Intensive care utilization in patients with end-stage liver disease: A population-based comparative study of cohorts with and without comorbid hepatocellular carcinoma in taiwan

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ABSTRACT

Background: End-of-life intensive care may be futile and can be a cause of distress to both patients and their families. This study aimed to understand the utilization of intensive care and its associated factors in patients with End-stage liver disease (ESLD) during terminal hospitalization.

Methods: Population-based retrospective cohort study using the National Health Institute Research Database of Taiwan. All adult patients with ESLD who died during their hospitalization in 2010−2013 were included.

Findings: Of the 14,247 patients with ESLD, the majority (60·8%) was comorbid with hepatocellular carcinoma (HCC). Patients with ESLD only were younger, more deprived, more alcohol-related, and less likely to receive palliative care prior to terminal hospitalization (6·0% vs 29·2% with HCC). Compared to patients with comorbid HCC, relatively more patients without HCC were admitted to ICU (59·6% vs 22·3%), receiving CPR (11·1% vs 4·3%) and mechanical ventilation (36·3% vs 12·5%) during terminal hospitalization. Etiology of alcoholic hepatitis, esophageal varices, septicemia, pneumonia and respiratory failure, and renal failure were associated with a higher probability of ICU admission (adjusted rate ratio (aRR) range: 1·09−2·09). Prior palliative care was associated with lower probability of ICU admission (aRR range: 0·24−0·38).

Interpretation: The intensive care utilization by patients with ESLD in their terminal hospitalization was substantial in Taiwan. Those who are not comorbid with HCC need more attention, especially in terms of their palliative care needs, choices regarding intensive care, and their healthcare utilization.

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Introduction

End-stage liver disease (ESLD) is the final stage of liver disease when liver failure is irreversible and liver transplantation is the only curative treatment [1]. A global estimate reported it accounted for 2% of all deaths worldwide [2,3]. It is the seventh leading cause of death in Europe [4], and the 12th leading cause of death in the United States [5]. Compared to other terminal illness, it disproportionally affects younger age groups, which results in premature mortality, high loss of working years, as well as complex physical and psychosocial problems [6,7].

In Taiwan, ESLD is also a major cause of death and an important public health issue. Different from western countries, the leading etiology of liver disease in Taiwan is viral hepatitis (especially hepatitis B), rather than alcoholic hepatitis or non-alcoholic steatohepatitis [8,9]. Patients with hepatitis B-related cirrhosis have 1000 times higher risk of developing hepatocellular carcinoma (HCC) compared to those who are not carriers of hepatitis B surface antigen [10]. HCC is therefore a common comorbidity of patients with ESLD in Taiwan.

The priority of medical care for patients with ESLD is usually curative treatment rather than palliative care because these patients are younger and not seen to be at the end of life [6,11]. However, only a minority of these patients receive liver transplantation owing to organ shortages and strict eligibility criteria. The prognosis of ESLD is hard to determine, and some patients live prolonged periods of poor health, interrupted by repeated catastrophe, and die suddenly [11]. Owing to the lack of early consensus of goals of care and palliative care service,

Research in context

Evidence before this study

We searched three electronic databases, including Medline, Embase, and PsycINFO, using the search terms ("intensive care" OR "critical care") AND "end stage liver disease". No restriction on language was implemented. However, research evidence in this area was scarce, especially while these patients were approaching their end of lives. The utilization of intensive care and its associated factors in patients with end-stage liver disease during terminal hospitalization are worth exploring.

Added value of this study

In this population-based study of 14,247 decedents with end-stage liver disease, patients without hepatocellular carcinoma were significantly more likely to be admitted to intensive care unit than those with hepatocellular carcinoma (59·6% versus 22·3%). Prior palliative care was associated with a lower probability of intensive care utilization during terminal hospitalization.

Implication of all the available evidence

For patients with end-stage liver disease, those who were not comorbid with hepatocellular carcinoma need more attention especially in terms of their palliative care needs, choices regarding intensive care, and their healthcare utilization.

these patients are at risk of receiving more futile intensive care and aggressive treatments. Intensive care is not always beneficial to patients at the end of life [12,13]. It may cause psychological distress to the patients and their family, and may deprive them of the companionship of their close relatives [14–17]. Although research increasingly suggests that palliative care should be integrated into the care of patients with ESLD, there is still insufficient evidence of palliative care intervention in these patients in terms of its association with healthcare utilization or outcomes [18–20].

Since September 2009, the National Health Insurance of Taiwan has expanded its palliative care coverage from advanced cancers and motor neuron diseases to eight non-cancer diseases, including ESLD [21]. The utilization of palliative care in patients with ESLD can therefore be identified and analyzed using the nationwide routinely collected health data – the National Health Institute Research Database (NHIRD). It provides a valuable opportunity to understand how these patients utilize intensive care and palliative care, especially during the end of their lives. The change in healthcare utilization after the policy implementation in 2009 is also noteworthy. In addition, we hypothesized that the two groups ("ESLD without HCC" versus "ESLD with HCC") might be different in socio-demographic and clinical characteristics, so we explored and checked these differences.

The aims of this study are to investigate the utilization of intensive care in patients with ESLD in Taiwan, to explore the factors associated with intensive care utilization during terminal hospitalization, and to understand the difference between patients with and without comorbid HCC for targeted improvement.

Methods

Study design

We did a nationwide retrospective cohort study, using the National Health Institute Research Database (NHIRD) of Taiwan, 2010−2013. The study is reported according to the STROBE guidelines [22].

Data source

The NHIRD of Taiwan is a reliable resource of healthcare utilization data because of its universal coverage and comprehensive details of services. It consists of healthcare data from over 25 million enrollees, representing more than 99% of the entire population of Taiwan [23−27]. The accuracy of diagnosis of some major diseases in the NHIRD has been validated [23,28].

Patient cohorts

Our population of interest was all adult patients (18 years and older) with ESLD who died during their hospitalization between 2010 and 2013. Patients were identified as having ESLD by the code from Registry for Catastrophic Illness Patients Database (RCIPD), a subpart of the NHIRD. In Taiwan, once any major complication of decompensation occurs and becomes irreversible, the patients with ESLD can be registered in RCIPD by qualified gastroenterologists, hepatologists, or liver transplantation providers (mostly transplantation surgeons). After the registration, these patients are issued an ESLD Catastrophic Illness Card, which can be identified by the web-based electronic system during every outpatient visit or inpatient hospitalization and then recorded in the original claim data.

Patients were excluded if they had a diagnosis of cancer other than HCC (International Classification of Diseases, 9th revision, Clinical Modification [ICD-9-CM]: 155.0), if they had received liver transplantation, or if they were admitted for less than one day or more than 90 days.

Variables of Interest

The primary outcome was intensive care unit (ICU) admission during terminal hospitalizations. Secondary outcomes were cardiopulmonary resuscitation (CPR) and mechanical ventilation during terminal hospitalizations.

The explanatory variables were age (<45, 45−54, 55−64, 65−74, 75−84, 85+), sex (female, male), year of death (2010, 2011, 2012, 2013), income level (5 groups), region of residence (northern, middle, southern, eastern and offshore islands, and not mentioned), and reasons for terminal hospitalization. For each patient, the number of reasons for hospitalization could be single or multiple, from one (ESLD only), two (ESLD plus HCC or any other reason of interest) to a maximum of five in the dataset. The reasons we studied were either complications of liver cirrhosis (e.g. hepatic encephalopathy, esophageal varices, ascites, peritonitis, and hepatorenal syndrome) or the other most common diagnoses for hospitalization (> 5% of the whole study population), including: septicemia, pneumonia and respiratory failure, renal failure, and peptic ulcer disease. The income level was classified according to the Taiwan minimum monthly wage (17,280 New Taiwan Dollars [NTD]) and income quartiles of 2011[29]. Level 1 was defined as lower than minimum monthly wage (17,280 NTD); level 2 was defined as between minimum wage and Q1 (25,348 NTD); level 3 was defined as between Q1 and Q2 (equal to median: 32,132 NTD); level 4 was defined as between Q2 and Q3 (32,132 NTD); level 5 was defined as not less than Q3. For those who had no income (mostly dependent on a family member paying for the insurance, that is, the insurer), we considered the insurers' income instead. Patients with neither income nor any insurer were classified as lowest income level (level 1).

In addition, we traced back any claim in the year before the terminal hospitalization to identify patients' etiology of ESLD (viral, alcoholic, mixed viral and alcoholic, and others or not mentioned), number of comorbidities (using the items from Charlson index [30]. with ESLD and HCC deducted), and prior palliative care (palliative care unit admission or shared care by palliative care teams). In Taiwan, all the palliative care units are hospital-based and covered by

the National Health Insurance. For those who are in need of palliative care but unable to be admitted to the palliative care units, an outreach service can be provided to them by palliative care teams, which is called "shared care". This kind of service is also covered by the National Health Insurance of Taiwan. No matter palliative care unit admission or shared care is introduced to the patients and their family, several key issues would be discussed, including: patients' perception of the disease, goals of care, the ways to relieve total suffering, and the choices of treatments (including but not limited to do-not-resuscitate orders, withdrawing/withholding certain treatments, advance care planning).

Statistical Analysis

Numerical data was summarized using mean (standard deviation) or median (interquartile range) according to its distribution. Counts and percentages were used to describe categorical data. Bivariate analyses were performed to check the difference of socio-demographics, clinical characteristics, and utilization between patients with and without HCC. Student's *t*-test was applied to compare "age at death" because this variable was near-normal distribution. Wilcoxon rank-sum test was applied to compare "length of terminal hospitalization" since this variable was not normally distributed (relatively right skewed). As for the other variables, the Chi-square test was applied.

For factors associated with ICU admission, modified Poisson regression models with robust variance were applied [31]. Univariate analyses were firstly performed to check if there was an association between each individual explanatory variables and ICU admission, and the unadjusted rate ratio was obtained. Those which were statistically significant in univariate analysis ($p < 0.05$) were included in the multivariate modeling to evaluate the multiple adjusted associations. We used the threshold of 0.05 to select variables because with this scale of sample size, a statistical test might be powered to detect even very weak association. The length of stay of terminal hospitalization was treated as a confounding variable and was adjusted in the models. The strength of association was measured using the adjusted rate ratio (aRR), estimated from multivariable models [32−34]. For factors associated with CPR and mechanical ventilation, similar methods were used.

Potential interactions between variables were tested, and sensitivity analyses were carried out by running separate models omitting one of the concerned variables or taking interactions into considerations. We used Stata/SE 14 (STATA, College Station, TX) for all analyses.

Ethics approval and consent to participate

This study was approved by the ethical review of the Research Ethics Committee D of the National Taiwan University Hospital and the National Health Research Institutes, Taiwan. (NTUH-REC No.201508023 W, NHIRD-105−002) This study was based on fully anonymized records and therefore no personal data could be identified.

This study is based in part on data from the NHIRD provided by the National Health Insurance Administration, Ministry of Health and Welfare and managed by National Health Research Institutes. The interpretation and conclusions contained herein do not represent those of National Health Insurance Administration, Ministry of Health and Welfare or National Health Research Institutes of Taiwan.

Data Statement

According to the data agreement we signed with the National Health Research Institutes of Taiwan, we are not allowed to share our data.

Role of funding

Results

Between 2010 and 2013, a total of 14,847 terminal hospitalizations of adult patients with ESLD were identified. There were 383 hospitalizations (2·6%) less than one day and 144 hospitalizations (1·0%) more than 90 days. In addition, 73 patients received liver transplantation (0·5%) prior to the terminal hospitalizations. After excluding these 600 patients, a total of 14,247 patients were kept in this study finally. The mean age of death was 63·6 (standard deviation [SD] 13·6). Among them, 8664 (60·8%) patients had a comorbid HCC, and 5583 (39·2%) did not. There were more men (69·4%) than women (30·6%). The income level of these decedents was extremely low. A total of 9686 patients (68·0%) was diagnosed as having viral hepatitis. The annual deaths decreased steadily from 3925 in 2010 to 2904 in 2013. The percentage of patients utilizing palliative care in the year before the terminal hospitalization increased gradually, from 10·3% in 2010 to 30·0% in 2013. Apart from ESLD and HCC, hepatic encephalopathy was the most common reason for admission (30·2%), followed by septicemia (29·9%), pneumonia and respiratory failure (28·1%), and esophageal varices (20·9%).

The socio-demographic and clinical characteristics between ESLD patients with and without comorbid HCC were different (Table 1). Those who died without HCC were younger (60.0[SD 14·3] vs 66.0[SD 12·1]) and more deprived. While viral hepatitis accounted for 80% of patients with HCC, alcoholic hepatitis was the main cause of patients without HCC (54·3%). Patients without HCC were less likely to receive palliative care prior to terminal hospitalization (6·0% vs 29·2%). The length of stay of terminal hospitalization was longer in patients without HCC (median: 14 vs 12).

The results of ICU admission and other outcomes of interest are shown in Table 2. The intensive care utilization of patients with ESLD in their terminal hospitalization was substantial. Relatively more patients without HCC were admitted to ICU than those with HCC (59·6% versus 22·3%, risk ratio 2·67 [95% confidence interval: 2·56−2·80]). They also had a longer length of stay in ICU (median: 6 vs 4, $p < 0.001$). Similarly, relatively more patients without HCC were receiving CPR (11·1% vs 4·3%, risk ratio 2·57[2·27−2·91]) and mechanical ventilation (36·3% vs 12·5%, risk ratio 2·91[2·73−3·11]) during terminal hospitalization, compared to patients with comorbid HCC.

The trends of ICU admission during terminal hospitalization by the status of comorbid HCC in 2010−2013 are shown in Fig. 1. The ICU admission rate decreased gradually in those who had ESLD only, while it decreased steadily between 2010 and 2012 and slightly increased in 2013 in those who had comorbid HCC. Meanwhile, the palliative care utilization in the year before terminal hospitalization increased markedly in both groups, although the proportion is still very low in those who had ESLD only. (Fig. 2)

Table 3 demonstrates the factors associated with ICU admission in patients with ESLD in their terminal hospitalization. Esophageal varices (aRR 1·13 [95% confidence interval 1·08−1·18] in ESLD only group; aRR 1·78 [1·64−1·92] in ESLD plus HCC group), septicemia (aRR 1·12 [1·07−1·16]; 1·36 [1·25−1·48]), pneumonia and respiratory failure (aRR 1·26 [1·21−1·31]; 2·09 [1·94−2·25]), and renal failure (aRR 1·10 [1·05−1·15]; 1·38 [1·25−1·52]) were associated with higher probability of ICU admission in both groups. In addition, etiology of alcoholic hepatitis (aRR 1·09 [1·02−1·16]; 1·29 [1·14−1·46]) and residential area as middle part of Taiwan (aRR 1·06 [1·00−1·12]; 1·29 [1·17−1·42]) were associated with a higher chance of ICU admission. On the contrary, prior palliative care (in the year before terminal hospitalization) was significantly associated with lower

Table 1
Socio-demographic and clinical characteristics[a] of study population (N = 14,247).

Variable	ESLD only	ESLD + HCC	p-value
Number (%)	5583 (39.2%)	8664 (60.8%)	
Age mean(SD)	60.0(14.3)	66.0(12.1)	<0.001
Age group			<0.001
<45	923 (16.5)	388 (4.5)	
45−54	1319 (23.6)	1315 (15.2)	
55−64	1242 (22.3)	2283 (26.4)	
65−74	1083 (19.4)	2482 (28.7)	
75−84	846 (15.2)	1807 (20.9)	
85+	170 (3.0)	389 (4.5)	
Sex			0.020
Female	1770 (31.7)	2587 (29.9)	
Male	3813 (68.3)	6077 (70.1)	
Year of death			0.030
2010	1598 (28.6)	2327 (26.9)	
2011	1518 (27.2)	2317 (26.7)	
2012	1384 (24.8)	2199 (25.4)	
2013	1083 (19.4)	1821 (21.0)	
Income level			<0.001
1 (less than minimum wage)	1780 (31.9)	2115 (24.4)	
2 (minimum wage - Q1)	2678 (48.0)	4302 (49.7)	
3 (Q1 - Q2)	343 (6.1)	593 (6.8)	
4 (Q2 − Q3)	358 (6.4)	606 (7.0)	
5 (more than Q3)	424 (7.6)	1048 (12.1)	
Region of residence			<0.001
Northern Taiwan	1694 (30.3)	2879 (33.2)	
Middle	1255 (22.5)	1527 (17.6)	
Southern	2073 (37.1)	3797 (43.8)	
Eastern and offshore islands	287 (5.1)	279 (3.2)	
Not mentioned	274 (4.9)	182 (2.1)	
Etiology			<0.001
Viral	1569 (28.1)	5943 (68.6)	
Alcoholic	1842 (33.0)	542 (6.3)	
Mixed	1192 (21.4)	982 (11.3)	
Not mentioned or others	980 (17.6)	1197 (13.8)	
Comorbidity (ESLD deducted)			<0.001
0	777 (13.9)	0 (due to HCC+)	
1	1800 (32.2)	1946 (22.5)	
2	1611 (28.9)	3406 (39.3)	
3	885 (15.9)	2127 (24.6)	
4+	510 (9.1)	1185 (13.7)	
LOS of terminal hospitalization (days) median (IQR), range	14 (19), range 1−90	12 (17), range 1−90	<0.001
Prior palliative care			<0.001
No	5246 (94.0)	6136 (70.8)	
Yes	337 (6.0)	2528 (29.2)	
Reason for terminal hospitalization			
HCC	0 (0)	8664 (100)	
Hepatic encephalopathy	1919 (34.4)	2378 (27.5)	<0.001
Septicemia	2574 (46.1)	1689 (19.5)	<0.001
Pneumonia and respiratory failure	2434 (43.6)	1565 (18.1)	<0.001
Esophageal varices	1230 (22.0)	1750 (20.2)	0.009
Ascites	1037 (18.6)	1692 (19.5)	0.157
Renal failure	1391 (24.9)	1063 (12.3)	<0.001
Peritonitis	742 (13.3)	691 (8.0)	<0.001
Peptic ulcer disease	381 (6.8)	532 (6.1)	0.104
Hepatorenal syndrome	365 (6.5)	433 (5.0)	<0.001

[a] N (%) unless otherwise stated.

Table 2
Intensive care unit admission, cardiopulmonary resuscitation, and mechanical ventilation in terminal hospitalization (N = 14,247).

Variable	ESLD only N = 5583	ESLD + HCC N = 8664	p-value
ICU admission			<0.001
Yes	3329 (59.6)	1932 (22.3)	
No	2254 (40.4)	6732 (77.7)	
If Yes: **LOS in ICU:** median (IQR), range	6 (11), range 1−82	4 (6), range 1−60	<0.001
Cardiopulmonary resuscitation			<0.001
Yes	618 (11.1)	373 (4.3)	
No	4965 (88.9)	8291 (95.7)	
Mechanical ventilation			<0.001
Yes	2028 (36.3)	1080 (12.5)	
No	3555 (63.7)	7584 (87.5)	

The factors associated with CPR and mechanical ventilation in terminal hospitalization were shown in supplemental material eTable 1 and eTable 2. Patients with pneumonia and respiratory failure had higher chances of receiving CPR during terminal hospitalization (aRR 1·22 [1·04−1·42] in ESLD only group; 2·18 [95% 1·77−2·67] in ESLD plus HCC group), and those received palliative care before admission had lowest chances of receiving CPR (aRR 0·18 [0·08−0·44]; 0·09 [0·05−0·17]). As for mechanical ventilation, esophageal varices (aRR 1·28 [1·19−1·37]; 1·66 [1·48−1·85]), septicemia (aRR 1·09 [1·02−1·16]; 1·21 [1·07−1·36]), pneumonia and respiratory failure (aRR 1·85 [1·72−1·99]; 3·44 [3·08−3·84]) were associated with higher chances of receiving mechanical ventilation. Those who received palliative care before admission were less likely to receive mechanical ventilation (aRR 0·21 [0·14−0·32]; 0·14 [0·11−0·19]).

Discussion

This is the first population-based study evaluating the utilization of intensive care in end-of-life patients with ESLD, particularly in Taiwan where viral hepatitis is the leading cause of ESLD. The majority (60·8%) of our study population was comorbid with HCC. The findings showed a considerable difference between patients with and without comorbid HCC in terms of sociodemographic characteristics and intensive care utilization. Patients without HCC were less likely to receive palliative care prior to terminal hospitalization. Relatively more patients without HCC were admitted to ICU, receiving CPR or mechanical ventilation during terminal hospitalization. Etiology of alcoholic hepatitis, esophageal varices, septicemia, pneumonia and respiratory failure, and renal failure were associated with a higher probability of ICU admission in both groups. On the contrary, prior palliative care was associated with a lower chance of ICU admission, as well as receiving CPR or mechanical ventilation.

In our study, the utilization of intensive care was substantial in patients with ESLD during their terminal hospitalization (overall 39·6%), which was much higher than that of terminal cancer patients in Taiwan (17·8% in last month of life)[35]. The reasons why patients without HCC were more likely to be admitted to ICU (59·6%) during their terminal hospitalization (compared to those with comorbid HCC: 22·3%) need further investigation. It is possible that without the diagnosis of HCC, the disease trajectory was more unpredictable, and this uncertainty was more challenging for healthcare professionals to manage [36]. Consequently, the goals of care might mainly focus on curative treatment only and lead to intensive interventions or even futile management [6,11]. A similar finding was shown in a single-center study of patients with ESLD who had been denied liver transplantation. As high as 48% of the study population were subsequently admitted to ICU and more than half of them died in ICU [37].

Although we highlighted the intensive care utilization in patients with ESLD during their terminal hospitalization, it does not

probability of ICU admission in both groups (aRR 0·38 [0·31−0·47]; 0·24 [0·21−0·29] respectively). Interestingly, age played a different role in the two groups. For patients with comorbid HCC, there was no significant difference of ICU admission rate among different age groups; however, for patients without HCC, a trend of decreasing ICU admission rate was noted if they were older. The sensitivity analyses demonstrated the robustness of the main results and key messages.
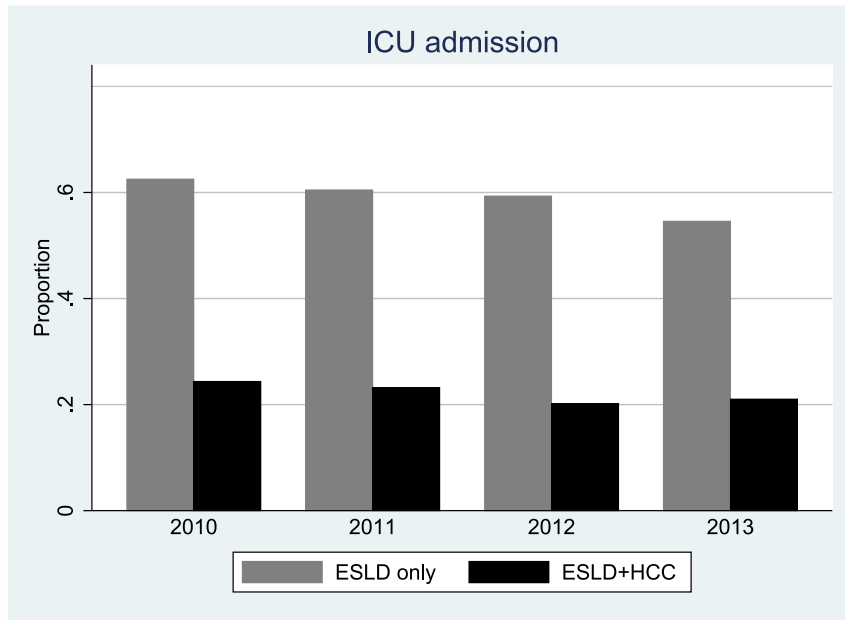
Fig. 1. Time trends of intensive care unit admission rate, with and without comorbid hepatocellular carcinoma, Taiwan 2010−2013. (ICU: intensive care unit. ESLD: end-stage liver disease. HCC: hepatocellular carcinoma.).
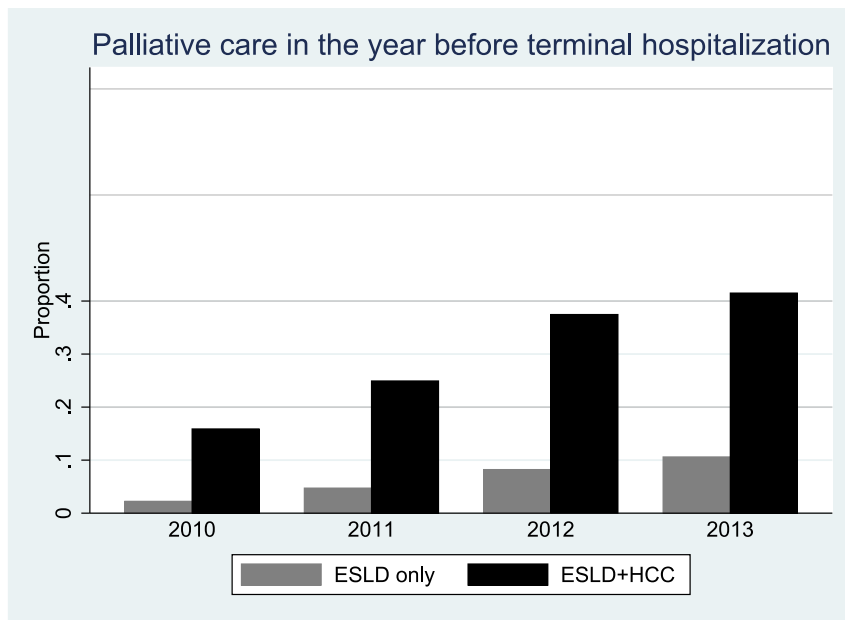

Fig. 2. Time trends of palliative care in the year before terminal hospitalization of study population, with and without comorbid hepatocellular carcinoma, Taiwan 2010−2013. (ESLD: end-stage liver disease. HCC: hepatocellular carcinoma.).

necessarily imply that intensive care is "inappropriate" or "too aggressive". As we illustrated in Table 1, some of the reasons for hospitalization seemed to be reversible at the beginning of the admission. Our findings reflect the challenges mentioned earlier: these patients might not be seen at the end of life, and the prognosis was difficult to predict. What are the potential clinical triggers for end-of-life discussion in these patients? Arvaniti et al. found that infections increase mortality four-fold and 30% of patients die within one month in patients with liver cirrhosis [38]. In addition to infection, Mazzarelli et al. proposed several clinical triggers for referral of ESLD patients to the palliative care service, including: those who are awaiting liver transplantation or are not eligible for transplantation, have had more than two hospital admissions with decompensated liver disease in previous one year, have complications related to ESLD

(refractory ascites, hepatic encephalopathy), are older and more frail, have HCC, Child-Pugh classification C, Model For End-Stage Liver Disease (MELD) score >=20, acute-on-chronic liver failure (ACLF) grade 2 or 3, or NECPAL CCOMS-ICO suggestion of high mortality risk [36,39,40]. Our findings suggest that palliative care should be initiated at the beginning of hospitalization or even earlier whenever there's a need or these triggers happen. The coexistence of intensive care and palliative care in patients with ESLD may seem paradoxical in the past, but nowadays intensive care has been as concerned with palliation in many aspects [41−43].

Our study showed that prior palliative care was associated with less utilization of intensive care, CPR, and mechanical ventilation during the terminal hospitalization of patients with ESLD, which was similar to the results demonstrated by Patel et al. that inpatient

Table 3
Factors associated with intensive care unit admission in terminal hospitalization.

Variable	ESLD only (N = 5583)		ESLD+HCC (N = 8664)	
	Unadjusted RR (95% CI)	Adjusted RR (95% CI)	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
Age of death (ref: <45)				
45−54	0.96 (0.91−1.02)	0.98 (0.93−1.03)	1.13 (0.92−1.39)	1.13 (0.94−1.35)
55−64	0.88 (0.83−0.93)	0.93 (0.88−0.99)	1.03 (0.85−1.26)	1.05 (0.88−1.26)
65−74	0.74 (0.69−0.79)	0.81 (0.75−0.88)	0.95 (0.78−1.16)	0.99 (0.83−1.18)
75−84	0.65 (0.60−0.71)	0.72 (0.65−0.79)	0.88 (0.71−1.08)	0.92 (0.76−1.11)
85+	0.54 (0.45−0.66)	0.60 (0.50−0.73)	0.87 (0.67−1.15)	0.91 (0.71−1.17)
Sex (ref: female)				
male	1.18 (1.12−1.24)	0.98 (0.93−1.04)	(not included)	
Year of death (ref: 2010)				
2011	0.97 (0.91−1.02)	0.97 (0.92−1.02)	0.95 (0.86−1.06)	1.02 (0.93−1.12)
2012	0.95 (0.90−1.01)	0.97 (0.92−1.02)	0.83 (0.74−0.92)	1.05 (0.95−1.16)
2013	0.87 (0.82−0.93)	0.95 (0.90−1.01)	0.86 (0.77−0.97)	1.15 (1.04−1.28)
Region of residence (ref: Northern)				
Middle	1.08 (1.02−1.14)	1.06 (1.00−1.12)	1.36 (1.22−1.51)	1.29 (1.17−1.42)
Southern	0.94 (0.89−0.99)	0.95 (0.90−1.00)	0.99 (0.90−1.08)	1.03 (0.94−1.13)
Eastern and offshore islands	1.14 (1.05−1.25)	1.08 (1.00−1.18)	0.96 (0.75−1.22)	1.11 (0.89−1.39)
Not mentioned	1.01 (0.91−1.12)	0.95 (0.86−1.05)	1.36 (1.07−1.73)	1.38 (1.11−1.73)
Etiology (ref: viral only)				
Alcoholic only	1.32 (1.25−1.40)	1.09 (1.02−1.16)	1.65 (1.44−1.88)	1.29 (1.14−1.46)
Mixed (viral and alcoholic)	1.19 (1.11−1.27)	1.03 (0.96−1.10)	1.40 (1.25−1.57)	1.16 (1.04−1.29)
Not mentioned or others	1.10 (1.02−1.18)	1.08 (1.01−1.16)	1.33 (1.20−1.48)	1.22 (1.11−1.35)
Comorbidity (ESLD deducted, ref: 0, 1 each)				
1	0.99 (0.93−1.06)	1.03 (0.97−1.09)	(ref group)	(ref group)
2	0.92 (0.86−0.98)	1.01 (0.95−1.07)	1.05 (0.94−1.17)	1.06 (0.96−1.17)
3	0.84 (0.77−0.91)	0.96 (0.89−1.04)	1.16 (1.03−1.30)	1.15 (1.04−1.29)
4+	0.82 (0.74−0.91)	0.97 (0.88−1.07)	1.24 (1.09−1.42)	1.22 (1.08−1.39)
Prior palliative care (ref: no)				
Yes	0.31 (0.25−0.39)	0.38 (0.31−0.47)	0.20 (0.17−0.23)	0.24 (0.21−0.29)
Reasons for terminal hospitalization				
Hepatic encephalopathy (ref: no)	0.77 (0.74−0.82)	0.87 (0.83−0.91)	0.69 (0.63−0.77)	0.86 (0.78−0.94)
Ascites (ref: no)	0.65 (0.60−0.70)	0.76 (0.70−0.82)	0.56 (0.49−0.64)	0.70 (0.62−0.80)
Esophageal varices (ref: no)	1.17 (1.12−1.23)	1.13 (1.08−1.18)	1.84 (1.70−2.00)	1.78 (1.64−1.92)
Hepatorenal syndrome (ref: no)	0.76 (0.68−0.86)	0.87 (0.79−0.98)	0.71 (0.57−0.89)	0.89 (0.72−1.10)
Septicemia (ref: no)	1.22 (1.17−1.27)	1.12 (1.07−1.16)	1.51 (1.39−1.65)	1.36 (1.25−1.48)
Pneumonia and respiratory failure (ref: no)	1.40 (1.35−1.47)	1.26 (1.21−1.31)	2.64 (2.45−2.84)	2.09 (1.94−2.25)
Renal failure (ref: no)	1.19 (1.13−1.25)	1.10 (1.05−1.15)	1.48 (1.33−1.65)	1.38 (1.25−1.52)

palliative care was associated with lower procedure burden [44]. Also, as shown in Figs. 1 and 2, while the proportion of palliative care before terminal hospitalization increased between 2010 and 2013, the utilization of ICU in terminal hospitalization decreased gradually in both groups of our study population. Although "early palliative care" has been shown to improve quality of life and to reduce symptom intensity in cancer patients [45], there is still a lack of evidence in its effect on patients with ESLD. To be noted, healthcare providers may not have optimal knowledge and understanding in early palliative care. A survey of liver transplant service providers in the United States showed that these participants described palliative care as "end-of-life care only"[46], which might result in late or even no referral. Low et al. also identified that among the healthcare professionals, there is a lack of skills and confidence to communicate with ESLD patients and their families and a lack of healthcare options if patients' condition deteriorating [47]. It is necessary to have more collaboration between different healthcare providers to provide empathetic communication with patients about their prognosis, advance care planning, symptom management, and quality of life.

There is a marked difference between patients with and without comorbid HCC in our study, which has not been highlighted in previous studies. The two groups significantly differed from each other in age, income level, and etiology of liver disease (alcoholic vs viral hepatitis). While the incidence and prevalence of viral hepatitis have decreased owing to vaccination (especially for hepatitis B)[48] and the improvement of medicine and healthcare coverage in Taiwan, alcoholic hepatitis may play an increasingly important role in the development of ESLD, resulting in tremendous personal health loss and social costs. Those who abuse or misuse alcohol might also use

more than one psychoactive substance, which makes healthcare more challenging [49]. Their healthcare utilization patterns need more attention, from the diagnosis of liver disease, disease progression, confirmation of cirrhosis, decompensation, to either liver transplantation or end of lives. In addition, the equality of health care and the accessibility of standard care as well as palliative care in these patients need further investigation.

Regarding clinical factors, esophageal varices was the only complication of decompensation that was constantly associated with higher intensive care utilization. Esophageal varices bleeding is characterized as vomiting large amounts of blood and probable sudden loss of consciousness, and these patients deteriorate abruptly. By contrast, other complications develop in a subtle way and the progression is relatively slow. That may be the reason why esophageal varices were associated with higher chance of ICU admission (in both groups), CPR (in ESLD only group), and mechanical ventilation (in both groups). Not surprisingly, septicemia, pneumonia and respiratory failure, and renal failure were associated with higher probability of ICU admission and mechanical ventilation. In these cases, preventive strategies may be more helpful than picking up the pieces in the end. In addition, the factors identified in our study may contribute to identifying the subsets of patients with ESLD who are most likely to benefit from palliative care and advance care planning.

Our study has several limitations. First, the causal relationship between intensive care utilization and explanatory factors cannot be easily established in this retrospective cohort study. Second, some findings related to socio-demographic factors may be subject to ecological fallacy, and the hospital-level factors (e.g. hospital size, ownership, hospital teaching status, infrastructure of intensive care and

palliative care, ICU bed availability) were not contained in our dataset. Third, although the provision of ICU admission was mainly initiated by physicians, the understanding of disease status, the willingness to receive further treatments, and personal preferences were still important. The physicians' attitude and concept of palliative care also vary across different healthcare settings. All these factors were not available in the NHIRD. Forth, there is a lack of other relevant clinical factors, such as severity of liver disease, results of clinical exams or laboratory findings, or previous therapies for HCC. However, according to our inclusion criteria by using RCIPD, our study population were relatively homogeneous (at least Child-Turcotte-Pugh class B and mostly class C). Fifth, there was no data showing who were listed for liver transplantation in our dataset. In fact, the organ donation rate of Taiwan has been around 4·7 to 7·2 per million people per year, which is much lower than that in Western countries [50]. In our study, we excluded those who had received liver transplantation because their healthcare utilization was markedly different from other ESLD patients. Finally, the NHIRD was not established for end-of-life research, so it was difficult to access the patients' symptoms or quality of life as well as the quality of palliative care, which may be related to the utilization of intensive care. The findings of our study should be interpreted with caution and correlated with clinical context.

In conclusion, the intensive care utilization by patients with ESLD in their terminal hospitalization was substantial in Taiwan. Prior palliative care is associated with a lower probability of intensive care utilization during terminal hospitalization. Those who are not comorbid with HCC need more attention especially in terms of their palliative care needs, choices regarding intensive care, and their healthcare utilization.

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Declarations

Availability of data and material
According to the data agreement we signed with the National Health Research Institutes of Taiwan, we are not allowed to share our data.

Competing interests

The authors declare that they have no potential competing interests.

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Authors' contributions

JKP and WG designed the study. HHC and JKP applied for the dataset. JKP performed analysis and wrote the first draft, supervised by WG. HHC gave advice related to the healthcare system and clinical experience in Taiwan. IJH provided clinical academic input in palliative care. JKP, WG and HHC had full access to all data in the study. All authors reviewed the findings, agreed on the interpretation, contributed to writing the paper, and read and approved the final version.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2020.100357.

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