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Original Papers

Assessment of Outcome Over a 10-year Period of Patients Admitted to a Multidisciplinary Adult Intensive Care Unit with Haematological and Solid Tumours

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SUMMARY

The risk factors for time to mortality, censored at 30 days, of patients admitted to an adult teaching hospital ICU with haematological and solid malignancies were assessed in a retrospective cohort study.

Patients, demographics and daily ICU patient data, from admission to day 8, were identified from a prospective computerized database and casenote review in consecutive admissions to ICU with haematological and solid tumours over a 10-year period (1989-99). The cohort, 108 ICU admissions in 89 patients was of mean age (±SD) 55±14 years; 43% were female. Patient diagnoses were leukaemia (35%), lymphoma (38%) and solid tumours (27%). Median time from hospital to ICU admission was five days (range 0-67). On ICU admission, 50% had septic shock and first day APACHE II score was 28±9. Forty-six per cent of patients were ventilated. ICU and 30-day mortality were 39% and 54% respectively. Multivariate Cox model predictors ($P<0.05$), using only ICU admission day data were: Charlson comorbidity index (CCI), time to ICU admission (days) and mechanical ventilation. For daily data (admission through day 8), predictors were: cohort effect (2nd vs 1st five-year period); CCI; time to ICU admission (days); APACHE II score and mechanical ventilation.

Outcomes were considered appropriate for severity of illness and demonstrated improvement over time. Ventilation was an independent outcome determinant. Controlling for other factors, mortality has improved over time (1st vs 2nd five year period). Analysis restricted to admission data alone may be insensitive to particular covariate effects.

Key Words: MALIGNANCY, HAEMATOLOGICAL: intensive care, mechanical ventilation, outcome, Cox model, random effects

The role of the intensive care unit (ICU) in the care of critically ill patients with haematological and solid malignancies has been a matter of controversy[1-4]. Recent reports suggest that the outcome of these patients may not have substantially improved over time[5-8]. The impact on survival of various interventions such as prior bone marrow transplantation (BMT; allogeneic or autologous), mechanical ventilation and multiple organ dysfunction and its treatment(s) has been variously assessed; outcome variations being presumably due to patient-specific factors (solid tumour versus haematological malignancy, medical versus surgical) and illness severity, and aetiology (respiratory failure and/or shock, extent of associated neutropaenia and proximity to chemotherapy).

Using a previously defined methodology[9] we reviewed potential risk factors for time-to-mortality, censored at 30 days post-ICU-admission, of patients admitted to a single multidisciplinary adult ICU at a university teaching hospital, over the 10-year period 1989 to 1999. Primarily, we were concerned to evaluate any change in outcome over time[10]; the effect of severity of illness[11], comorbidity burden[12] and

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mechanical ventilation[13] on outcome. Secondarily, we gauged the ability of Cox regression to adequately model survival, given recent cautions that the Cox model may not be optimal in acute severe illness[14], and sought evidence for latent patient heterogeneity about important covariates (cohort effect and mechanical ventilation) using random effects models[15].

METHODS

All ICU patient admissions with haematological or solid malignancies from 1989 to 1999, directly referred by the haematology-oncology unit, were identified from the prospective ICU computerized database, incorporating the APACHE II scoring system. Casenotes and ICU data sheets of the patients were subsequently reviewed to confirm diagnoses and to extract relevant study data (which had not been recorded in the computerized ICU database). Access to these records was obtained under extant guidelines of The Queen Elizabeth Hospital (TQEH) Ethics of Research Committee and informed consent was waived.

The following data were extracted by two investigators independently (PJS, JLM):

1. Baseline demographics and diagnosis: date of birth and gender; nature and initial time of malignancy diagnosis; Karnofsky score[16]. Information was obtained from hospital sources and referring medical officers.
2. Hospital admission data: cohort (1st five years October 1989-July 1994; 2nd five years: August 1994-March 1999); admission status (index admission, repeat hospital and ICU admission or repeat ICU admission within a hospital admission); Charlson comorbidity score (CCI)[17]; ICU admission diagnosis; source (ward or emergency service); hospital admission to ICU admission time (lead time); recent surgery (within seven days); time of last chemotherapy; performance of stem cell transplantation; prescription on ICU admission of steroid, granulocyte colony-stimulating factor [G-CSF] and antibiotics; leucocyte and platelet count on ICU admission, on days 1 (admission) through 8 following ICU admission; details of mechanical ventilation, ICU therapeutics, APACHE II score (recorded on admission from the ICU database and calculated retrospectively for subsequent days), organ failure[18] and sepsis status (noted as systemic inflammatory syndrome (SIRS), sepsis, severe sepsis and septic shock)[19] on days 1 (admission) through 8 following ICU admission; ICU and hospital length of stay and outcome.
3. Follow-up—casenote and computerized information systems review and telephone contact with local medical officers.

Patient Exclusions

To preserve a uniform cohort, only patients being directly cared for by the haematology-oncology unit were included in the review. Thus, for example, cancer patients being subjected to "routine" surgical resection and such patients referred from the surgical wards to the ICU for postoperative complications, were not considered. The haematology-oncology unit is a stand-alone integrated unit, caring for a wide range of haematological and solid malignancies; during the time of review, allogeneic bone marrow transplants were not recorded.

Statistical Methodology

Variables are reported as mean±SD. Interval data were analysed by t-test and categorical data by Fisher exact test, where appropriate. Stata(r) statistical software (Version 8 SE, Stata Corp, College Station, TX) was used.

Time to mortality for the index admissions, right censored at day 30, was assessed using Kaplan-Meier and Cox model estimates. The Cox model was structured for (i) pre-morbid and ICU admission day variables and (ii) pre-morbid, admission day and ICU day 1 to 8 time-varying covariates using both first degree lagged and differenced values[20]. Time-varying covariates were identified as those having significant interactions ($P<0.05$) of the (continuously time-varying) covariate with failure times (time to death) over 30 days. Predictor variables were identified using a backward selection procedure based on the Akaike information criterion[21]; initial bi-variable selection screening was not undertaken[22]. Specific attention was directed to (i) model selection with correlated variables (ii) the potential effect of multi-colinearity (iii) the presence of (first order) interactions and (iv) non-linearity of covariate effect. Overall Cox model fit was assessed by residual plots and specific tests for goodness-of-fit, concordance (Harrell's C statistic) and non-proportionality[23,24].

The Cox analysis for multiple record patient data (days 1 through 8) was extended to a random effects model using the Stata® module GLLAMM[25]. Mortality was modelled using a Poisson analysis and the exponentiated regression coefficients were interpreted as conditional hazard ratios. The baseline log hazard was modelled via restricted cubic splines[26]. For instances observed within subjects (785 within 89 patients), random effects were modelled at the sub-

ject level and both the ventilation and cohort effect were also allowed to vary randomly between subjects. Overall utility of the random effects model compared with the fixed effects Poisson model was determined by the likelihood ratio test. Frailty variance [θ], defined as the exponential of the random intercept, was reported; values of >1 were interpreted as reflecting a greater than average hazard and for <1, the hazard was less than average[24].

TABLE 1
Patient variables

ICU referral diagnosis (n, (%))		
Septic shock	28	(25.93)
Acute respiratory failure (non-specific)	23	(21.30)
Sepsis	22	(20.37)
Pneumonia	13	(12.04)
Hypovolaemic shock	8	(7.40)
Tumor lysis syndrome	6	(5.56)
Cardiac arrest	3	(2.78)
Pulmonary embolus	2	(1.85)
Status epilepticus	2	(1.85)
Gastrointestinal perforation	1	(0.93)
Pre-morbid		
Malignancy diagnosis (%)		
Leukemia (acute & chronic)		35
Lymphoma (+ multiple myeloma)		38
Solid tumour		27
Median time from diagnosis to ICU admission (months)		
Leukemia		1
Lymphoma		8.7
Solid tumour		6.4
Karnofsy score (%)		57 (22)
Charlson comorbidity index*		3 (range 2-12)
ICU Admission		
Chemotherapy within 30 days (%)		57
Stem cell transplant (%)		20
Steroid on admission (%)		40
G-CSF on admission (%)		18
Age (years)		54.5 (14)
Gender (% female)		43
Lead time (days) *		5 (range 0-67)
APACHE II score		28 (9)
WCC*#		1.2 (0.1-45.8)
Platelet count*#		32 (2-552)
Ventilated (%)		34
Inotropes / vasopressors (%)		50
SIRS (%)		99
Sepsis (%)		81.5
Severe sepsis (%)		66
Septic shock (%)		50

*Median (range); #×10⁹/l

RESULTS

During the study period there were 108 admissions in 89 patients (13 admissions were repeat ICU admissions in a hospital admission and there were six repeat hospital and ICU admissions). Fifty-four per cent of admissions were in the early cohort. ICU admission diagnoses and patient variables are presented in Table 1.

Graphical display of the time change (days 1 (admission) through 8) for 30-day survivors vs non-survivors for (i) APACHE II score, white blood cell (WBC) count, platelet count and plasma bilirubin and (ii) percentage of patients ventilated, inotrope-dependent, cardiovascular, respiratory, renal, haematologic and neurologic failure[18], are presented in Figures 1 and 2 respectively. The most apparent differences over time between 30-day survivors versus non-survivors were for the APACHE II score, ventilation and haematological and neurologic failure. For variables WBC and platelet count and plasma bilirubin, due to skewness of distribution, time points were plotted as median, interquartile range.

Overall, 46% of patients were ventilated in ICU. Ventilated patients had an APACHE II score 34±8, with 73% mortality. For the early versus late cohort, there was no difference in APACHE II score (28±8.4 vs 28±10, P=0.9), the percentage of patients ventilated (56% vs 44%, P=0.99) or unadjusted mortality (78% vs 67%, P=0.49). Median length of mechanical ventilation was 3.5 days (range, 0.5-26 days); median ICU and hospital length of stay were 3 (range, 0.5-41) and 20 (range, 0.5-141) days respectively. ICU and 30-day mortality were 39% (95% CI, 30%-52%) and 54% (95% CI: 45%-65%) respectively.

Kaplan-Meier estimates of 30-day survival probability and the corresponding smoothed hazard plot[27] are shown in Figure 3 A and B respectively. Using

TABLE 2
Cox model estimates (hazard ratio±SE) for significant predictors

	Cohort (2nd vs 1st 5 year period)	CCI (range 2-12)	Time to ICU admission (days)	Apache II score	Mechanical ventilation
Admission day Data					
Hazard Ratio ± SE		1.15±0.063	1.02±0.012		3.21±0.981
P value		0.009	0.05		0.001
Admission to day 8 Data					
Hazard Ratio±SE	0.62 ± 0.20	1.12±0.056	1.02±0.001	1.05±0.023	2.59±0.723
P value	0.05	0.02	0.02	0.02	0.01

CCI: Charlson comorbidity index.

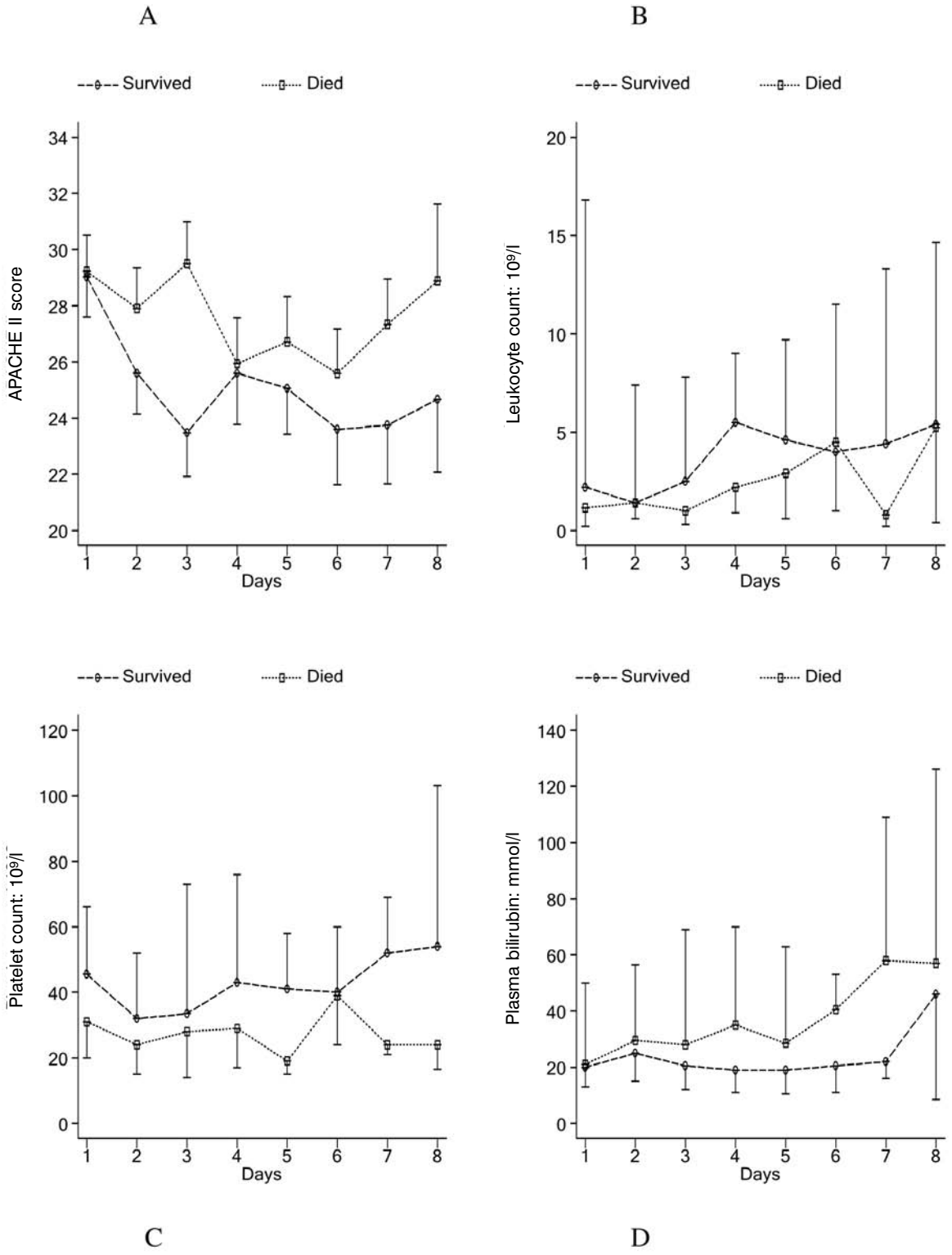

FIGURE 1: Time course of change of variables for survivors (dashed line) and non-survivors (dotted line) over the first 8 days of ICU stay.
A. APACHE II score (as mean values with vertical bars as 95% CI).
B. Leucocyte count (10^9/l).
C. Platelet count (10^9/l) .
D. Plasma bilirubin (mmol/l).
For variables B-D values are median with vertical bars as inter-quartile range.

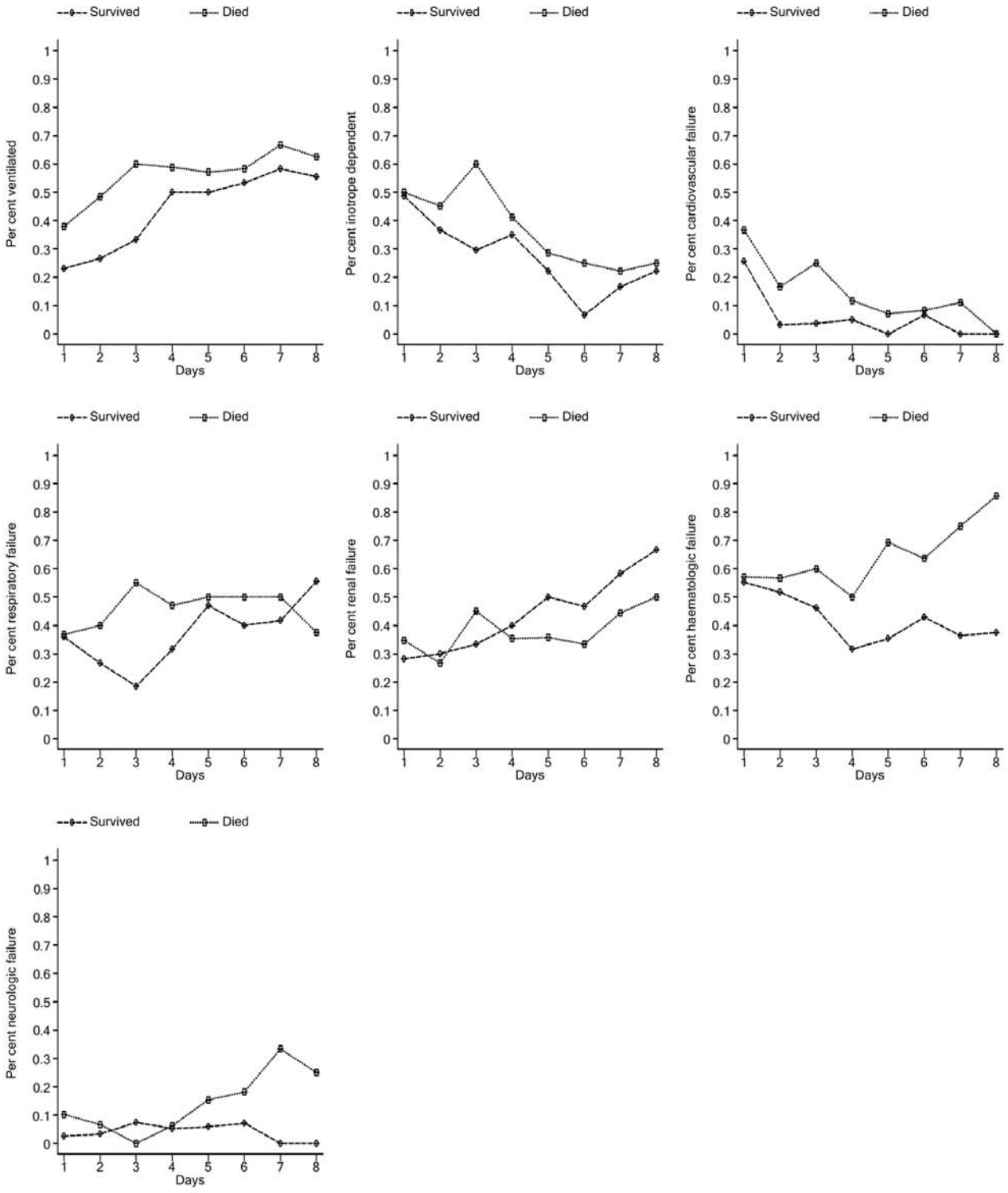

FIGURE 2: Time course of change of variables (as percentages) for survivors (dashed line) and non-survivors (dotted line) over the first 8 days of ICU stay.
Upper panel, left to right: ventilation, inotrope dependence and cardiovascular failure.
Middle panel, left to right: respiratory, renal and haematologic failure.
Lower panel: neurologic failure.
Criteria for organ failures are as in Methods section, above.

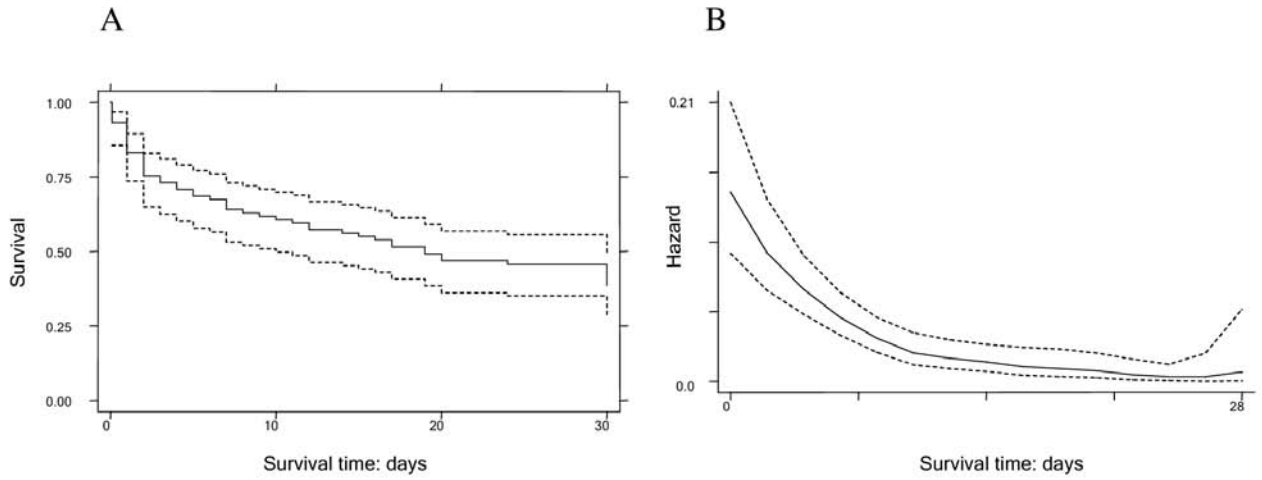

FIGURE 3: A. Kaplan-Meier survival estimates with 95% point-wise CIs (dashed lines). B. Smoothed hazard (vertical axis) with 95% CIs (dashed lines); horizontal axis; time(days).

admission day data only, Cox regression predictors of survival were: Charlson comorbidity index, lead time (in days) and mechanical ventilation. For the multiple-record data Cox model (using patient data over days 1-8 in ICU), predictors of survival were Charlson comorbidity index, lead time (in days), mechanical ventilation, APACHE II score and cohort effect (considered as a categorical variable; second versus first five-year period) (Table 2). Multicolinearity was not present and no significant interactions were evident despite careful consideration of the potential interactions between (i) lead time and cohort effect (ii) cohort effect and malignancy diagnosis (iii) mechanical ventilation, APACHE II score and malignancy diagnosis (iv) inotrope dependency and APACHE II score and (v) age at diagnosis and specific malignancy diagnosis. Non-linear covariate effect was not demonstrated.

The Cox model demonstrated good fit ($P>0.1$ across all deciles), Harrell's C concordance statistic was 0.70 and the global proportionality test was non-significant at $P=0.16$ (Day 1 model) and $P=0.9$ (multiple patient record data model). Time-varying covariate effects were not found for any variables, including the predictors noted above, WBC count, platelet count, and inotrope dependency. Graphical display of the survival probabilities for the four distinct categorical groups (multiple record patient data model), at covariate values of APACHE II score=26, CCI=4 and lead time=5 days, is presented in Figure 4 (back-projected to a common survival probability of 100% at day "0").

Table 3 presents parameter estimates from the random effects model: the Cox and fixed effects Poisson models yielded similar estimates for the predictor variables (Charlson comorbidity index, lead time, mechanical ventilation, APACHE II score and cohort) signifying that the modelling of the baseline hazard was sufficient. The random effects model parameters suggested an increased impact of both the cohort effect and mechanical ventilation. However, the likelihood ratio test comparing this model with the fixed effects Poisson model was non-significant ($P>0.5$), indicating no unmeasured subject heterogeneity.

TABLE 3
Comparison of Cox, fixed effect Poisson and random effects regression model estimates

	Cox model	Poisson	GLLAMM	θ
Cohort (2nd vs 1st 5 year period)	0.62±0.2	0.61±0.19	0.54±0.207	1.03
CCI	1.12±0.056	1.12±0.06	1.16±0.082	
TIME to ICU admission (days)	1.02±0.009	1.02±0.01	1.02±0.013	
APACHE II score	1.05±0.023	1.05±0.022	1.06±0.025	
Mechanical ventilation	2.59±0.723	2.61±0.868	3.07±1.344	1.02
Log Likelihood	–185.72	–148.5	–148.28	

Cox model: estimates as hazard ratios±SE for multiple record patient data (days 1-8, cf Figure 5). Poisson; fixed effects Poisson model with baseline hazard modelled with restricted cubic spline (point estimates as incidence rate ratios±SE). GLLAMM; random effects model (subject, mechanical ventilation and cohort), estimates as conditional hazard ratios±SE. θ: frailty variance.

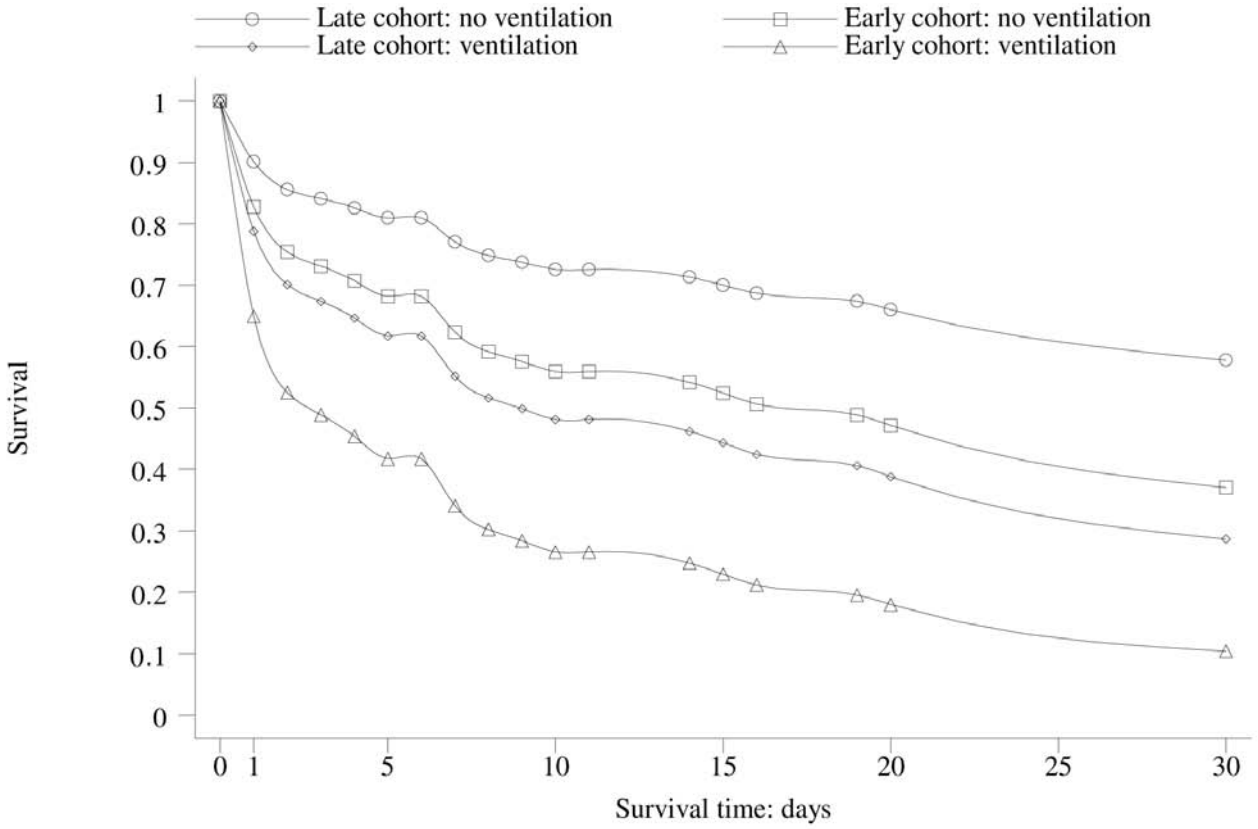

FIGURE 4: Cox model survival probabilities for the 4 distinct categorical groups (multiple record patient data model), at covariate values of: APACHE II score=26, CCI=4 and lead time=5 days (back-projected to a common survival probability of 100% at day "0").
Circles: late cohort, no mechanical ventilation.
Squares: early cohort, no mechanical ventilation.
Diamonds: late cohort, mechanical ventilation.
Triangles: early cohort, mechanical ventilation.

DISCUSSION

Numerous articles have reviewed the outcome of ICU patients suffering from haematological and solid tumours and have addressed the question of predictive variables at a descriptive[2,28-30] and modelling level[8,31-34]. A dominant theme has been the poor outcome, with hospital or 30-day mortalities ranging from 40 to 50% in general cancer patients[5], and up to 80% or greater in ventilated, inotrope-dependent patients undergoing bone marrow transplantation[3]. Not surprisingly, mortality has also been observed to increase with severity of illness. The current study attests to a high mortality, revealed by the patient subsets displayed in Figure 4.

Modelling Considerations

The analytic approach was to contrast the more conventional premorbid/admission variable analysis with that of an "updated" covariate model, using patient data recorded over the first eight days of ICU admission. As noted above, no time-varying covariate effect for the predictors could be demonstrated and thus, in the "updated" covariate model, the coefficients were interpreted as an "average" over all days for which failures occurred. That is, the coefficients representing covariate effect were "time-invariant"[20]. Of interest, no prognostic effect of tumour type or leukocyte or platelet count (at least over the first 8 days) was evident, which would argue against any policy of optimism that depended upon recovery of haematological indices.

Neither the cohort effect nor the APACHE II score were predictors using the day 1 data set, which would therefore indicate advantage for the "updated" covariate model. The improvement of statistical efficiency by repeated subject observation (in the pres-

ence of information loss due to censoring), has been previously noted[35].

The (mortality) hazard over the 30 days showed a monotonic decline (Figure 3B), which was different from the peaked (non-monotonic) hazard curve reported by Knaus and co-workers[14]. A monotonic decline suggests a maximal hazard on or before ICU admission, indicated presumably by the high admission APACHE II scores and the predictive importance of time to ICU admission.

The cohort effect in this study was modelled as a categorical variable as this approach had an intuitive interpretability and was a compromise between a long study period (10 years) and relatively small study numbers. There are problems with such a "cut-point" approach: those of increase in Type I error, overestimation of effect at each of the cut-point levels and the conceptual problem of sudden marked changes in effect at the various levels[36]. A post hoc search for an "optimal cut-point" for the cohort effect (using the maximal chi-square of the generalized log-rank statistic via isotonic regression analysis[37]) identified the same cut-point (July to August 1994) as was used in the study (data not shown).

Cohort Effect

A cohort effect was demonstrated, with the second five-year period having a better (risk adjusted) prognosis (Table 3). That this was not an effect of a change in referral pattern or severity and/or type of illness was indicated by the non-significance of the interaction between the cohort effect and lead-time, APACHE II score and tumor diagnosis. There was also no difference in the percentage of censored patients, nor in the distribution of censored survival times, early versus late cohort ($P=0.13$, $P=0.9$, respectively), which could have potentially explained this cohort effect.

There would appear to be little comment in the specific haematological-oncological literature about ICU mortality improvement over time: two recent notes have suggested that this may not be the case[7,38]. However, Azoulay et al[39] reported a single institution study with an improved survival in a 1996 to 1998 cohort compared with a 1990 to 1995 cohort and proposed that the increased use of non-invasive mechanical ventilation over time was a possible explanation for the survival improvement, although a (significant) treatment-cohort interaction was not reported. While the use of non-invasive mechanical ventilation may explain the improvements seen over time, the interpretation of treatment effects (causality) is known to be problematic in cohort studies[40] and the positive effect of non-invasive mechanical ventilation on mortality in randomized studies involving non-COPD patients has yet to be demonstrated[41]. Furthermore, an analysis of the differences between patients who received non-invasive mechanical ventilation to those who did not, yielded differences ($P<0.1$) in seven patient characteristics, six of which favoured improved outcomes in the non-invasive mechanical ventilation patients, suggesting that other changes in patient characteristics over time may have made this form of ventilation look more favourable.

The factor(s) responsible for the improvements over time in the current study were not immediately apparent. Overall power considerations may have been important, especially in the detection of treatment effects through the use of interaction terms, given the requirement for increased patient numbers (approximately 4×) to demonstrate significance of interactions as compared with the main effects[42]. It is possible that the observed improvement in outcome with time may be consonant with the overall improvement in ICU outcomes noted by Azoulay et al[39] and Kress et al[43] and identified in other specific patient groups[10].

IMPACT OF MECHANICAL VENTILATION

Most studies have found mechanical ventilation to be an independent adverse predictor of outcome, as with the present report. Some cautions may apply to the interpretation of the effect of mechanical ventilation. There was significant statistical association between APACHE II score, mechanical ventilation use and inotrope dependency (data not shown). Ventilation may also be considered as a surrogate for outcome, as in the paper by Crawford and Peterson[44]. Thus, within the same data sets, these outcomes are correlated and, therefore, it may be no surprise to find a significant effect of ventilation. The bias of estimators that adjust for a concomitant variable affected by treatment has been noted[40]. This being said, no colinearity was demonstrated between APACHE II score, mechanical ventilation and inotrope dependency and there was no substantive change in the point estimates and standard errors of the hazard ratios of the Charlson comorbidity index, lead-time, APACHE II score and cohort when mechanical ventilation (considered as a categorical variable) was excluded from the estimation. This would suggest that the estimates of the effect of mechanical ventilation obtained in this study were not biased by overly strong correlations with other variables.

Premorbid Assessment

Although the APACHE II score incorporates an assessment of chronic health status, the predictive ability of other composite chronic health indices, Karnofsky score and Charlson comorbidity index, was also assessed. The Karnofsky score was not found to be predictive. Other referenced studies used univariate assessment of chronic health status, which is paradoxical as the multivariable Charlson index[17], introduced in 1987, was validated in a cohort of patients with breast cancer and has been found to be of predictive value in other patient groups[45].

Random Effects (Frailty) Model

The notion of frailty or individual (or group) heterogeneity and its extension to survival studies has assumed some importance recently[15]. A frailty model is a random effects model for time variables where the random effect has a (latent) multiplicative effect on the hazard. Frailty addresses unexplained variability (in time to failure) in terms of omitted covariate(s) or measurement error; thus, if frailty is ignored, an underestimation of covariate effect will be observed[46]. The use of frailty in this analysis was to identify patient heterogeneity with respect to both ventilation and cohort effect, where some uncertainty existed about the adequacy of modelling of the effect. This may be particularly apposite in indicating "system" (treatment and case-composition) changes over time that were unable to be precisely specified from the data set. Although the random effects point estimates suggested a modification of the effect of the covariates (Table 3), we were unable to demonstrate significant advantage for the random effects approach.

CONCLUSIONS

We would conclude that 30-day survival improved over a 10-year period. Questions of excess mortality or appropriateness of care must be considered against the background of the level of severity of illness and cohort composition, including comorbidity burden. Analysis restricted to admission data alone may be insensitive to particular covariate effects. Neither tumour type nor recovery of neutrophil or platelet count over first eight days after admission was prognostic, but mechanical ventilation would appear to be an independent mortality determinant. Peak mortality hazard occurs proximate to ICU admission and declines monotonically thereafter.

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