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Outcomes of critically ill patients with cirrhosis admitted to intensive care: an important perspective from the non-transplant setting.

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3 Outcomes of critically ill patients with cirrhosis admitted to intensive care:
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6 an important perspective from the non-transplant setting.
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ABSTRACT

Background:

Hospital admissions for cirrhosis are increasing in the UK, leading to increased pressure on intensive care (ICU) services. Outcome data for patients admitted to ICU are currently limited to transplant centre reports, with mortality rates exceeding 70%. These tertiary reports could fuel a negative bias when patients with cirrhosis are reviewed for ICU admission in secondary care.

Aims:

To determine whether disease severity and mortality rates in non-transplant general ICU are less severe than those reported by tertiary datasets.

Methods:

A prospective dual-centre non-transplant ICU study. Admissions were screened for cirrhosis, and physiological and biochemical data were collected. Disease specific and critical illness scoring systems were evaluated.

Results:

Cirrhosis was present in 137/4198 (3.3%) of ICU admissions. ICU and hospital mortality were 38% and 47%, respectively; median age 50 [43-59] years, 68% male, 72% alcoholic cirrhosis, median Child Pugh Score (CPS) 10 [8-11], Model for End-stage Liver Disease (MELD) 18 [12-24], Acute Physiology and Chronic Health Evaluation II score (APACHE II) 16 [13-22].

Conclusion:

Mortality rates and disease staging were notably lower than in the published literature, suggesting that patients have a more favourable outlook than previously considered. Transplant centre data should therefore be interpreted with caution when evaluating the merits of intensive care admission for patients in general secondary care ICUs.

INTRODUCTION

The rates of hospital admission and mortality for patients with cirrhosis have dramatically risen over the past 25 years in England and Wales (1) and it is likely that clinicians in secondary care will be exposed to increasing numbers of patients with complications of cirrhosis in the future. As well as being the primary factor in the presenting illness, cirrhosis will also become a common co-morbidity in patients admitted to hospital for other reasons.

Patients with cirrhosis are amongst the most physiologically challenged of in-patients and appear to have a higher risk of mortality (2). The complexity and severity of acute illness in this setting means that close liaison is required between Gastroenterologists and Critical Care physicians to decide on appropriate escalation of therapy to the intensive care unit (ICU). The extent of current physiological derangement, presence of co-morbidity and an evaluation of baseline function are all important contributory factors. With the availability of increasingly sophisticated medical therapies and a rise in public consumer expectation on medical services, increasing pressure will be placed on intensive care units to provide an escalated level of care. It is therefore imperative that an evidence base exists which can be drawn upon to guide the decision making process.

The main body of literature reporting on the impact and outcomes of critically ill patients with cirrhosis currently offers a bleak prognosis. The weighted mean ICU and hospital mortality rates from seventeen studies are 45% and 58% respectively but in prominent cases mortality rates in excess of 70% are reported [3-20]. Without careful consideration, these headline figures could engender a negative clinical approach to this cohort. Were this to be transposed to clinical practice and decisions about care delivery, there is a risk that some patients may be inappropriately denied the opportunity for potentially life saving treatment.

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3 Further examination of the literature reveals that the majority of the reports originate from liver
4 transplant centres. Specialist ‘hepato-gastroenterology ICUs’ or dedicated ‘medical’ critical care
5 units account for the rest (3-20). Only three studies originate from UK centres (6-7, 20); two are
6 drawn from the same data source in a single unit, and all are from tertiary ICUs in transplant
7 centres. Half of the remaining studies originate in the Far East, Middle East and Asian sub-
8 continent.
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19 The case mix described by the published literature is therefore quite different to that experienced
20 by the majority of district centres throughout the UK and there is a need for an evidence base to
21 which these clinicians can refer. Mainstream ICU services in the UK are designed to offer general
22 care to all comers from different clinical specialities. The phenotype of cirrhotic patients
23 presenting to these services will be different to that seen in the tertiary specialist centre. Many
24 patients will be presenting to hospital for the first time and will be at an earlier stage in their
25 disease process. Those managed in tertiary centres may be known to the transplant service and are
26 likely to have been listed for future transplant, implying the presence of end stage disease.
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39 We have collected a body of data representative of the case mix seen in non-transplant secondary
40 care ICUs in the UK. We hypothesised that the overall ICU and hospital mortality rates would be
41 lower than reported in other datasets and that this would be due to a less severe disease staging in
42 the examined cohort. In addition the study examines the effects of specific organ failure on
43 outcome and evaluates the performance of general critical illness and disease specific scoring
44 systems. Few of these systems have been developed to specifically evaluate the critically ill
45 cirrhotic patient but they are frequently applied in this setting. The utility of the more established
46 systems will be evaluated and newer scores validated for the first time in an unselected cirrhotic
47 cohort.
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MATERIALS & METHODS

Study design and setting

The study was approved as a clinical survey by local ethics and research & development departments (Refs: 0053.07; RJ1 07/0213). Data was prospectively collected over a period of 20 months (31st October 2007-1st July 2009) from two large general secondary care ICUs in St George's (SGH) and St Thomas' Hospitals (STH), London, UK. Both centres are large, multi disciplinary teaching hospitals which carry some specialist tertiary services (Cardiothoracic, Neurosurgical) but the general ICU's cater for a case mix of general medical and surgical admissions. Neither centre offers a tertiary liver transplant or dedicated hepatological critical care service. The two ICU's have a combined capacity of 47 critical care beds and serve a catchment area covering most of south west London.

Patients & Data collection

All ICU admissions at SGH were screened daily for inclusion criteria by the primary investigator (SJT) with the assistance of departmental nursing and audit staff. The biological and physiological data necessary to calculate clinical scoring systems were collected at the time of admission. Patients at STH were continuously screened on admission to ICU by a team of dedicated research staff and prospectively entered into a 'screening log'. Biological and physiological data were then extracted from the electronic patient record (CareVue[®]) for all identified cases during a site visit undertaken by the principle investigator at six weekly intervals.

Patients with cirrhosis were identified using clinical or histological criteria. Clinical criteria included an established 'out-patient' diagnosis of cirrhosis and/or clinical evidence of portal hypertension (ascites, oesophageal varices) and/or classic appearances of cirrhosis on radiological testing (ultrasound, CT). Cirrhosis was biopsy proven in 19 patients (16%). Data for readmissions and inter hospital transfers were collected but later excluded. All analyses were undertaken on

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2
3 'first' admission data only. Any patients subsequently transferred to a liver transplant centre were
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5 also excluded.
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10 Patients were followed up throughout their ICU admission. Hospital lengths of stay and outcome
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12 data were later obtained from the central hospital electronic record. Data analysis was performed
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14 with the statistical package for the social sciences (SPSS) v.16.0.
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18 **Scoring systems and definitions**

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20 Three general critical illness and organ failure scoring systems (Acute Physiology And Chronic
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22 Health Evaluation II (APACHE II), Simplified Acute Physiology Score II (SAPS II) and
23
24 Sequential Organ Failure Assessment (SOFA)) (21-23) and five disease specific systems (Child
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26 Pugh Score (CPS), Model for End stage Liver Disease score (MELD), United Kingdom End stage
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28 Liver Disease score (UKELD), Glasgow Alcoholic Hepatitis Score (GAHS) and Royal Free
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30 Hospital (RFH) score) were evaluated (7, 24-27). The latter three scores are evaluated for the first
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32 time in this patient cohort. UKELD is a newly devised UK version of the established MELD
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34 score intended for use in stratifying patients for liver transplant assessment (26). The Glasgow
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36 Alcoholic Hepatitis Score (GAHS) (24) is intended for use specifically in alcoholic hepatitis but
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38 may have a role in the evaluation of a general critically ill cirrhotic population, and the Royal
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40 Free Hospital (RFH) score was first reported in 2006 (7) having been developed in a cohort of
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42 312 cirrhotic patients and awaits validation in a different population.
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49 Some scoring systems traditionally require biological and physiological data to represent the
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51 worst value obtained during the first 24 hours of admission. For practical reasons, all data in this
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53 study was collected at the point of ICU admission. A consistent approach was used throughout
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55 the study for all patients in both centres. In systems requiring a Glasgow Coma Score (GCS)
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57 assessment of conscious level, status has been universally scored as 'normal'. Assessment of
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3 neurological morbidity in critical care is prone to observer bias and can be affected by sedative
4 and analgesic drugs. Similarly, documentation of consciousness at the point of ICU admission
5 was inconsistent and variable in quality. A majority of patients were intubated on admission,
6 again confounding any adequate assessment of GCS. Similar difficulties are present in the
7 adequate assessment and documentation of hepatic encephalopathy (HE), an integral component
8 of the Child Pugh score. We are of the opinion that a degree of HE is invariably present in
9 cirrhotic patients during periods of critical illness and have therefore applied a Child Pugh score
10 of two points for all patients. This score encompasses the presence of grade I/II HE. No previous
11 studies have reported their approach to this methodological challenge
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25 Patients are further sub-classified and evaluated at the point of admission according to organ
26 failure criteria. It was not valid to categorise according to 'admission diagnosis' as has been
27 described in previous literature as many patients will present with a combination of patho-
28 physiological conditions e.g sepsis, renal failure, respiratory failure and no single diagnostic label
29 can be readily applied. Instead, patient data has been analysed to identify those with objective
30 evidence of organ failure, defined using a SOFA sub-component score of ≥ 2 .
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40 **Statistical techniques**

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42 Continuous data is reported as median [interquartile range] and differences between groups
43 analysed with Mann-Whitney tests. Categorical data is reported as whole number and percentage
44 (%) and differences have been evaluated with Chi-square tests. In circumstances where group
45 sizes were less than six, Fishers exact test has been used. Associations between binary factors and
46 mortality outcome are expressed as percentage (%) of the mortality or survivor group and are
47 detailed in table footnotes. Where appropriate, sensitivity and specificity have been reported with
48 a Youden index (28). This acts as a composite assessment of the two measures ([sensitivity +
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3 specificity] -1). An ideal test with 100% sensitivity and specificity would therefore score a
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5 Youden index of 1.
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10 Factors demonstrating significant differences in univariate testing were entered into a forward
11
12 stepwise multivariate regression model. Two models were evaluated, one including individual
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14 scoring systems and another without. The discriminative ability of each scoring system to identify
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16 patients with a mortality outcome was analysed by the area under the receiver operating
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18 characteristic curve.
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For Peer Review

RESULTS

Demographics & disease staging

In the 20 month study period a combined total of 4198 patients were admitted to both ICUs of which 137 (3.3%) met inclusion criteria for the study. Twelve of these were readmissions (second admissions (n=10), third (n=2)) and were excluded from analysis. Four patients had been transferred from other secondary care institutions due to lack of bed capacity and three others were subsequently transferred out to tertiary liver centres for ongoing management. These patients were also excluded leaving a study cohort of 118 patients.

Median age was 50 years [43-59], 80 (68%) were male and 102 (86%) were Caucasian. Eight (7%) were Asian and eight (7%) Afro-Caribbean. Five (5%) of the Caucasian patients were from continental Europe. Eighty-seven (74%) were active smokers and 78 (66%) were classified as unemployed. Median length of stay on ICU was 4.5 days [2-10] and total hospital stay 14 days [7-27]. Overall mortality was 38% (45/118) on ICU and 47% (55/118) in hospital. The breakdown of cirrhosis aetiology, type of admission and associated mortality within each group is shown in (Table 1). **Of the patients with alcoholic liver disease (ALD) 85% (72/85) were still drinking up to the point of admission, however, there was no significant difference in hospital mortality between this group (49%, 35/72) and the patients who had been abstinent (54%, 7/13), p=0.77.**

Median Child Pugh score was 10 [8-11] of which three (3%) were classified as grade 'A', 50 (42%) grade 'B' and 65 (55%) grade 'C'. Median MELD score was 18 [12-24]. Pre-admission data was available for 84 patients in whom CPS and MELD were calculated. In the stable out-patient state median CPS was 7 [6-8] (40 (48%) grade 'A', 32 (38%) grade 'B' and 12 (14%) grade 'C') and MELD was 10 [7-13]. Differences between pre-admission and ICU scores were evaluated. The critical illness physiological insult increased MELD by a median 6 points [1-13]

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3 and CPS by 2.5 points [1-4] shifting 23 (58%) from grade 'A' to 'B', 14 (35%) from 'A' to 'C'
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5 and 23 (72%) from 'B' to 'C'.
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10 Of the nine admissions classified as emergency surgery, two had post-traumatic orthopaedic
11 intervention, one emergency skin debridement for necrotising fasciitis and one had traumatic
12 haemopneumothoraces requiring chest drains and respiratory support. The remaining five all had
13 emergency laparotomies for intra-abdominal pathology and accounted for all the mortality in that
14 group (5/9, 56%). Four of the elective surgery group (4/9) had long, complex maxillofacial
15 procedures for oro-pharyngeal malignancy while the rest were composed of general, orthopaedic,
16 urological and vascular surgery patients.
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24 25 26 27 **Univariate & multivariate analysis**

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29 Summary data and results of univariate analysis for the biophysiological parameters and scoring
30 systems evaluated are shown in (Table 2) and the factors which remained independently
31 associated with mortality after multivariate analysis are listed in (Table 3). In the model with
32 scoring systems excluded, serum bilirubin, PaO₂/FiO₂ ratio, INR, urea and bicarbonate remained
33 significant. With the inclusion of the scoring systems, APACHE II, CPS and the RFH score held
34 the strongest associations.
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44 45 **Scoring system utility**

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47 ROC curve analysis revealed comparable performance for all of the scores in predicting hospital
48 mortality. The lowest value was 0.76 for UKELD and the best performing was the RFH score
49 (0.81); (Table 4.1). The individual cut offs producing the best sensitivity and specificity for each
50 individual score are shown in (Table 4.2). Hospital mortality rates for each scoring system
51 population quartile are demonstrated in (Figure 1).
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Organ failure

The number of patients, mortality rates and odds ratios for those defined as having specific organ failure on admission according to SOFA sub-component score ≥ 2 , and those requiring various ICU interventions for organ support are shown in (Table 5). With this definition, mortality for a single organ failure was 21% (6/29), two organ failure 61% (22/36) and for three or more organs 63% (26/41). Inotropic support and the use of renal replacement therapy (RRT) at any point also had an association with mortality outcome. The odds ratio for death with RRT was 9.6 (3.7-24.8) with a sensitivity 55% and specificity 89%.

Notably, the application of mechanical ventilation on admission did not demonstrate an association with mortality. (Table 6) reports the breakdown of patients by indication for intubation. This shows that patients who were intubated for medical pathologies triggering respiratory failure had a higher mortality (60 vs 40%, Odds ratio 2.7 (1.0-7.0)) and those with gastrointestinal bleeding who were intubated for airway protection had better outcomes (33 vs 67%, Odds ratio 0.4 (0.1-1.3)) although neither difference reached statistical significance.

DISCUSSION

This study has evaluated the prevalence, case mix and outcomes of patients with cirrhosis who were admitted to the general intensive care units of two large non-transplant ICUs in London, UK. Cirrhosis was present in 3.3% (137/4198) of ICU admissions. Alcoholic liver disease accounted for 72% (85/118) of the studied cohort representing 2% of the overall admissions. This is comparable to the figure for alcoholic liver disease reported by Welch *et al* in a recent UK national ICU database study (29). Overall ICU and hospital mortality rates were 38% and 47% which compare favourably to the weighted means of the rates in published datasets (45%, 58%). By reporting the clinical experiences of the non-transplant ICU setting the results have broad relevance and stand as a unique reference point for general intensive care units across the UK.

This study was purely observational in design and only those patients actually admitted to ICU were reviewed. Patients who were either not referred or were reviewed and declined by the ICU service were not identified. Although the analysis of pure ICU 'admissions' could lead to referral bias, designing a protocol where all hospital admissions with cirrhosis were reviewed and considered for ICU admission was impractical and outside the scope of this study.

It is likely that the lower mortality rates seen in this study are related to a less severe disease staging and illness severity in the examined population. Child Pugh C disease accounted for 55% (65/118) of cases. This figure sits at the lower end of the numbers described in the published literature. The eight studies which categorised patients by Child Pugh grade reported grade C in between 53-89% of admissions. Median MELD in our dataset was 18 compared with (12-28) in four published studies and APACHE II was 16 versus (18-27) in seven studies.

The notable overestimation of disease stage based on the results obtained during acute illness versus stable pre-admission data should also be acknowledged. The Child Pugh score was

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3 originally developed in acutely unwell patients but has since developed a profile in staging stable
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5 out-patient disease. The difference between the two clinical states and the influence of critical
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7 illness on physiological and biochemical parameters should be considered when interpreting
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9 disease severity. **Despite this concern the clear association between disease stage and mortality**
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11 **remains with Child Pugh grade C patients experiencing 66% (43/65) mortality versus 24%**
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13 **(12/50) in grade B and 0% in grade A.**
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19 MELD was originally developed in a stable patient population and continues to be used in that
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21 fashion when assessing candidates for planned liver transplant. The differences between pre-
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23 admission and acute illness MELD scores in this patient cohort were striking. The median values
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25 respectively fell below and above the cut off value of 15 used for transplant listing in the United
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27 States and highlight the care that should be taken when interpreting clinical scoring systems in
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29 critical illness.
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34 The difficulties faced when using conscious level or encephalopathy grade in the calculation of
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36 clinical scoring systems have been highlighted. It should again be acknowledged that this dataset
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38 reports summary critical illness scores (APACHE II, SAPS II, SOFA) with neurological status
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40 scored as 'normal' and has universally applied Grade I/II encephalopathy when calculating Child
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42 Pugh data. Without clear specification in study methods it is not known how other groups have
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44 dealt with this issue but it is likely that similar difficulties have been encountered. Notably, both
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46 Wheler *et al* and the original SOFA publication allude to the difficulties of assessing neurological
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48 status in their study discussion (17, 23).
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53 In line with the published literature this study has again confirmed the negative impact that renal
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55 failure has in the context of cirrhosis and critical illness. The presence of renal failure on
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57 admission (Creatinine >2.0 mg/dl (171 μ mol/l)) had an odds ratio of 3.4 (1.4-8.4) and the use of
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3 renal replacement therapy during admission an OR 9.6 (3.7-24.8) for hospital mortality. In
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5 addition to this creatinine based definition of renal failure, serum urea demonstrated independent
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7 predictive value for outcome in a multivariate logistic regression model which excluded the
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9 established scoring systems. Although urea rarely features in the academic definitions of renal
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11 failure it is often utilised in the clinical setting where subtle changes can hold greater significance
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13 due to the relatively lower levels seen in patients with cirrhosis. Notably urea also achieved
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15 independent significance in the Cholongitas *et al* study and is one of the factors used to calculate
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17 the RFH score (7). The links between renal failure and mortality in cirrhosis have been
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19 established for over twenty years. Despite recent advances in many aspects of medical care this
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21 remains a challenging problem and further underlines the importance that must be attached to
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23 maximizing renal perfusion in these patients.
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29 In contrast to renal failure, patients admitted for airway protection and management of variceal
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31 bleeding had lower mortality rates compared to patients who were intubated for other medical
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33 reasons (33% vs 60%). The mortality odds ratio for variceal bleeding airway protection was in
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35 fact less than one (0.4 (0.1-1.3), $p=0.09$). Although this does not reach significance the trend
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37 supports the important notion proposed by other studies that tracheal intubation for airway
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39 protection during gastrointestinal bleeding carries a better prognosis compared to those intubated
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41 for respiratory failure.
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46 There was no difference in length of ICU stay between survivors and non-survivors, while non-
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48 survivors had significantly shorter lengths of total hospital stay. This suggests that the overall
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50 healthcare costs in this group are not wasted. Although length of stay on its own is a crude
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52 measure of healthcare costs (30), it appears that it is not an important factor on this occasion. This
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54 pattern is also mirrored in the majority of the other published datasets.
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3 Evaluation of the clinical scoring systems revealed fairly equal discriminative ability between
4 general and liver specific systems. Of the established scores, Child Pugh (0.78), MELD (0.78),
5 APACHE II (0.77), SAPS II (0.80) and SOFA (0.77) produced similar ROC values. Three further
6 scores were evaluated in this cohort for the first time. UKELD (0.76) performed comparably to its
7 American predecessor. The recently developed RFH score (0.81) produced the best ROC value of
8 all and maintained an independent association with outcome after multivariate logistic regression.
9 This analysis represents the first external validation of this score and suggests that further
10 investigations into its potential utility should be performed.
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22 GAHS (0.77), which was developed for use specifically in alcoholic hepatitis also performed well
23 in this cohort of cirrhotics with heterogeneous critical illness. **This is perhaps unsurprising as the**
24 **majority of cases were of an alcoholic aetiology but it could also suggest that the utility of GAHS**
25 **be extended to generic critical illness in cirrhosis. Further evaluation of GAHS in this setting**
26 **would therefore be of value.**
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36 Despite the earlier critique of its encephalopathy component it is interesting to observe that the
37 CPS performs comparably well to the other available scores. Alongside APACHE II and RFH it
38 maintained an independent association with mortality outcome. Of all the evaluated scores, CPS
39 and GASH can be calculated at the bedside as they rely on simple addition of individual
40 numerical scores ascribed to abnormalities in readily available clinical parameters. The other
41 systems rely on more complex equations using specific blood results to calculate the final score.
42 While this may have been problematic in the past, the increasing availability of handheld portable
43 computer technology may enhance clinical utility in the future.
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55 Unfortunately, when considering rationalisation of healthcare measures and access to critical care
56 services, pre-conceived assumptions can sometimes feature in the decision making process.
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3 Because of the predominant aetiological role of alcohol in chronic liver disease, cirrhosis is often
4 seen as a 'lifestyle' disease which carries a bleak prognosis. In order to overcome this judgement
5 and to maximise opportunities for patient recovery in the short term, frontline clinicians dealing
6 with the complexities of critical illness in cirrhosis in secondary care have a responsibility to
7 approach each case on an individual basis without falling foul of generalisation. To prevent
8 recidivism and justify the intensive levels of care provision during the acute illness, significant
9 improvements are needed in the long term management of the underlying psychosocial factors.
10 Sadly this has long been a poorly funded and disregarded aspect of healthcare provision in the
11 UK, however a recent position statement published by the British Society of Gastroenterology
12 aims to overhaul this deficit and proposes far reaching developments in the national care of
13 alcohol related disorders (31).
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29 In conclusion, this dataset represents an important advance in the understanding of the critical
30 illness outcomes of patients with cirrhosis admitted to non-transplant general ICUs in the UK.
31 Although the mortality rates are unarguably significant they are lower than the majority of the
32 published datasets. We propose that clinicians ignore the 'whispers' and apply a more considered
33 and optimistic approach to this complex and interesting patient cohort in the future.
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Table (1): Clinical characteristics of cirrhotic population studied (n=118)

Characteristic	All patients (n=118)	Hospital survivors (n=63)	Hospital non-survivors (n=55) (47%)
Cirrhosis aetiology			
ALD	85 (72%)	43 (51%)	42 (49%)
Viral	All	6 (66%)	3 (33%)
	<i>HBV</i>	2	2
	<i>HCV</i>	3	0
	<i>HBV + HCV</i>	1	1
ALD + Viral	17 (14%)	10 (59%)	7 (41%)
Other ^a	7 (6%)	4 (57%)	3 (43%)
Type of admission			
Emergency medicine	100 (84%)	50 (50%)	50 (50%)
Emergency surgery	9 (8%)	4 (44%)	5 (56%)
Elective surgery	9 (8%)	9 (100%)	0 (0%)

Abbreviations: ALD – Alcoholic liver disease, HBV – Hepatitis B virus, HCV – Hepatitis C virus

% figures refer to the percentage mortality and survival within each sub-group

a 'Other' include non alcoholic fatty liver disease (NAFLD), primary sclerosing cholangitis (PSC), primary biliary cirrhosis (PBC) and granulomatous liver disease.

Table (2): Clinical, biological and physiological characteristics on admission to the intensive care unit according to final outcome.

Variable	All patients (n=118)	Hospital survivors (n=63)	Hospital non-survivors (n=55) (47%)	p value
Age (years)	50 [43-59]	50 [42.5-55]	50 [43-60.5]	0.33
Sex (male)	80 (68%)	43 (68%)	37 (67%)	0.91
Interval to ICU (days)	1 [0-4]	1 [0-3]	1 [0-5.5]	0.49
ICU LOS (days)	4.5 [2-10]	4 [2-9]	6 [3-10.5]	0.36
Hospital LOS (days)	14 [7-27]	20 [9-35]	11 [5.5-18.5]	0.002
Hb (g/dl)	9.6 [8.1-11]	9.7 [8.4-11.2]	9.4 [7.7-10.7]	0.45
WCC (10 ⁹ /l)	10.9 [6.5-16.8]	10.7 [6.3-16.1]	11.9 [6.7-18.6]	0.73
Plt (x10 ⁹ /l)	120 [69-219]	128 [80-269]	115 [55-167]	0.03
MCV (fL)	96.2 [90.7-104]	95 [89-99.5]	98.2 [92-105.1]	0.03
INR	1.5 [1.2-1.9]	1.3 [1.1-1.6]	1.9 [1.6-1.2]	<0.001
Na ⁺ (mmol/l)	138 [133-142]	138 [134-142]	137 [131-142]	0.5
K ⁺ (mmol/l)	4.1 [3.8-4.6]	4.1 [3.9-4.4]	4.3 [3.6-4.8]	0.65
Urea (mmol/l)	7.6 [4.3-14.5]	6.0 [4.1-9.1]	11.7 [6.1-18.1]	0.001
Creat (µmol/l)	87 [57-165]	64 [52-103]	140 [77-196]	<0.001
Bili (µmol/l)	40 [16-103]	23 [14-54]	64 [26-227]	<0.001
Albumin (g/l)	21 [17-27]	23 [18-28]	19 [16-25]	0.01
CRP (mg/l)	44 [14-106]	22 [10-78]	61 [31-129]	0.008
BG (mmol/l)	6.3 [4.9-8.0]	6.8 [5.2-8.2]	5.5 [4.4-7.9]	0.03
pO ₂ /FiO ₂ ratio	281 [176-439]	342 [227-471]	207 [142-400]	0.008
pH	7.32 [7.25-7.40]	7.34 [7.26-7.41]	7.32 [7.21-7.4]	0.37
HCO ₃ ⁻ (mmol/l)	21.2 [17.6-24.9]	22.2 [19.1-25.1]	19.5 [16.2-23.1]	0.01
Lactate (mmol/l)	2.4 [1.5-4.8]	1.9 [1.3-3.0]	3.8 [2.0-6.8]	<0.001
Temp (C °)	36.5 [36-37.3]	36.9 [36.2-37.3]	36.4 [35.7-37.4]	0.07
Heart rate (bpm)	103 [87-115]	99 [87-114]	103 [87-115]	0.53
MAP (mmHg)	82 [70-95]	85 [72-95]	77 [70-95]	0.33
Child Pugh Score	10 [8-11]	8 [8-10]	11 [10-12]	<0.001
Grade A	3 (3%)	3 (100%)	0 (0%)	<0.001
Grade B	50 (42%)	38 (76%)	12 (24%)	
Grade C	65 (55%)	22 (34%)	43 (66%)	
MELD	18 [12-24]	13 [9-18]	23 [18-29]	<0.001
UKELD	51 [46-56]	47 [44-53]	54 [51-60]	<0.001
GAHS	7 [7-8]	7 [6-7]	8 [7-10]	<0.001
RFH	-0.5 [-3.3, 1.3]	-2.0 [-4.1, -0.2]	1.3 [-0.5, 2.6]	<0.001
APACHE II	16 [13-22]	14 [11-18]	21 [16-23]	<0.001
SAPS II	28 [20-37]	22 [18-29]	35 [29-41]	<0.001
SOFA	6 [4-9]	4 [3-7]	8 [6-11]	<0.001

Data is expressed as median [interquartile range] or whole numbers and (%).

Abbreviations: LOS – Length of stay, Hb – Haemoglobin, WCC – White cell count, Plt – Platelet count, MCV – Mean cell volume, INR – International normalised ratio, Na – Serum sodium, K – Serum potassium, CRP – C reactive protein, BG – Blood Glucose, pO₂ – partial pressure of oxygen (kPa), FiO₂ – concentration of inspired oxygen (%), MAP Mean arterial pressure, CPS - Child Pugh score, MELD – Model for end stage liver disease, UKELD – United Kingdom model for end stage liver disease, GAHS - Glasgow alcoholic hepatitis score, RFH – Royal free hospital score, APACHE II – Acute physiology and chronic health evaluation II score, SAPS II – Simplified acute physiology II score, SOFA – Sequential organ failure assessment score

Table (3): Summary of factors maintaining an independent association with mortality after multivariate logistic regression

Variable identified as independently predictive	p value
Model excluding scoring systems	
Bilirubin	0.02
pO ₂ /FiO ₂ ratio	<0.001
INR	<0.001
Urea	0.02
Bicarbonate	0.03
Model including scoring systems	
RFH	0.02
CPS	<0.001
APACHE II	0.004

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Table (4.1): Area under receiver operator characteristic curve for each clinical scoring system

Clinical score	Area under ROC	95% CI
CPS	0.78	(0.69-0.86)
MELD	0.78	(0.70-0.87)
UKELD	0.76	(0.67-0.85)
GAHS	0.77	(0.69-0.86)
RFH	0.81	(0.73-0.89)
APACHE II	0.77	(0.69-0.86)
SAPS II	0.80	(0.72-0.88)
SOFA	0.77	(0.68-0.86)

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Table (4.2): Individual cut off points for each scoring system producing the best sensitivity, specificity and Youden index for predicting mortality in the examined population.

Clinical score	Cut off value	Sensitivity	Specificity	Youden Index
CPS	≥ 9	78%	65%	0.43
MELD	≥ 15	87%	60%	0.47
UKELD	≥ 50	80%	67%	0.47
GAHS	≥ 8	71%	78%	0.49
RFH	≥ 0.14	70%	80%	0.5
APACHE II	≥ 16	76%	67%	0.43
SAPS II	≥ 28	80%	73%	0.53
SOFA	≥ 6	80%	70%	0.5

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Table (5): Admission characteristics - organ failure according to SOFA sub component score, requirements for organ support and relationship with mortality

Admission characteristic	All patients (n=118)	Hospital survivors (n=63)	Hospital non-survivors (n=55)	<i>p</i> value	Odds Ratio (95% CI)	Sensitivity	Specificity	Youden index
SOFA ≥ 2*								
Hepatic	61 (52%)	23 (38%)	38 (62%)	<0.001	3.9 (1.8-8.4)	69%	63%	0.32
Renal	29 (25%)	9 (31%)	20 (69%)	0.005	3.4 (1.4-8.4)	36%	86%	0.22
Respiratory	66 (56%)	28 (42%)	38 (58%)	0.007	2.8 (1.3-6.0)	69%	56%	0.25
Cardiac	41 (35%)	16 (39%)	25 (61%)	0.02	2.5 (1.1-5.3)	45%	75%	0.20
Platelet	50 (42%)	24 (48%)	26 (52%)	0.31	1.5 (0.7-3.0)	47%	62%	0.09
Requirement for organ support								
Mechanical ventilation	73 (62%)	37 (51%)	36 (49%)	0.45	1.3 (0.6-2.8)	65%	41%	0.06
Inotropic support	41 (35%)	16 (39%)	25 (61%)	0.02	2.5 (1.1-5.3)	45%	75%	0.20
RRT ^a	37 (31%)	7 (19%)	30 (81%)	<0.001	9.6 (3.7-24.8)	55%	89%	0.44

*SOFA sub component scores of 2 equate to:

Hepatic - Bilirubin ≥ 2.0 mg/dl (33 μ mol/l), Renal - Creatinine 2.0mg/dl (171 μ mol/l), Respiratory - PaO₂/FiO₂ ratio <300 mmHg, Cardiac - Adrenergic agents administered for at least 1hr (Dopamine ≤ 5 μ g/kg/min or Dobutamine (any dose)), Coagulation – Platelet count <100 (10³/mm³)

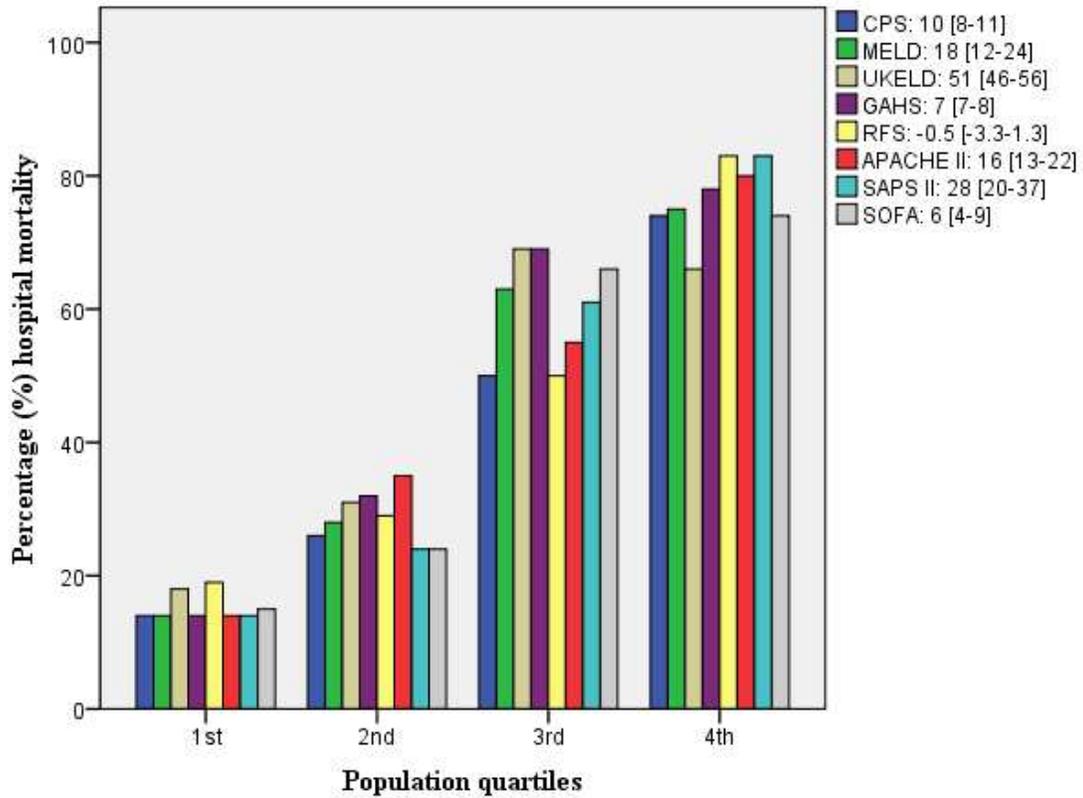
^a The use of RRT (renal replacement therapy) at any point during admission

Table (6): Breakdown of patients intubated on day of admission

Reason for intubation	All patients (n=73)	Hospital survivors (n=37)	Hospital non-survivors (n=36)	<i>p</i> value*	Odds ratio (95% CI)
Gastrointestinal bleeding	18 (25%)	12 (67%)	6 (33%)	0.09	0.4 (0.1-1.3)
Other medical ^a	42 (57%)	17 (40%)	25 (60%)	0.06	2.7 (1.0-7.0)
Emergency surgery	8 (11%)	3 (27%)	5 (63%)	0.48	1.8 (0.4-8.3)
Elective surgery	5 (7%)	5 (100%)	0 (0%)	NA	NA

a 'Other medical' includes medical causes for respiratory failure other than airway protection during GI bleeding e.g pneumonia, sepsis, reduced GCS

Figure (1): Hospital mortality rates for each scoring system within each population quartile.



Median and IQR for each scoring system are shown in legend (top right)

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