Outcomes for critically ill patients with haematological malignancies in specialist and non-specialist centres in the United Kingdom

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Abstract

Background: Patients with haematological malignancies admitted to critical care units have a high mortality. Specialist cancer centres may demonstrate better survival rates than non-specialist centres. We compared the outcomes of patients with haematological malignancies admitted to three different centres in the United Kingdom, and examined possible reasons for differences in outcomes.

Methods: We compared the characteristics and outcomes of patients with haematological malignancies admitted to critical care units at the Christie, Royal Liverpool University and Glan Clwyd hospitals between 1st January 2007 and 1st July 2011. Differences between hospitals were compared using ANOVA or Chi-squared test, as appropriate. Factors associated with hospital mortality were analysed using logistic regression analysis.

Results: 187 patients with haematological malignancies were identified. More patients with Hodgkin’s lymphoma were admitted to Glan Clwyd hospital (25%) compared to Royal Liverpool (5.8%) and the Christie (8.1%), p=0.0087. Patients admitted to the Christie had lower severity-of-illness scores compared to patients admitted to the other hospitals (p<0.001). Overall, 91 patients died before hospital discharge (48.7%). Unadjusted hospital mortality at the Christie was significantly lower (41.4%), compared to the Royal Liverpool (61.5%) and Glan Clwyd hospitals (54.2%), p=0.0240. On logistic regression analysis, the only factor associated with higher odds of hospital mortality was increasing APACHE II score (p=0.035, odds ratio 1.06 [95% CI 1.04-1.13] per point). Admission to a non-specialist centre was associated with higher odds of critical care unit mortality (p=0.036, odds ratio 2.17 [95% CI 1.05-4.46]), but was not associated with higher odds of hospital mortality (p=0.065).

Conclusions: Admission to a specialist centre was not associated with lower hospital mortality compared to non-specialist centres for patients with haematological malignancies. However, admission to a specialist centre was associated with lower critical care unit mortality. Possible explanations for these differences in survival between centres could be the identified significant differences in casemix, or lower severity of illness at admission. In addition the severity of illness on admission to the critical care unit as indicated by the APACHE II score increased the odds of hospital mortality.

Keywords: Hematologic malignancies, organ dysfunction scores, APACHE II score, hospital mortality

Introduction

About 7% of patients with haematological malignancies (HM) admitted to hospital become critically ill [1]. Admission to the critical care unit (CCU) carries a high risk for such patients, with some studies demonstrating that only 40% of admissions to CCU with HM survived to hospital discharge [2-4]. Six month survival
is 20-23% [5,6], and one year survival is approximately 15% [7,8]. Survival rates may be increasing however since recent data demonstrate hospital and one year survival of 54-60% and 43%, respectively [9,10]. Outcomes after haemopoietic stem cell transplantation (HSCT) appear to be worse [11], although there have been a number of papers suggesting that the prognosis may have improved even among HSCT recipients [12-15].

Factors that consistently predict poor outcome in patients admitted to the CCU with haematological malignancies include: invasive mechanical ventilation [16-18], multiple organ dysfunction, and increasing severity-of-illness score (Acute Physiology and Chronic Health Evaluation (APACHE) II, Simplified Acute Physiology Score (SAPS) II, or Intensive Care National Audit and Research Centre (ICNARC) score) [2,4,5,15,19]. APACHE II is the most accurate score in this group of patients [2]; however it may still underestimate mortality in HM patients [1]. In a study comparing patients with HM to medical critical care patients, outcomes in patients with HM were significantly worse, with only 27% of patients with HM surviving to hospital discharge [20]. However, in another study comparing patients with a similar SAPS II score, there was no significant difference in outcome [21]. The characteristics of the malignancy (such as adverse cytogenetics, and Eastern Co-operative Oncology Group score) appear to be less important to hospital survival than to longer-term survival [3,5]. However, outcomes in specialist cancer centres appear to be better than in more general CCU [9,17]. Better outcomes in high-volume units have been described in other areas of critical care medicine, for example in the management of mechanically ventilated patients [22,23]. The reasons for these variations in outcomes include patients being referred to specialist centres that already have good outcomes, leading to an increase in case volume [24]. Another reason is that with increased volume comes increased clinical experience, and this leads to better outcomes. Under this mechanism, high volume leads to high quality. Third is the possibility that healthcare is organized differently at high-volume centres, with multidisciplinary teams, clear protocols, and better staffing levels that lead to better outcomes. Differences in casemix may also influence outcomes; however if the differences in outcome between centres cannot be explained by differences in casemix, there are implications for cancer care being concentrated in specialist centres. This study aimed to compare the casemix and outcomes of patients with HM admitted to three different CCU in the United Kingdom.

Methods
The local Research Ethics Committee at each participating hospital waived the requirement for formal consent, since this was a retrospective review of routinely collected audit data. We conducted a retrospective study of an electronic patient database at three CCU in three hospitals in the United Kingdom: The Christie Hospital (CH) (a specialist cancer hospital); the Royal Liverpool University Hospital (RLUH) and Glen Ciwyd Hospital (GCH) (both non-specialist hospitals). The CH houses a “high-volume” 8-bedded CCU that admits >30 patients with HM per annum. Patients in this unit do not routinely receive invasive mechanical ventilation (IMV), and are transferred to another CCU if a prolonged period of IMV is required (more than 24h). The RLUH and GCH are not specialist hospitals for cancer, the CCU in these hospitals admit <30 patients per annum with HM. The RLUH receives tertiary referrals with HM, and has 13 beds in the CCU. GCH has an 8-bedded CCU. We performed a search of the admissions database at each unit to identify patients with HM admitted to CCU in each hospital. Admissions to RLUH and GCH between 1st January 2007 and 1st July 2011, and to the CH between 1st October 2008 and 30th September 2011 were identified. The following search criteria were applied.

Search criteria
Admissions with any of the following conditions in any diagnostic field: bone marrow transplant, graft versus host disease, acute lymphoblastic leukaemia, acute myeloid leukaemia, chronic lymphocytic leukaemia, chronic myeloid leukaemia, Hodgkin’s lymphoma, non-Hodgkin’s lymphoma or myeloma. Admissions that had any of the following conditions in their past medical history were also included in the analysis: acute myeloid leukaemia or lymphoblastic leukaemia or multiple myeloma; chronic myeloid leukaemia or chronic lymphocytic leukaemia; or lymphoma. All conditions coded had to be present in the six months prior to admission to the CCU.

Patients admitted after planned surgical procedures were excluded from analysis. If a patient had more than one CCU admission, only the first admission was included in analysis. “Hospital mortality” was defined as death during the same hospital stay as CCU admission—patients transferred between hospitals were followed up to their ultimate discharge from hospital. For each admission with HM, the following data was extracted and entered onto an Excel spreadsheet (Microsoft Corporation): age, duration of critical care stay, length of hospital stay prior to admission, number of organ failures on admission, APACHE II score, admission diagnoses, and underlying HM diagnosis. Admission diagnoses were grouped into the most relevant clinical reason for admission to critical care. Patients admitted with complications of bone marrow suppression (e.g., bleeding secondary to thrombocytopenia) were classified as “Haematological” admissions. Data were entered onto the database by a separate researcher in each unit, with data checking and validation occurring at one centre. Data were checked and resubmitted if necessary by each participating centre. Descriptive statistics and comparative analysis were performed.

Statistics
Our primary outcome was the hospital mortality at each hospital. Our secondary outcomes were the critical care unit...
mortality at each hospital, and the admission characteristics of patients with HM. We compared admission characteristics of patients admitted to each CCU, as well as unit and hospital mortality between the three hospitals. Characteristics and outcomes between critical care units were compared using ANOVA and chi-squared tests, respectively. Potential factors associated with hospital mortality were analysed using univariate analysis. Multiple logistic regression analyses were performed with CCU and hospital mortality as the dependent variable. Specialist (CH) and non-specialist centres (RLUH and GCH) were coded as categorical variables. Two-sided P values <0.05 were regarded as statistically significant. MedCalc software version 12.0 (MedCalc software, Belgium) was used for all statistical analyses.

Results

187 admissions with HM were identified in total. Between 1st January 2007 and 1st July 2011 there were 52 admissions at the RLUH and 24 at GCH. Between 1st October 2008 and 30th September 2011 there were 111 admissions with HM identified at CH. We were able to analyze outcome data from all 187 patients with HM in multiple logistic regression analysis.

Comparison of case mix between hospitals

Comparative data for patients admitted to the three different units in shown in Table 1. The mean (SD) age overall was 57 (15) years; patients admitted to GCH were older (65 [13.7] years) compared to those admitted to RLUH (mean age 51.7 [15.5] years) and CH (mean age 57.8 [14.2] years), p=0.001. A lower proportion of patients with acute myeloid leukaemia (AML) were admitted to GCH (5/24, 20.8%) compared to RLUH (18/52, 34.6%) and CH (46/111, 41.4%), although this difference was not statistically significant (p=0.153) (Table 1) and there was a greater proportion of admissions with Hodgkin’s lymphoma to GCH (6/24,25%) compared to RLUH (3/52, 5.8%) and CH (9/111, 8.1%), p=0.021; (Table 1). A significantly greater proportion of patients were admitted to the RLUH with acute respiratory failure (26/52, 50%), compared to GCH (9/24, 37.5%) and CH (40/111, 36%), p<0.001 (Table 1).

The overall mean (SD) APACHE II score was 22.4 (6.0). Patients admitted to the CH had lower APACHE II scores (mean 21 [5.5]) compared to patients admitted to RLUH (24.3 [5.9]) and GCH (25.2 [6.4]), p<0.001 (Table 1).

Table 1. Characteristics of patients admitted to critical care units in the study with haematological malignancies.

| All centres | GCH | RLUH | CH | P value |
|-------------|-----|------|----|---------|
| Patients (n) | 187 | 24  | 52 | 111 | -- |
| Age (mean, SD) | 57 (15.0) | 65 (13.7) | 51.7 (15.5) | 57.8 (14.2) | -- |
| APACHE II score (mean, SD) | 22.4 (6.0) | 25.2 (6.4) | 24.3 (5.9) | 21 (5.5) | <0.001 |
| Readmissions (n, %) | -- | 5 (20.8%) | 1 (1.9%) | -- | -- |
| Unit length of stay (days, median, IQR) | 3.4 (1.8-6.3) | 2.3 (1-5.2) | 3.8 (1.8-8.5) | 3.5 (2-6.2) | 0.232 |
| Hospital length of stay prior to admission (days, median, IQR) | 7 (2-17.8) | 2 (0-7) | 6.5 (2-17) | 9.75 (2-20.8) | <0.001 |

| Haematological diagnosis: (n, %) |
|-----------------|
| Myeloma | 26 (13.9) | 3 (12.5) | 8 (15.4) | 15 (13.5) | 0.928 |
| Acute myeloid leukaemia | 69 (36.9) | 5 (20.8) | 18 (34.6) | 46 (41.4) | 0.153 |
| Acute lymphoblastic leukaemia | 14 (7.5) | 3 (12.5) | 6 (11.5) | 5 (4.5) | 0.171 |
| Chronic lymphocytic leukaemia | 21 (11.2) | 2 (8.3) | 2 (5.8) | 17 (15.3) | 0.086 |
| Chronic myeloid leukaemia | 5 (2.7) | 2 (8.3) | 3 (5.8) | 0 | 0.019 |
| Non-Hodgkin’s lymphoma | 30 (16.0) | 3 (12.5) | 12 (23.1) | 15 (13.5) | 0.264 |
| Hodgkin’s lymphoma | 18 (9.6) | 6 (25) | 3 (5.8) | 9 (8.1) | 0.021 |
| Other | 4 (2.1) | 1 (4.2) | 1 (1.9) | 2 (1.8) | -- |

| Admission diagnosis: (n, %) |
|-----------------|
| Acute respiratory failure | 75 (40.1) | 9 (37.5) | 26 (50.0) | 40 (36.0) | <0.001 |
| Sepsis | 38 (20.3) | 10 (41.7) | 12 (23.1) | 16 (14.4) | 0.479 |
| Acute kidney injury | 10 (5.3) | 1 (4.2) | 4 (7.7) | 5 (4.5) | 0.273 |
| Cardiac | 12 (6.4) | 2 (8.3) | 3 (5.8) | 7 (6.3) | 0.174 |
| Abdominal catastrophe | 6 (3.2) | 0 | 3 (5.8) | 3 (2.7) | 0.683 |
| Neurological | 5 (2.7) | 1 (4.2) | 3 (5.8) | 1 (0.9) | 0.449 |
| Drug reaction | 2 (1.1) | 0 | 0 | 2 (1.8) | -- |
| Haematological | 8 (4.3) | 1 (4.2) | 1 (1.9) | 6 (5.4) | 0.044 |
| Graft v Host disease | 4 (2.1) | 0 | 0 | 4 (3.6) | -- |
| Other | 22 (11.8) | 0 | 0 | 22 (19.8) | -- |
admission. Patients admitted to the CH spent significantly longer in hospital before CCU admission (median 6.5 [IQR 2-17] days) compared to the RLUH (median 3.8 [IQR 1.8-8.5] days) and GCH (median 2 [IQR 0-7] days), p=0.001 (Table 1).

Unit and hospital mortality
Overall, 55 (29.4%) of patients died during their CCU admission, and 91 (48.7%) died before hospital discharge. Both CCU and hospital mortality were significantly lower in the specialist centre (20.7% and 41.4%, respectively) when compared to the non-specialist centres. CCU and hospital mortality at GCH was 33.3% and 54.2%, respectively; and at RLUH was 46.2% and 61.5%, respectively (Table 2). p values were 0.0028 for unit and 0.0240 for hospital mortality, respectively. Factors associated with higher odds of CCU mortality were increasing age and APACHE II score (odds ratio 1.06 [95% CI 1.04-1.13, p=0.035), although there was a trend to significance in admission to a non-specialist unit using logistic regression analysis (Table 3).

Table 2. Outcomes at unit discharge and hospital discharge compared at specialist and non-specialist centres participating in the study.

| Variable          | GCH  | RLUH  | CH   | P value |
|-------------------|------|-------|------|---------|
| CCU mortality     | 8/24 (33.3) | 24/52 (46.2) | 23/111 (20.7) | 0.0028  |
| (n, %)            |      |       |      |         |
| Hospital mortality| 13/24 (54.2) | 32/52 (61.5) | 46/111 (41.4) | 0.0240  |

Factors associated with hospital mortality
In univariate analysis, admission to the specialist centre (p=0.024) and the APACHE II score (p=0.0051) were the only factors associated with an increased risk of hospital mortality (Table 2).

On logistic regression analysis, the only variable associated with increased odds of hospital mortality was the APACHE II score (odds ratio 1.06 [95% CI 1.04-1.13, p=0.035), although there was a trend to significance in admission to a non-specialist centre (p=0.065) (Table 4).

Discussion
In this study we have found significant differences in the casemix and outcomes of patients with HM admitted to different critical care units. The unit with the best outcomes is sited in a specialist cancer hospital, and admits the highest caseload of patients with HM, although we did not find a statistically significant association between admission to a specialist centre and hospital outcome using logistic regression.

The strengths of this study are that it was a multicentre study, involving specialist and non-specialist centres. This allows us to generalize the results of our study to both specialist and non-specialist centres, and discuss possible underlying reasons for the varying survival of patients with HM in published studies. Another strength of the study is that the database used to collect data on CCU admissions analyzed in this study is well validated and undergoes rigorous error checks.

There are several weaknesses which result from this study as data was collected retrospectively. There is a risk that some patients with HM were omitted from the database used as the primary source for this study. Standardized admission criteria across the units were not specified, and may differ, which may reduce the validity of analysis of the outcomes between centres. Finally, the data was collected from three different study sites, with our results demonstrating significant differences in casemix and severity of illness on admission.

The overall hospital survival rates for patients with HM in this study compare favourably with those described in a specialist centre in London (54%) [9]. Overall hospital survival in this study was 51.3% for all centres, and 58.6% at the specialist cancer centre. The proportion of patients admitted to the non-specialist centres with CLL may seem high (8.3% at GCH and 5.8% and RLUH), but this is comparable with patients admitted with chronic leukaemia in other studies [4,9]. The proportion of patients surviving at the specialist centre was significantly greater than at the non-specialist centres, supporting the idea that a volume-outcome relationship may exist in critically ill patients with HM [17]. However, the present study involved small numbers of patients, reducing our ability to further explore any possible relationship between case volume and outcomes. Similar volume-outcome relationships have previously been described in both specific groups of critically ill patients (such as patients with HM and respiratory failure, and cancer patients with septic shock) [17,25], and in more general CCU patients [22,23]. However, other important factors may account for the differences seen in outcome between centres in this study. Casemix affects outcome and significant
differences in casemix were seen in this study. For example, at the specialist centre, a greater proportion of patients with AML were admitted. Patients in the specialist centre also had significantly lower admission APACHE II scores, indicating that this group were less severely ill than those admitted to non-specialist centres. Since APACHE II score was associated with increased odds of hospital mortality, we must be cautious in ascribing the differences in outcome to increased case volume alone. In addition, patients admitted to GCH were significantly older than those admitted to the other two centres in the study. In addition to these differences, other factors may influence outcome. For example, different admission policies may exist in different centres. In non-specialist centres, the pressure to admit patients with a poor prognosis may be higher; or, in specialist centres, salvageable patients may be identified and admitted at an earlier stage when multiple organ dysfunction can be pre-empted. There is evidence that a significant proportion of critically ill patients with HM are managed on general wards [1]; the proportion of such patients may vary from centre to centre, again influencing the outcome from each centre. Other factors such as expertise gained through caring for a large number of similar patients, multidisciplinary teams, standardized protocols and referral patterns to high-quality centres may influence the outcome of such patients.

Conclusions
This study suggests that survival may be improved for critically ill patients with HM treated in specialist cancer centres, although other factors such as the severity of the acute illness are also significant influences on the mortality of patients with HM. The non-specialist centres in this study had demonstrably worse outcomes and this could be due to poorer patient selection. Denying critical care admission to such patients based solely on the basis of the underlying haematological disease without consideration of the severity of the acute illness appears to be unjustified.

List of abbreviations
AML: Acute Myeloid Leukaemia
ALL: Acute Lymphoblastic Leukaemia
APACHE II: Acute Physiology and Chronic Health Evaluation II
CCU: Critical Care Unit
CH: Christie Hospital
CI: Confidence Interval
CLL: Chronic Lymphocytic Leukaemia
CML: Chronic Myeloid Leukaemia
GCH: Glan Clwyd Hospital
HL: Hodgkin’s Lymphoma
HM: Haematological malignancies
HSCT: Haemopoietic stem cell transplant
ICNARC: Intensive Care National Audit and Research Centre
IMV: Invasive Mechanical Ventilation
IQRF: Intercquartile range
NHL: Non-Hodgkin’s Lymphoma
RLUH: Royal Liverpool University Hospital
SAPS II: Simplified Acute Physiology Score II

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions

| Authors’ contributions          | PAH | RP | PH |
|--------------------------------|-----|----|----|
| Research concept and design    | ✓   | ✓  | ✓  |
| Collection and/or assembly of data | ✓   | ✓  | ✓  |
| Data analysis and interpretation | ✓   | -- | -- |
| Writing the article            | ✓   | -- | -- |
| Critical revision of the article | ✓   | ✓  | ✓  |
| Final approval of article      | ✓   | ✓  | ✓  |
| Statistical analysis           | ✓   | -- | -- |

Acknowledgement and funding
We would like to acknowledge the contribution of the audit teams at each study centre. We would also like to thank Dr. Richard Wenstone for his comments on the manuscript.

Publication history
Senior Editor: Paolo Fortina, Thomas Jefferson University, USA.
Received: 27-Feb-2014 Final Revised: 15-Jul-2014
Accepted: 01-Aug-2014 Published: 07-Aug-2014

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