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Prevalence and outcome of cirrhosis patients admitted to UK intensive care: a comparison against dialysis-dependent chronic renal failure patients

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Abstract *Purpose:* Patients with decompensated liver cirrhosis who are admitted to intensive care units (ICU) are perceived, within the UK, as having a particularly poor prognosis. *Methods:* We performed a descriptive analysis of cirrhosis patients admitted to general critical care units 1995–2008 compared to patients admitted with pre-existing chronic renal failure. Data were obtained from the Intensive Care National Audit and Research Centre Case Mix Programme Database incorporating 192 adult critical care units in England, Wales and Northern Ireland. *Results:* Cirrhosis accounted for 2.6 % (16,096 patients) of total admissions with mean age 52.5 years and male preponderance (~60 %). Hospital mortality was high (>55 %) although this improved 5 % in recent years, and median length of stay was short (2.5 days). Mortality in cirrhotics with severe sepsis requiring organ support was 65–90 %, compared to 33–39 % in those without. Conversely, patients with chronic renal failure had lower mortality (42 %) despite similar characteristics and higher acute physiology and chronic health evaluation (APACHE) II scores. The APACHE II score underpredicted mortality in cirrhotics. *Conclusions:* Cirrhosis patients exhibit worse outcomes compared to pre-existing renal failure patients, despite similar characteristics. Survival worsens considerably with organ failure, especially with sepsis. They represent a small number of admissions, albeit increasing over recent years, and, in general, have a short ICU stay. Patients with single organ failure have acceptable survival rates and mortality has improved; although we have no data on those refused ICU admission potentially causing survival bias. Given the extremely high mortality in patients with multi-organ failure, support should be limited/withdrawn in such patients.

Keywords Cirrhosis · Chronic renal failure · Intensive care · Sepsis · Organ support · ICNARC

Abbreviations

APACHE	Acute physiology and chronic health evaluation
CCMDS	Critical care minimum data set
CMPD	Case mix programme database
CRF	Chronic renal failure patients requiring renal replacement therapy prior to ICU admission
ICNARC	Intensive Care National Audit and Research Centre
ICU	Intensive care unit
PMH	Past medical history
RRT	Renal replacement therapy

Introduction

Liver disease is the fifth leading cause of death in the UK and the second commonest cause of death in middle-aged men [1]. Management of complications of cirrhosis, such as gastrointestinal bleeding, sepsis or renal failure, frequently involves intensive care unit (ICU) admission [2]. However, many studies report a poor prognosis with an overall hospital mortality of 44–71 % [3–10]. Patients admitted for airway protection following an upper gastrointestinal bleed fare better with a mortality of 20 % [11]. However, mortality in those with organ failure such as septic shock or hepatorenal syndrome may approach 85–100 % [12–15]. An improvement of mortality over time has been described [5]; however a recent study from a specialist liver transplant centre showed overall hospital mortality of 54 %, which increased to 89 % in patients with three organ failures after three days of ICU care. These figures are similar to those previously reported [16]. A valid criticism of these studies is their reliance upon cohorts from single specialist centres that often provide liver transplantation, with the largest cohort comprising 582 patients [3].

Liver transplantation is the only curative therapy for established cirrhosis, giving excellent 5-year survival rates of 75 % [17]. However, as only approximately 650 are performed annually in the UK, the majority of cirrhotic patients presenting acutely to hospital will not be listed for transplantation. US studies report high costs in caring for cirrhotics in critical care, and these are increased in non-survivors [18, 19]. Moreover, even those who survive to hospital discharge subsequently have a poor prognosis, with a median survival of only 4 months if their admission acute physiology and chronic health evaluation (APACHE) III score exceeded 90, and 17 months if below 90 [20]. In addition, 72 % of survivors reported a poor quality of life [21].

It is thus not surprising that a common perception within the UK is that large numbers of cirrhosis patients are admitted to ICU for lengthy periods of time and these patients fare far worse than most other patients. However no study to date has accurately addressed this. We had three original study aims, to determine:

1. The numbers of cirrhosis patients admitted to ICU and their length of stay.
2. Whether cirrhosis patients actually have poorer outcomes than patients with other chronic medical conditions (in this case dialysis dependent chronic renal failure—CRF).
3. Whether the advances in ICU management during the study period have improved outcome in patients with cirrhosis.

With the increasing burden of liver disease in the UK, a limited number of ICU beds and the high cost of care, in these times of likely strict economic rationing we consider our study well-timed.

To address these three issues we interrogated data from the Intensive Care National Audit and Research Centre (ICNARC) Case Mix Programme Database (CMPD) to assess characteristics and outcomes for admissions to adult general critical care units in England, Wales and Northern Ireland over a 12-year period with advanced liver disease or requiring chronic renal replacement therapy prior to admission. Dialysis-dependent CRF patients were chosen as a comparator as their 1-year mortality of 20 % [22] is similar to those with advanced liver cirrhosis (Childs Pugh B) [23] and a high hospital mortality (43 %) following ICU admission is also described [24]. As effective organ support exists for such patients unlike those with advanced chronic liver disease, the latter may be expected to be more unwell on admission. We therefore included APACHE score data in our analysis in an attempt to reduce this bias. As sepsis is a major problem in both cirrhosis [2] and dialysis patients [25], with defects in innate immunity described in each [26, 27], and that requirement for organ support is considered to carry a particularly poor prognosis in cirrhosis [19], we examined these factors in a priori identified subsets. None of these cirrhosis patients analysed were transplanted during their admission and as a comparison we have also included data from patients who underwent liver transplant during this period.

Finally, the value of several predictive scoring systems has been previously examined in an attempt to identify cirrhotic patients who might benefit from ICU admission [3–10, 28]. However, no score has been considered sufficiently accurate to be included in routine clinical practice within the UK. We therefore compared the predictive power of the two scoring systems collected by ICNARC in these patients, namely the APACHE II score and the ICNARC risk prediction model [29].

Patients and methods

The Case Mix Programme is the national comparative audit of adult, general critical care units (ICUs and combined intensive care and high-dependency units) in England, Wales and Northern Ireland, coordinated by ICNARC. The database (CMPD) contains pooled case mix and outcome data on consecutive admissions to participating units, which have undergone extensive validation. Data are gathered to precise rules and definitions by trained collectors [30]. The CMPD has been independently assessed to be of high quality [31]. Support for the collection and use of patient-identifiable data without consent has been obtained under Section 251 of the NHS Act 2006 [approval no. PIAG 2–10(f)/2005]; ethical approval was therefore not required. Data were obtained

for all adult patients considered to have cirrhosis as a reason for admission or past medical history (PMH) from 626,953 admissions to 192 general ICUs between December 1995 and June 2008.

Admissions in the CMPD with cirrhosis were identified from either the 'primary', 'secondary' or 'ultimate primary reason for admission' fields, from either of two other conditions relevant to the admission, and from their PMH. Reasons for admission and other conditions relevant to admission are coded using the ICNARC Coding Method [31]. Case selection was divided into four specific groups:

(1) *Reason for admission with cirrhosis-related complications*. Any of the following conditions as primary or secondary reason for admission, and not identified as a liver transplant admission: oesophageal varices; bleeding gastric varices; variceal bleeding; infective hepatitis; alcoholic cirrhosis; acute alcoholic hepatitis; chronic cirrhosis cause not defined; autoimmune hepatitis; primary hepatic tumour and portal hypertension.
(2) *Past medical history of cirrhosis*. Admissions with any of the above conditions as an ultimate primary reason for admission, or other conditions relevant to the admission (and not a primary or secondary reason for admission), or any of the following conditions in their PMH that were evident in the 6 months prior to admission to the unit: biopsy-proven cirrhosis; portal hypertension; hepatic encephalopathy.
(3) *Chronic renal failure patients*. Admissions with any of the following: admission currently requiring chronic renal replacement therapy for irreversible renal disease or received in the 6 months prior to admission. This includes, but is not limited to, chronic haemodialysis, chronic haemofiltration and chronic peritoneal dialysis.
(4) *Liver transplant*. As a primary or secondary reason for admission.

A statistical analysis plan was agreed a priori:

Descriptive statistics

Case mix and physiology

Organ system failures were identified according to established definitions [32]. Severity of illness was measured by the APACHE II acute physiology score [33] and the ICNARC physiology score [29]. Both scores encompass a weighting for acute physiology defined by derangement from the normal range for 12 physiological variables in the first 24 h following admission to ICU. The APACHE II score additionally encompasses weighting for age and PMH of specified conditions. Patients were defined as having severe sepsis if they met at least three of the four systemic inflammatory response syndrome (SIRS) criteria with evidence of infection and at least one organ dysfunction during the first 24 h following ICU admission. Physiological definitions of SIRS criteria and organ dysfunctions were matched to those used in the PROWESS trial [34]. Advanced respiratory support was indicated by admissions receiving one or more of the following: invasive mechanical ventilatory support; bilevel positive airway pressure (BiPAP) applied via a translaryngeal tracheal tube or a tracheostomy; continuous positive airway pressure (CPAP) via a translaryngeal tracheal tube; and extracorporeal respiratory support. Renal support was defined as patients receiving continuous veno-venous haemofiltration or daily intermittent haemodialysis.

Outcome and activity

Survival data, ICU and total hospital length of stay were extracted at discharge from the ICU and at ultimate discharge from the acute hospital. Readmissions to ICU within the same hospital stay were identified from postcode, date of birth and sex of the patient, and were not included in analyses of acute hospital mortality. A comparison was made between patients admitted between 1995–2003 and 2004–2008.

Analysis of cirrhosis and chronic renal replacement therapy patients that had a diagnosis of severe sepsis and/or received mechanical ventilation and/or renal replacement therapy from two patient subsets

Data were collected from (1) a subset of patients that took part in a separate audit of specific treatment (64,063 admissions to 87 ICUs, 1 May 2003—29 April 2005) and (2) a further subset of patients contributing data for an updated version of the CMPD, the critical care minimum data set (CCMDS), collected from 18,564 patients admitted to 75 ICUs between 15 April 2006 and 29 June 2008.

Prognostic ability of APACHE II and ICNARC model in cirrhosis admissions

These models were evaluated for discrimination (ability of the model to distinguish survivors from nonsurvivors), by assessing the area under the ROC curve (AUROC or *c* index) [35], calibration (accuracy of the estimated probability of survival) by the Hosmer-Lemeshow C* statistic [36] and Cox's calibration regression [37] and the standardised mortality ratio (SMR). Patients who stayed <8 h in the ICU were excluded from calculation of

APACHE II scores and probabilities. There were no exclusions from the ICNARC model.

All analyses were performed using Stata 9.2 (Stata Corp., College Station, TX, USA).

Results

A total of 626,953 admissions to 192 adult general critical care units in England, Wales and Northern Ireland from 1 December 1995 to 30 June 2008 were included in the analysis.

Patients with liver cirrhosis

Cirrhosis accounted for 2.6 % of all admissions (16,096 patients), 1.8 % as a primary or secondary reason for admission and 0.8 % in their past history (Table 1). Patients had a mean age of 52–55 years, a male preponderance (~60 %), hypotension on admission and a mean APACHE II score of 19–22. Median critical care length of stay was short (2.2–2.6 days). The incidence of sepsis in patients with a past history of cirrhosis was considerably higher than in those with a liver-specific admission (28 vs. 10.2 %). Overall hospital mortality exceeded 55 %. Table 2 shows that both ICU and acute hospital mortality improved by approximately 5 % in cirrhosis patients admitted between 2004 and 2008 compared to 1995–2003. Also approximately 1,000 more patients with cirrhosis were admitted during 2004–2008 compared to 1995–2003.

Patients with chronic renal failure prior to admission

CRF patients accounted for 1.4 % of all admissions (8,991 patients). Compared to cirrhotics, mean age (58.5 years), male preponderance (60 %), hypotension on admission and APACHE II score (24.6) were similar (Table 1). Median ICU length of stay was also short (2 days), the incidence of sepsis was similar (25 %), but overall hospital mortality (42 %) was lower.

Subset analyses

(1) A total of 64,063 admissions to 87 ICUs were analysed in the audit of specific treatments performed between 2003 and 2005. Of these, 1,772 patients were admitted with cirrhosis (2.8 %) and 801 patients with pre-existing CRF requiring dialysis. In these cohorts, 883 patients with cirrhosis as a primary/secondary reason for admission, 424 with a past history of cirrhosis and 648 with CRF either developed severe sepsis before or within the first 24 h of admission, and/or received mechanical ventilation and/or renal replacement therapy during their ICU stay (Table 3). Hospital mortality was higher in cirrhotics (65 vs. 48 %) despite similar APACHE II score, age, admission blood pressure and ICU length of stay. Likewise, if organ support was required the cirrhosis

Table 1 All admissions in the Case Mix Programme Database

	Cirrhosis as primary or secondary reason for admission	Cirrhosis in past medical history	Chronic renal replacement therapy	Liver transplant
Number of admissions (%)	11,333 (1.8)	4,763 (0.8)	8,991 (1.4)	2,340 (0.4)
Age (years), mean (SD)	52.2 (13.1)	55.6 (14.3)	58.5 (15.7)	50.5 (11.9)
Sex (male), *n* (%)	7,036 (62.1)	2,825 (59.3)	5,423 (60.3)	1,410 (60.3)
APACHE II score, mean (SD)	19.0 (8.1)	22.0 (8.4)	24.6 (7.0)	16.0 (6.4)
ICNARC model score, mean (SD)	22.9 (11.3)	23.7 (11.3)	24.5 (9.6)	15.9 (8.0)
Lowest mean arterial pressure (mmHg), mean (SD)	62.3 (15.3)	62.0 (15.6)	64.7 (18.5)	70.5 (12.4)
Severe sepsis in first 24 h of admission, *n* (%)	1,133 (10.0)	1,343 (28.2)	2,259 (25.1)	50 (2.1)
Critical care unit mortality, *n* (%)	4,640 (40.9)	1,835 (38.5)	2,130 (23.7)	137 (5.9)
Ultimate acute hospital mortality[a], *n* (%)	6,136 (57.4)	2,350 (55.4)	3,377 (42.1)	216 (10.1)
Critical care unit length of stay (days), median (IQR)				
Unit survivors	2.3 (1.0–5.7)	2.8 (1.1–6.8)	2.0 (0.9–4.2)	1.8 (1–3.3)
Unit non-survivors	2.0 (0.7–5.9)	2.2 (0.8–6.1)	2.0 (0.7–6.7)	7.9 (2.4–19.3)
All	2.2 (0.9–5.8)	2.6 (1.0–6.6)	2.0 (0.9–4.7)	1.8 (1–3.8)
Total acute hospital length of stay (days)[a], median (IQR)				
Hospital survivors	19 (10–36)	23 (13–44)	22 (11–46)	21 (13–35)
Hospital non-survivors	8 (3–17)	10 (3–21)	15 (5–34)	26 (12–52)
All	12 (5–25)	15 (7–31)	19 (9–41)	21 (13–37)

SD standard deviation, *IQR* inter-quartile range

[a] Excluding readmissions within the same acute hospital stay

Table 2 All admissions in the Case Mix Programme Database for liver cirrhosis divided into two periods, 1995–2003 and 2004–2008

	Cirrhosis as primary or secondary reason for admission		Cirrhosis in past medical history	
	1995–2003	2004–2008	1995–2003	2004–2008
Number of admissions (%)	5,267	6,066	2,257	2,506
Age (years), mean (SD)	51.9 (13.4)	52.5 (12.9)	54.5 (14.5)	56.5 (14.1)
Sex (male), *n* (%)	3,267 (62.0)	3,770 (62.1)	1,328 (58.8)	1,497 (59.7)
APACHE II score, mean (SD)	19.2 (8.3)	18.8 (7.9)	22.1 (8.5)	21.9 (8.3)
ICNARC model score, mean (SD)	23.2 (11.7)	22.6 (11.1)	24.2 (11.6)	23.2 (10.9)
Lowest mean arterial pressure (mmHg), mean (SD)	62.0 (15.9)	62.6 (14.7)	61.4 (16.4)	62.5 (14.8)
Severe sepsis in first 24 h of admission, *n* (%)	470 (8.9)	663 (10.9)	606 (26.8)	737 (29.4)
Critical care unit mortality, *n* (%)	2,301 (43.7)	2,339 (38.6)	922 (40.9)	913 (36.4)
Ultimate acute hospital mortality[a], *n* (%)	2,997 (60.7)	3,140 (54.6)	1,167 (57.7)	1,183 (53.3)
Critical care unit length of stay (days), median (IQR)				
Unit survivors	2.1 (1.0–5.3)	2.4 (1.1–5.9)	2.6 (1.0–6.6)	2.8 (1.2–6.9)
Unit non-survivors	2.0 (0.7–5.9)	1.9 (0.6–5.9)	2.0 (0.8–5.9)	2.4 (0.9–6.6)
All	2.1 (0.9–5.6)	2.2 (1.0–5.9)	2.3 (0.9–6.3)	2.8 (1.1–6.8)
Total acute hospital length of stay (days)[a], median (IQR)				
Hospital survivors	19 (11–36)	18 (10–35)	24 (13–43)	22 (12–44)
Hospital non-survivors	7 (3–17)	8 (3–18)	9 (3–20)	10 (4–22)
All	12 (5–24)	12 (5–25)	14 (6–31)	15 (7–32)

SD standard deviation, *IQR* inter-quartile range
[a] Excluding readmissions within the same acute hospital stay

Table 3 All admissions between May 2003 and April 2005 who had severe sepsis in the first 24 h of admission and/or mechanical ventilation and/or renal replacement therapy at any time during their stay in the critical care unit

	Cirrhosis as primary or secondary reason for admission	Cirrhosis in past medical history	Chronic renal replacement therapy
Number of admissions	883	424	648
Age (years), mean (SD)	51.9 (12.3)	54.4 (13.9)	58.7 (16.2)
Sex (male), *n* (%)	553 (62.6)	253 (59.7)	390 (60.2)
APACHE II score, mean (SD)	20.3 (8.0)	24.5 (9.0)	26.2 (6.8)
ICNARC model score, mean (SD)	26.1 (10.6)	27.4 (11.0)	27.3 (8.8)
Lowest mean arterial pressure (mmHg), mean (SD)	61.1 (14.6)	59.6 (15.8)	63.4 (18.2)
Critical care unit mortality, *n* (%)	442 (50.1)	215 (50.7)	191 (29.5)
Ultimate acute hospital mortality[a], *n* (%)	543 (65.8)	243 (66.6)	274 (48.2)
Critical care unit length of stay (days), median (IQR)			
Unit survivors	4.2 (1.9–10.1)	3.9 (1.9–8.5)	2.8 (1.3–5.7)
Unit non-survivors	2.1 (0.7–7.3)	2.7 (1.1–7.4)	2.3 (0.8–7.7)
All	3.5 (1.0–8.9)	3.4 (1.3–8.0)	2.6 (1.1–5.9)
Total acute hospital length of stay (days)[a], median (IQR)			
Hospital survivors	26 (13–49)	32 (17–50)	23 (13–44)
Hospital non-survivors	9 (3–19)	10 (3–23)	16 (5–37)
All	13 (5–28)	16 (6–33)	20 (9–42)

[a] Excluding readmissions within the same acute hospital stay

patients fared worse (90 vs. 73 %), in particular if both ventilation and renal support were required (Fig. 1a). Patients without sepsis or not requiring ventilation or renal replacement fared better, with hospital mortality rates of 33–39 % in 165 cirrhosis patients and 28 % in 40 CRF patients (Fig. 1a).

(2) Data were collected using CMPD version 3.0 for 999 admissions with cirrhosis and 699 with CRF to 75 ICUs between 2006 and 2008. Cirrhosis accounted for 5.4 % of all admissions. Of these 447 with cirrhosis as a primary/secondary reason for admission, 238 with a past history of cirrhosis and 540 CRF patients either had

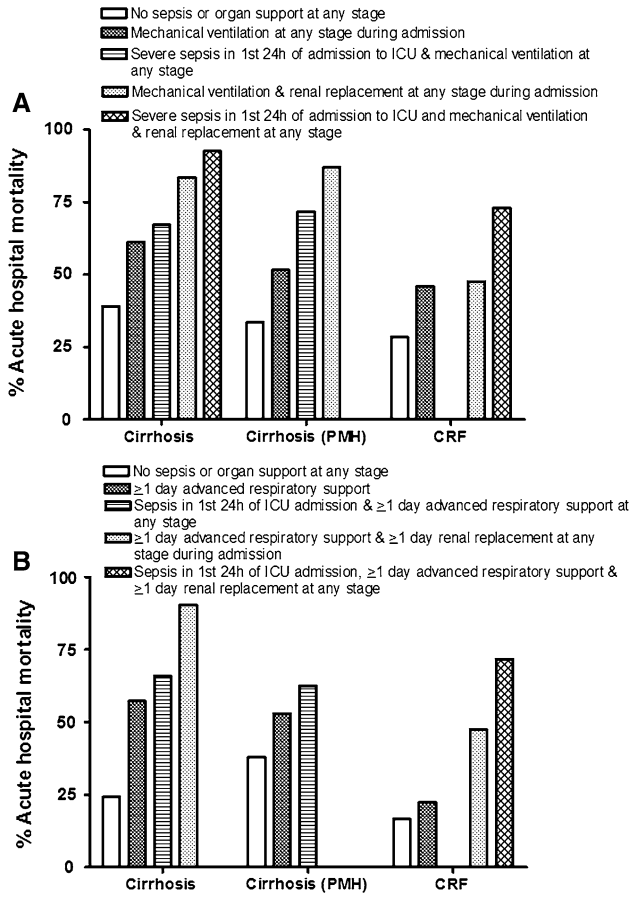

Fig. 1 % Acute hospital mortality in cirrhosis (either primary/secondary reason for admission or past medical history—PMH) and dialysis-dependent chronic renal failure (CRF) patients admitted to UK ICUs according to presence of sepsis and/or organ failure. **a** Shows data for patients admitted between May 2003 and April 2005 and **b** April 2006–June 2008. Mortality for either cirrhosis or CRF patients was increased by the presence of sepsis and/or organ failure and was higher in cirrhosis compared to CRF patients for either cohort. % mortality was not calculated if the number of patients that had died in any group was <20 (this was the case in **a** for CRF patients with severe sepsis in 1st 24 h of admission and mechanical ventilation at any stage; and in **b** for CRF patients with sepsis in 1st 24 h of admission and >1 day of advanced respiratory support at any stage during admission in **b**)

severe sepsis in the first 24 h of admission and/or required at least 1 day of advanced respiratory support and/or at least 1 day of renal support during their ICU stay (Table 4). Again, despite similar APACHE II scores, age and length of stay, the cirrhosis patients fared worse with overall acute hospital mortality of ~60 versus 38 % for CRF. Similarly, cirrhosis patients with new organ failure had poorer outcomes (up to 90 % hospital mortality) compared to those with CRF who developed new organ failures (Fig. 1b). Patients without sepsis or who did not require advanced respiratory or renal support fared better, with acute hospital mortality rates of 24–38 % in 84 cirrhosis patients and 16.7 % in 25 CRF patients (Fig. 1b).

Liver transplantation

A total of 2,340 patients were admitted over the 12-year period with a diagnosis of liver transplant. These patients had similar mean age and male preponderance, but a lower APACHE II score than those admitted with cirrhosis (without transplant) and a much better outcome, with 10.1 % hospital mortality (Table 1). In both subset analyses the ultimate hospital mortality of transplant patients with a diagnosis of sepsis and/or advanced respiratory support and/or renal support was low, 8–11.2 % (658 admissions in total, data not shown).

Comparison was made of the of discrimination and calibration of APACHE II and ICNARC model for liver cirrhosis patients. Both scores under-predicted mortality in cirrhosis patients with SMR >1. The AUROC for the ICNARC score was >0.8 for cirrhosis admissions and 0.77 for APACHE II (Table 5). Both the Cox's regression calibration tests and likelihood ratio χ^2 test for the ICNARC and APACHE II scores were highly significant ($P < 0.001$), indicating a lack of calibration for both models.

Discussion

To our knowledge, this is the first direct comparison of mortality following ICU admission between patients with cirrhosis and those with another pre-existing chronic disease, and the largest cohort of ICU admissions with liver cirrhosis reported to date. We selected patients with dialysis-dependent renal failure as they, like cirrhosis patients, have a high overall mortality and a predisposition to infection [2, 3, 24, 25]. Cirrhotic patients had a higher hospital mortality if admitted to intensive care than those with CRF (55 vs. 42 %). This mortality rate is comparable to ICU admissions of patients with hematological malignancy [38]. Mortality has improved in patients with cirrhosis by approximately 5 % in recent years. The cirrhosis and CRF patients were well matched in terms of age and sex, with the cirrhosis patients slightly younger and a male preponderance observed in both. Both groups had similar median lengths of ICU stay, low blood pressures in the first 24 h, and APACHE II and ICNARC prognostic scores. The subset analyses of >2,500 patients confirmed that those patients with cirrhosis in combination with sepsis and organ failure requiring support had a worse prognosis (mortality rates of 65–90 %, even in recent years) than equivalent patients with CRF (mortality 45–73 %). However, patients without sepsis or organ

Table 4 All admissions recorded between April 2006 and June 2008 who had severe sepsis in the first 24 h of admission and/or at least 1 day of advanced respiratory support and/or at least 1 day of renal support during their stay in the critical care unit

	Primary or secondary reason for admission	Past medical history	Chronic renal replacement therapy
Number of admissions	447	238	540
Age (years), mean (SD)	51.6 (11.8)	54.7 (15.0)	59.9 (16.0)
Sex (male), *n* (%)	282 (63.1)	148 (62.2)	326 (60.4)
APACHE II score, mean (SD)	20.5 (7.5)	21.6 (7.3)	24.5 (6.3)
ICNARC model score, mean (SD)	26.1 (10.1)	24.1 (9.7)	24.0 (9.0)
Lowest mean arterial pressure (mmHg), mean (SD)	59.7 (12.4)	62.6 (12.7)	64.3 (16.8)
Critical care unit mortality, *n* (%)	222 (49.7)	90 (37.8)	123 (29.6)
Ultimate acute hospital mortality[a], *n* (%)	267 (64.0)	122 (57.8)	182 (37.8)
Critical care unit length of stay (days), median (IQR)			
Unit survivors	4.3 (1.9–8.8)	4.8 (2.0–9.2)	2.1 (1.0–4.3)
Unit non-survivors	1.9 (0.7–5.5)	2.4 (0.8–7.4)	2.7 (1.0–7.3)
All	3.0 (1.1–7.4)	3.9 (1.4–9.0)	2.2 (1.0–4.8)
Total acute hospital length of stay (days)[a], median (IQR)			
Hospital survivors	21 (11–36)	25 (15–43)	20 (11–45)
Hospital non-survivors	6 (2–16)	11 (4–20)	15 (5–34)
All	10 (4–23)	15 (7–32)	18 (7–41)

[a] Excluding readmissions within the same acute hospital stay

Table 5 Comparison of discrimination and calibration of APACHE II and ICNARC models among all cirrhosis admissions identified from their reason for admission or past medical history

	1°/2° Reason for admission		Past medical history	
	APACHE II	ICNARC model	APACHE II	ICNARC model
Eligible admissions	9,173	10,663	3,643	4,237
Expected deaths	4,123.2	5,465.9	1,728.4	1,827.5
Observed deaths	5,116	6,125	1,973	2,348
Mortality ratio (observed/expected deaths), (95 % CI)	1.24 (1.22–1.26)	1.12 (1.10–1.14)	1.14 (1.11–1.18)	1.28 (1.25–1.32)
Area under ROC curve (95 % CI)	0.77 (0.76–0.78)	0.80 (0.80–0.81)	0.77 (0.75–0.79)	0.82 (0.80–0.83)
Hosmer-Lemeshow C* statistic				
χ^2 [10]	627.8	491.1	143.0	476.3
P value	<0.001	<0.001	<0.001	<0.001
Cox's calibration regression				
Intercept (95 % CI)	0.54 (0.49–0.59)	0.35 (0.30–0.39)	0.33 (0.25–0.40)	0.68 (0.60–0.76)
Slope (95 % CI)	0.90 (0.86–0.95)	0.79 (0.76–0.83)	0.80 (0.74–0.86)	0.88 (0.82–0.93)
χ^2 [2]	590.1	379.4	128.1	410.7
P value	<0.001	<0.001	<0.001	<0.001
Brier score	0.208	0.184	0.200	0.192

failure fared better with hospital mortalities of 25–35 % in cirrhosis and 17–28 % in CRF. Not surprisingly liver transplant patients have a low mortality (10 %), and this was not significantly altered in those requiring organ support.

Perhaps contrary to expectation, cirrhotic patients only accounted for 2.6 % of admissions, excluding those admitted after liver transplantation. However, a higher proportion (5.4 % of 18,564 patients) were admitted between 2006 and 2008 compared to 2.8 % of 64,063 patients admitted in 2003–2005, and 1,000 more patients with cirrhosis were admitted to ICU between 2004 and 2008 compared to 1995–2003. Also contrary to expectation, the median ICU stay was short in both cirrhosis and CRF groups and did not differ between survivors and non-survivors. Median hospital stay for cirrhosis survivors was double that of non-survivors ($\sim$20 vs. 10 days). A similar trend was seen for patients with CRF. This might represent, at least in part, withdrawal of life-prolonging treatment in patients considered terminally ill or unlikely to recover; however data concerning withdrawal or limitation of care are not collected by ICNARC. The improvement in mortality observed in recent years despite similar patient characteristics may reflect improvements in general ICU management, but also the more widespread use of terlipressin in

hepatorenal syndrome or steroids in alcoholic hepatitis [2] and the threefold decrease in mortality for variceal hemorrhage over the past 3 decades [39].

Surprisingly, in the subset analyses only 66–73 % of the CRF patients underwent renal replacement. As such patients undergo dialysis twice/three times a week, perhaps this was not required for those patients with short-term admissions (median duration of stay was 2–3 days), e.g. after elective surgery. Such patients would be expected to do well and thus perhaps might not represent a good comparator for patients with advanced liver disease. The mean APACHE and ICNARC scores were higher in the CRF patients than in either group of cirrhosis patients, suggesting that they do represent a valid comparator group. Equally, in view of the higher APACHE scores in CRF patients, it possible that RRT may have been withdrawn in patients with a very poor prognosis (in particular those with advanced septic shock). Unfortunately ICNARC does not collect data regarding treatment withdrawal.

The incidence of severe sepsis in the first 24 h of admission was high in patients with a previous history of cirrhosis (28 %) compared to those with cirrhosis as a primary/secondary reason for admission (10 %). In CRF patients, the 25.1 % incidence of sepsis is similar to that previously described in dialysis patients [25] but higher than the 15–19 % incidence reported in two large cohorts admitted to ICUs in Canada and the UK [24, 40]. An impaired ability to adequately combat infection has been previously described in cirrhosis [41] with sepsis being responsible for 30 % of deaths in this population [2].

Both APACHE II and ICNARC scores significantly under-predicted mortality in patients with cirrhosis. The ICNARC score, providing an AUROC of 0.8, is comparable to the SOFA and OSF organ dysfunction models in predicting mortality, but superior to the liver-specific scores Child's Pugh and MELD [28]. Whereas these prognostic models may be used for quality assessment, clinical research or evaluating therapeutic interventions, they are not sufficiently accurate to be relied upon as the basis for individual decision-making. The CMPD was not specifically designed to analyze outcomes of critically ill patients with cirrhosis. Only routinely collected admission data were available, and it was not possible to analyse prognostic factors such as plasma bilirubin nor calculate liver-specific scores (e.g. MELD or Child's Pugh).

Study limitations

The comparison between cirrhosis and CRF patients is imperfect. Evidently the requirement of RRT is not the same for a patient with CKD and a patient with liver cirrhosis, as with the latter we are confronted with an additional organ failure. Therefore the data presented in Fig. 1 concerning mortality in patients requiring renal support in each group cannot be regarded as a direct comparison but rather as demonstrating the very poor outcome in patients with cirrhosis who develop renal failure. However the figure does clearly demonstrate the worse outcome in cirrhosis compared with CRF patients with sepsis and who require respiratory support. It is also possible that APACHE II over-scores CRF patients that are in receipt of regular supportive dialysis, in which case we cannot be sure that cirrhosis patients actually fare worse. However this scoring system has been well validated for many years [33] and has been used in numerous published studies. However we did not intend this comparison to be foolproof, rather we used it to demonstrate that patients with liver cirrhosis do actually fare worse on ICU than those with CRF.

There may have been inclusion bias secondary to differences in admission policies among the contributing units. However, data were entered prospectively by trained collectors and so we conclude that the differences observed are genuine. We cannot be certain that the patients actually had cirrhosis as we have no information on biopsy results or radiological imaging, and it is possible that a small number of those coded as having infective or autoimmune hepatitis may have had acute liver disease. However, we are confident that our search terms included the vast majority of patients with cirrhosis. Patients on dialysis are likely to be coded correctly as this state is clearly defined and identifiable, whereas liver disease may not be so clearly delineated; therefore there is a risk that the data were weaker in identifying all such patients, especially those with well-compensated cirrhosis (Child A) who may be expected to do better. However, the cirrhosis patients had lower admission APACHE scores compared to CRF patients and yet still had a higher mortality; we therefore feel that such selection bias was unlikely. We also included patients with a PMH of cirrhosis but who had been admitted primarily for a non liver-related illness. As such patients are likely to have less advanced liver disease, this reduces bias towards including only the sickest cirrhotics (who would be expected to do badly). Cirrhotic patients generally have low mean arterial blood pressures but data concerning vasoactive drug use (a marker of poor prognosis [3]) were not recorded in the CMPD. We are also unable to report on long-term outcomes or treatment measures. No data were available concerning previous history of cirrhosis-related complications, e.g. hepatorenal syndrome (HRS) or gastrointestinal bleed, which would predict a poor outcome irrespective of APACHE score. Unfortunately ICNARC does not collect information that would allow us to differentiate between HRS and non-HRS renal impairment in cirrhosis patients and therefore refers to the patients as requiring RRT rather than having HRS. However, many of these complications require ICU admission and so readmissions within the same hospital stay were excluded to reduce bias. We were unable to compare high volume

versus low volume units or transplant versus non-transplant centres, although it should be noted that the largest liver ICU in the UK at King's College Hospital does not contribute to ICNARC. Interestingly our overall mortality data were similar to previous studies [3–10], which tend to originate from specialist centres perhaps suggesting that management in non-specialist centres was not dissimilar. Equally restriction of access to ICU for patients with liver cirrhosis or CRF is likely to vary from unit to unit, but ICNARC does not collect these data. We therefore do not have the actual denominator of patients who were eligible for ICU admission, which may lead to a survival bias. It is possible that the improvement in survival in the more recent cohort may simply reflect changes in admission policy rather than improved ICU supportive care, i.e. patients likely to have poor prognoses may have been declined ICU admission. We could not assess the influence on outcome of clinical/biochemical status beyond the first 24 h of ICU stay, when deteriorating physiology may be useful in making treatment decisions. Indeed, prognostic models in cirrhotic patients assessed at 48 h or even 72 h were better predictors of outcome than when performed at 24 h [16, 42]. The CMPD does not collect data on long-term mortality nor development of other complications during follow-up.

In summary, we demonstrate for the first time that, in a large-scale cohort, patients with cirrhosis do have poorer outcomes following ICU admission than those with dialysis-dependent CRF. We have also shown that cirrhosis patients only represented a small number of total ICU admissions and had a short median length of ICU stay, although the prevalence has increased in recent years. Acute hospital mortality has improved in cirrhosis patients when 1995–2003 is compared with 2004–2008, in spite of other characteristics including APACHE II score remaining the same. However subset analysis has shown that even in more recent admissions the mortality in cirrhosis patients with multi-organ failure remains very high. Neither APACHE II nor ICNARC scores are suitably accurate to guide individual decision making in these patients. Patients without sepsis or with single organ failure have acceptable survival rates and it would seem entirely appropriate to manage such patients on ICU. However, our large-scale multicenter study has confirmed the poor prognosis of cirrhotic patients who require >1 organ support, with mortality rates of >90 % seen in patients who develop multi-organ failure. We would therefore advocate attempts at early identification of patients with a likely poor prognosis to enable discussion with the patients and relatives about setting appropriate limits of care and furthermore, support should be withdrawn in patients who continue to deteriorate and develop multi-organ failure during their ICU stay.

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Conflicts of interest None.

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