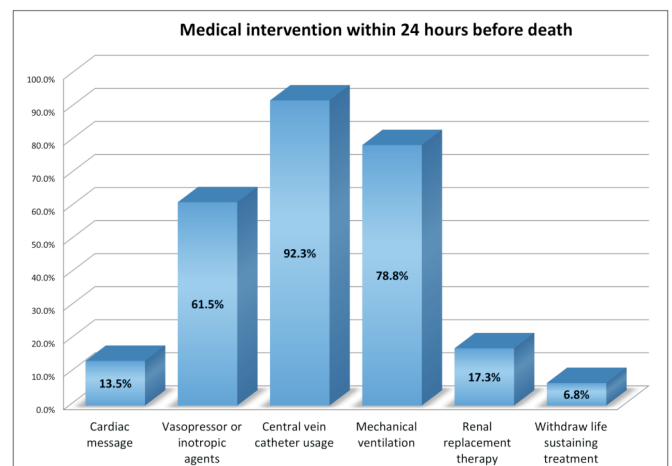

Fig 3. Life-support management and invasive procedures administered to terminal cirrhotic patients in the period 24 hours prior to death.

analysis of terminal hepatocellular carcinoma patients admitted to a hospice care unit previously determined that age is not significantly different between decompensated and compensated cirrhotic patients.[25] Another study in a palliative care unit showed patients with ESLD were significantly younger than those with other noncancer diseases.[7] Younger patients may be less likely to seek palliative care, due to expectation of a longer life span than elderly patients. However, higher severity and mortality rate was observed among younger patients in our study population. Identifying markers that can reliably predict prognosis in ICU cirrhotic patients may assist medical staff in the selection of candidates for palliative care. Within our study population, a MELD score of 24.5 appears to act as an effective cut-off point for predicting outcomes.

4.2. Palliative information before admission

Over one third of our study population died during hospitalization, indicating that these patients were at a late stage of life and mortality could be expected in the near future. Among these patients, very few interventions could improve survival and palliative care might be indicated for them. However, very few (2.5%) had DNR orders prior to admission. This could potentially be attributed to the patients' low average age and the difficulty of prognostication in non-malignant diseases.

Palliative care aims to optimize quality of life for patients and their families by anticipating, preventing, and treating suffering. It should be considered for patients with advanced or decompensated chronic diseases. It is necessary for physicians to explain disease status, prognosis, and the concept of palliative care to patients and families, and to discuss end-of-life care. A major barrier to obtaining palliative care is a lack of awareness among patients and their families, who often do not consider noncancer conditions to be terminal diseases. Compared to cancer patients, fewer patients with noncancer diseases are referred to palliative care.[8,26] This is despite the fact that these patients often experience similar illness severity, symptom burden, and prognosis. The need for palliative care in critical ESLD patients may also be underestimated. A recent study demonstrated a low frequency of palliative consultation in ESLD patients.[6] In line with previous studies, our results showed an extremely low rate of DNR consent prior to ICU admission.

Accurate estimation of the numbers of patients requiring palliative care is essential for service planning. A population-based study estimated that in a minimum of 63% of all deaths, patients required palliative care.[27] Regional requirement estimates could assist in evaluation of the sufficiency of palliative care service provision. However, local data sources necessary to calculate such estimates for cirrhotic patients are lacking. There is also a lack of guidance on timing in relation to provision of palliative care for ESLD patients.[28,29] Early discussion of end-of-life issues is essential for all patients with ESLD. Evidence has shown that implementation of early palliative care intervention improves symptom burden and reduces depression in ESLD patients.[30] Therefore, early identification and appropriate management of candidates who may benefit from palliative care is necessary.

4.3. Palliative care after admission

The key purpose of this study was to evaluate whether end-stage cirrhotic patients received appropriate care. Among those with higher disease severity, 52 (61.9%) patients died during hospitalization. In our opinion, all of these patients were candidates for hospice care. In fact, DNR was applied in 86.5% of patients; however, in

68.9% of these cases, DNR consent was given by an SDM less than 24 hours before death. This means that it was often too late to employ hospice care. This may be attributed to the unpredictable disease course of ESLD. Cirrhotic patients may not appear ill at the expected time and may not be considered to be at risk of dying; the onset and severity of complications can change prognosis rapidly and result in a rapid decline of physical function.[5,6,30] Furthermore, terminal patients are often excluded from decision making due to family members attempting to prevent feelings of hopelessness. DNR orders also tend to be decided by SDMs, particularly in ESLD patients due to a high frequency of communication difficulties resulting from hepatic encephalopathy.[30,31] SDMs often experience stress in making decisions and difficulty communicating truthfully with patients. They therefore generally take a longer time to reach a decision.[32]

Among the 52 ESLD patients who died during hospitalization, life support measures and invasive procedures were frequently employed. Over half of these patients received vasopressor/inotropic agents for hypotension or mechanical ventilation for respiratory failure. A proportion also received renal replacement therapy in the pre-dying period. These interventions can result in physical and psychological distress to patients, families, and medical staff, and often result in considerable expense. The high frequency of these interventions resulted from a lack of communication, education, and implementation of palliative care. Under these circumstances, life-prolonging treatments likely cause discomfort without any direct benefit and can be considered a disservice to patients. Invasive management and resuscitation are rarely beneficial in critically-ill ESLD patients.[33,34] Among ICU clinicians, perceptions of inappropriate care in patients with terminal illness have been frequently reported.[35,36] Some physician-related barriers to adequate communication within the medical team and with patients and families have also been described.[37] It is necessary to address these barriers to improve the quality of end-of-life care for patients and their families. Physicians have the ability to prevent patients from undergoing futile life-sustaining interventions with increased awareness of end-of-life issues and adequate communication.

There are some limitations in our study. First, this is a retrospective study in one hospital covering a single area. We were unable to collect population-based data to calculate a comprehensive estimation. Second, this observational study described the reality of clinical practice for ESLD patients. We were unable to investigate the impact of early integration of palliative care for study patients. Finally, most information was obtained by reviewing patient charts. This made it difficult to assess patients' physical and psychological symptom burden, which hindered objective evaluation of quality of life. Further evaluation about the impact of palliative care on patients' quality of life, like quality-of-life questionnaire, may be more informative to clinical health care teams.

In conclusion, only a very small proportion of patients had given DNR consent prior to their ICU admission. Instead of palliative care, many critical ESLD patients received futile life-support interventions shortly before death. In our study, MELD score seems one of the good predictors and reasonable markers. However, further large cohort to confirm the result is suggested. Therefore, end-stage cirrhotic patients and their families should be adequately informed about the natural course of the disease and adequate end-of-life care should be provided at an earlier stage in order to improve quality of life and avoid unnecessary invasive medical treatment.

Declaration of conflicts

All authors have seen and agree with the contents of the manu-

script and there are no conflicts of interests.

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