Survival of Critically Ill Medical Patients is Time-Critical

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ABSTRACT

Objective: *Survival from acute coronary syndromes and major trauma has been shown to depend on timely access to definitive treatment. We sought to identify the significance of intensive care unit (ICU) admission delay (lead-time) on the outcome of critically-ill medical patients with other diagnoses.*

Methods: *From 1 January 1997 to 31 December 2003, a prospective cohort study was performed in critically-ill patients requiring mechanical ventilatory support (MV) and/or renal replacement therapy (RRT), admitted directly to the Northern Hospital ICU within 24 hours of arrival in the emergency department (ED). Patients were excluded if, a) they were admitted following surgery, major trauma or transfer from another hospital, or b) their duration of ICU stay was < 8hours. Data collected included de-identified patient demographics, final diagnosis, APACHE II mortality risk (p_m) and lead-time (i.e. difference between times of entrance to the ED and ICU.) The primary outcome measure was hospital discharge status.*

Results: *Six hundred and nineteen consecutive ICU admissions from the ED met the inclusion criteria and required MV (n = 557) and/or RRT (n = 162.) Non-survivors were older (median age 73 vs. 54yrs) and sicker (median p_m 0.72 vs. 0.23) compared with survivors. Multivariate analysis using logistic regression identified lead-time as a significant predictor of mortality (RR = 1.06 per hour, 95% CI =1.01 - 1.10; p=0.015) in addition to age, diagnosis and illness severity.*

Conclusions: *ICU admission delay (lead-time) is associated with a greater mortality-risk in critically ill medical patients requiring MV and/or RRT.* (**Critical Care and Resuscitation 2004; 6: 261-267**)

Key words: Intensive care, lead time, admission delay

Timely resuscitation and definitive care is believed to improve the survival of critically ill patients.[1,2] This has resulted in the development of mobile emergency services, triage systems and hospital emergency departments (ED) with specific resuscitation areas and highly skilled staff. These dedicated, costly and rapid response systems have improved the outcome from emergency surgical,[3] major trauma[4,5] and acute coronary syndromes.[6,7] The impact of a delay in definitive care on other critically ill patients is unclear.

Intuitively, survival from any form of acute illness is likely to be time-critical, but the relative importance of timely access to definitive care for patients with acute respiratory or renal failure is not known. As a consequence sufficient priority may not be afforded this group.

The lead-time interval, between arrival in hospital and admission to an intensive care unit (ICU), is dependent upon a number of inter-related processes (Table 1). Resuscitation and stabilisation of critically ill patients is a significant workload issue[8] for most emergency departments making triage, resource allocation[9] and timely access,[10] complex issues. Does the duration of lead-time affect the outcome of critically ill patients who are admitted directly to ICU?[9,10] We have previously documented that inter-hospital transfer of critically ill patients delays their recovery,[11] but we were unable to quantify the impact of the lead-time delay[10] to

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Table 1. Lead-time components for patients admitted to the intensive care unit

Emergency department triage
Initial assessment
Resuscitation and stabilisation
Initial investigations
Specialist referral and assessment
Intensive care referral and assessment
Transfer to intensive care unit

ICU admission *vis a vis* the physiological disturbance that occurs during transportation.[12]

To our knowledge, no outcome study has directly addressed this question. Since a randomised controlled trial of lead-time (i.e. delayed admission to ICU) is unethical, we undertook a prospective cohort study of critically ill patients, with acute respiratory or renal failure, requiring urgent intensive care services. We sought to establish what impact, if any, lead-time has on the outcome of critically ill medical patients at The Northern Hospital (a Melbourne metropolitan University-affiliated teaching hospital providing acute-care health services except cardiac surgery and organ transplantation).

METHODS

All adult patients requiring intensive care services at The Northern Hospital between 1 January 1997 and 31 December 2003 were entered in the study if they, a) were admitted directly from the ED to the ICU within 24 hours of hospital arrival, and b) required invasive mechanical ventilatory support (MV) and/or renal replacement therapy (RRT) – therapies not available elsewhere within the hospital. These patients represent a high-risk group for whom lead-time is more likely to be important, and for whom ICU admission is unequivocal. Patients requiring emergency surgery, major trauma care or urgent coronary intervention were excluded.

All subjects were resuscitated and stabilised within the ED, and referred to the ICU medical team, prior to transfer to ICU. Suitability for ICU admission was based on the clinical judgement of the on-duty intensive care specialist.

Entered subjects were excluded from the analysis if; a) they were subsequently transferred to another hospital for definitive care; b) MV was initiated after admission to ICU; c) RRT was initiated more than 24 hours after admission to ICU; d) they were less than 16 years of age; or e) they remained in ICU less than 8 hours. The primary end point was hospital discharge status.

Hospital ethics committee approval was obtained. Patient consent was deemed unnecessary due to the absence of patient identification and the observational nature of the study using the pre-existing hospital dataset. The study was unfunded. Data were recorded prospectively, by the authors, and included de-identified patient demographics, date and time of admission and transfer, physiological and laboratory data in ICU (Table 2), final diagnosis and hospital outcome. *Lead-time* was defined as the time difference between patient arrival at the ED and arrival in the ICU.

Table 2. Summary of APACHE II variables and methodology[13]

Variables

- Physiological data: temperature, blood pressure, heart rate, respiratory rate, Glasgow coma score.
- Pathological data: haematocrit, total white cell count, sodium, potassium, creatinine, urea, albumin, glucose, and arterial pH and PaO_2.
- Clinical data: age, diagnosis, presence of acute respiratory and/or renal failure, chronic health status.

Formula for p_m score

$\log_n(p_m/1-p_m) = -3.517 + 0.146(k_1+k_2+k_3)+k_4+k_5$

Where

- k_1 = a variable score based on physiological and pathological data;
- k_2 = a variable weighting for age;
- k_3 = a variable weighting for chronic health status;
- k_4 = a constant weighting for emergency surgical patients; and
- k_5 = a variable weighting for principal diagnostic category

Physiological and laboratory data were used to calculate predicted mortality-risk (p_m) as an index of illness severity using the Acute Physiology and Chronic Health Evaluation (APACHE) II method (Table 2.).[13] The highest and lowest values within the first 24 hours of admission to ICU were collected for each variable, except the Glasgow coma score (GCS), to optimise calculation of illness severity. The GCS was recorded as the lowest value prior to initiation of sedation and/or intubation in the ED. Raw data and APACHE II derived p_m, for the entire cohort, were submitted to the Adult Patient Database[14] (the Australian and New Zealand Intensive Care Society and government funded national data repository) for validation, data quality checks and comparison with national benchmarks. Missing or suspicious data (e.g. 00:00 hr), and admission and transfer times for all subjects, were checked for accuracy by retrospective case record review.

Statistical analysis

Based on our previous observations of a 40% increase in relative mortality-risk from delayed admission,[11] we calculated (using p = 0.05, and power of 80%) that a population of at least 300 patients would be required. Comparison of survivors with non-survivors (using Fisher's exact and Mann-Whitney tests) was undertaken to identify univariate factors associated with in-hospital mortality. Group data are presented as median (inter-quartile range) unless otherwise indicated. Multivariate analysis using a logistic regression model (SPSS)[15] was undertaken to identify independent factors predictive of in-hospital mortality. A stepwise regression procedure was used to derive the model. Variables finally entered into the multivariate analysis included lead-time, patient age and sex, severity of illness (APACHE II score [APS]), diagnosis, premorbid (chronic health) status,[13] acute renal and respiratory failure the time and the weekday of admission.

RESULTS

Over the study period 3461 patients were admitted to the ICU (83% as emergencies) of whom 1593 (46%) were admitted directly from the ED. After excluding major trauma and coronary intervention patients, 669 (19%) of these patients required MV and/or RRT on arrival in ICU. Of the 669 eligible patients 50 (7.5%) were later excluded from the analysis (37 transferred to another acute-care facility; 9 due to short ICU stay; and 4 under 16 years) leaving 619 subjects (93%) for analysis (Table 3).

The study group were a more severely ill subgroup of the parent population (all ICU admissions), as evidenced by APACHE II score, predicted mortality (p_m) and fatality rates (Table 3). The study population was a heterogeneous group as evidenced by the diagnostic categories and their fatality rates (Table 4).

Table 4. Ten most common primary diagnostic categories

Primary Diagnosis	*n (%)*	*Case fatality rate (%)*
Drug overdose	111 (18%)	3 (3%)
Cardiac arrest	84 (14%)	63 (75%)
Pneumonia	41 (7%)	11 (27%)
Exacerbation COPD	40 (7%)	8 (20%)
Septic shock	40 (7%)	20 (50%)
Congestive heart failure	36 (6%)	18 (50%)
Cardiogenic shock	32 (5%)	24 (75%)
Respiratory arrest	29 (5%)	3 (10%)
Acute renal failure	22 (4%)	4 (18%)
Acute asthma	16 (3%)	0
Subtotal	451 (73%)	154 (34%)

The cumulative frequency distribution of *lead-time* interval for survivors and non-survivors is displayed in Figure 1. Four hundred and ninety five patients (80%) were admitted to ICU within 8 hours of arrival in hospital. Admission times were evenly spread across the three nursing-shifts of the day (Table 5). Non-survivors were significantly older and sicker (cf. APACHE II score and p_m) than survivors and experienced a small, but statistically significant, increase in lead-time (Table 5). A detailed analysis of admission times revealed no clear diurnal, weekly, or seasonal patterns to the observed variations in lead-time. No association between lead-time and severity of illness (based on APACHE II scores and p_m; Figure 2.), or diagnosis, or age or travel distances to hospital (based on postcode of patient origin) could be identified.

Multivariate analysis of all subjects, using logistic regression, confirmed that lead-time was a small but

Table 3. Population and study group demographics

	All ICU admissions	*Admissions from ED*	*Study Group*
n (% male) =	3461 (56%)	1593 (55%)	619 (58%)
Case fatalities	603 (17%)	275 (17%)	206 (33%)
Age (years)	64 [45 - 75]	56 [36 - 71]	62 [42 - 74]
Lead-time (hours)	n/a	4.0 [2.3 - 6.1]	4.0 [2.4 - 6.8]
APACHE II score[a]	16 [11 - 22]	17 [11 - 23]	24 [19 - 30]
APACHE II p_m [a]	0.16 [0.06 - 0.37]	0.14 [0.03 - 0.38]	0.39 [0.12 - 0.68]
RRT; n=	370 (11%)	173 (11%)	162 (26%)
MV; n=	1301 (38%)	628 (39%)	557 (90%)
Chronic health points[a]	802 (23%)	343 (22%)	142 (23%)
Glasgow coma score[a]	15 [11 - 15]	14 [8 - 15]	7 [3 - 13]
ICU length of stay (hours)	31 [9 - 78]	30 [9 - 71]	72 [47 - 167]

a = as per APCHE II methodology.[13] Data presented as median [inter-quartile range], unless otherwise indicated.

Table 5. Parameters for survivors vs. non-survivors

	Non-survivors	*Survivors*	*p-value*
n (% male)	206 (60%)	413 (57%)	0.60
Lead-time (hours)	4.4 [2.9 - 7.5]	3.8 [2.0 - 6.4]	0.0003
Age (years)	73 [63 - 80]	54 [36 - 69]	<0.0001
APACHE II score	31 [25 - 35]	21 [17 - 26]	<0.0001
APACHE II p_m	0.72 [0.56 - 0.84]	0.23 [0.03 - 0.43]	<0.0001
RRT; n=	87 (42%)	75 (18%)	<0.0001
MV; n=	192 (93%)	365 (88%)	0.065
Chronic health points[a]	70 (34%)	72 (17%)	<0.0001
Glasgow coma score	4 [3 - 11]	8 [5-14]	<0.0001
Admission shift (D:E:N)[b]	64:81:60	122:147:144	0.37
ICU length of stay (hours)	60 [20 - 120]	72 [38 - 194]	0.0002

Data presented as median [inter-quartile range], a = as per APCHE II methodology.[13]
b: D = 0730 - 1500hr, E = 1500 - 2230hr, N = 2230 - 0730hr.

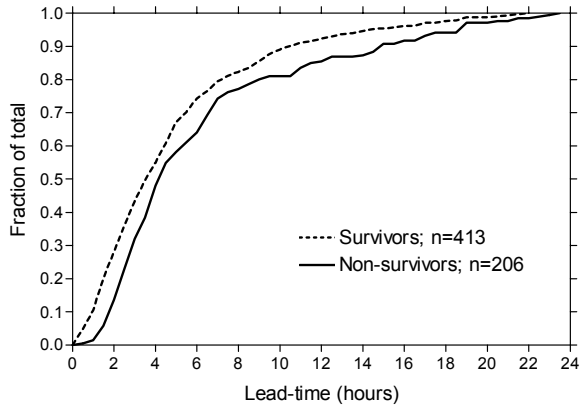

Figure 1. Cumulative lead-time frequency for survivors and non-survivors

significant independent predictor of mortality (RR = 1.06 per hour, 95%CI = 1.01 - 1.1; p = 0.015.). The other predictive variables identified in this model are listed in Table 6. The Glasgow Coma Score was the most important of all the APACHE II variables. The absence of respiratory failure as a predictive variable is due to its high prevalence (cf. Tables 3 and 5.) The predictive power of lead-time on outcome was very similar even if the individual APACHE II variables were replaced by the p_m. A post-hoc analysis of the 80% who were admitted within 8 hours of hospital arrival indicated that lead-time remained a significant outcome predictor in this subgroup.

DISCUSSION

Lead-time appears to be an important factor in the outcome of critically ill medical patients with respiratory or renal failure – a clinical group that carries a high mortality-risk (Table 3). This mortality-risk appears to increase in proportion to the delay in ICU admission (i.e. lead-time) – a relative risk of approximately 6% per hour (Table 6). Although severity of illness has a much greater impact on patient outcome, lead-time is the only variable in the predictive model that is open to intervention.

Table 6. Variables in the final logistic regression model

Dependent variables	*RR*	*95% CI*	*p-value*
APACHE II score[a]	1.14	1.10-1.18	0.001
Age (per year)[a]	1.03	1.02-1.05	0.001
Lead-time (per hour) [a]	1.06	1.01-1.1	0.015
Cardiac arrest[b]	5.1	2.7-9.7	0.001
Cardiogenic shock[b]	3.5	1.4-9.0	0.01
COPD[b]	0.37	0.38-0.95	0.04
Chronic health status	2.2	1.3-3.7	0.002

a= continuous variable, b= primary diagnosis.

The significant difference in median lead-times between survivors and non-survivors (36 minutes) appears to be too small to be clinically relevant (Table 5).

This apparent discrepancy may be due to the limitations of simple statistical tools in a heterogeneous population (see Table 2 and Figure 2) where lead-time is skewed (Figure 1). Therefore, we cannot conclude from these data that there is a definite link between lead-time and outcome of critically ill patients as there were many confounding issues and potential sources for bias.

Firstly, this study was based on an uncontrolled and heterogeneous cohort of critically ill patients admitted to one hospital. There may have been unobserved changes in clinical practice over the study period. We were unable to identify any particular seasonal or chrono-logical pattern and the numbers in each diagnostic categ-

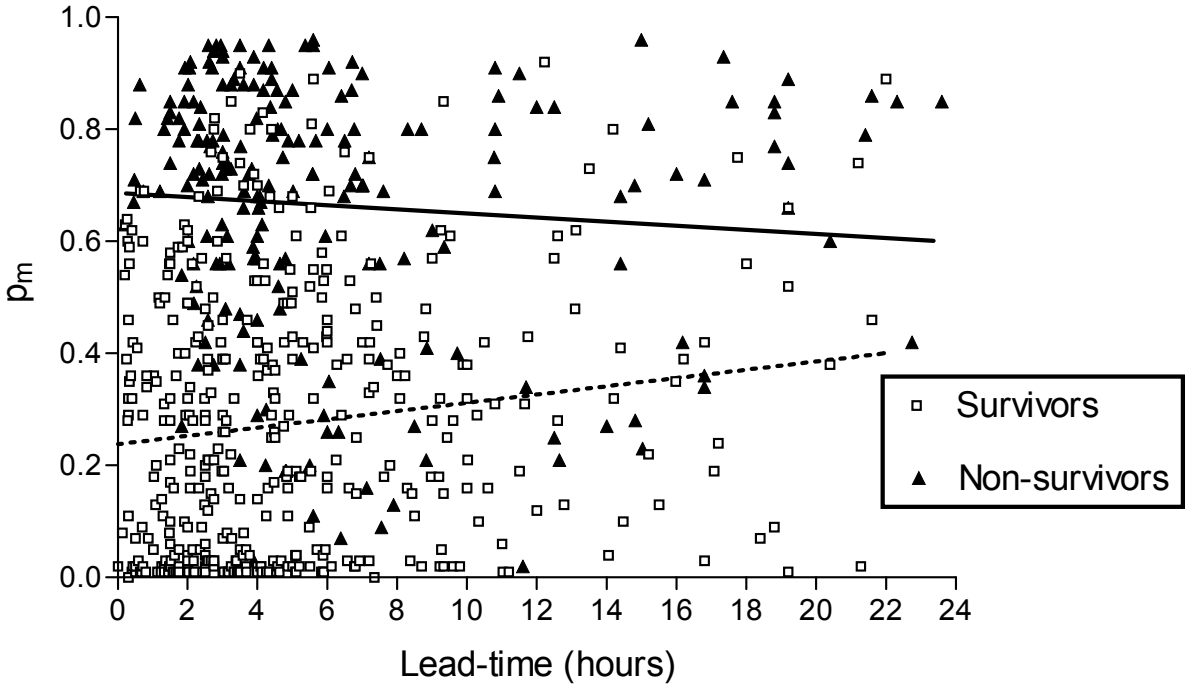

Figure 2. Lead-time vs. mortality-risk (p_m) for survivors (squares) and non-survivors (triangles). Linear regression for survivors (dotted-line; p = 0.10) and non-survivors (solid-line; p = 0.24)

ory (Table 2) were insufficient to power a subgroup analysis according to casemix. Analysis of a larger (multi-centre) population would be helpful in confirming our findings.

A large number of patients were excluded. Post-operative and major trauma patients, and those requiring urgent coronary intervention, were excluded because rapid intervention and timely access to definitive care is known to influence their survival.[3-7] Lower acuity patients (i.e. those not requiring invasive life-support for respiratory or renal dysfunction) were excluded, although we have subsequently carried out an identical analysis of these patients and failed to identify any association between lead-time and outcome.

Secondly, lead-time itself is a complex mix of distinct, but inter-related, components (Table 1). Duration of each component is influenced by patient factors such as complexity, diagnosis, and illness severity, and by staff factors such as availability, experience and workload. We did not quantify the duration of each component and are unable to state which, if any, may have been preventable causes of an increase in lead-time. It is likely that the relative importance of lead-time components (Table 1) varies under different circumstances (e.g. time of day, workload, staffing levels, triage category, etc) irrespective of the casemix. By far the majority of patients were triaged as category 1 (i.e. requiring immediate medical attention) but we did not have complete data for this variable and cannot state to what extent, if any, incorrect triage may have contributed to lead-time.

We do not conclude from these data that management in the ED was suboptimal.[9-11] Anecdotally, we found it was often the sickest patients who were dealt with more rapidly and experienced shorter lead-times; whilst, for others, the primary component of lead-time was not a delay in resuscitation, but was a delay in ICU access[9] (i.e. bed availability). In practice, we found considerable lead-time variability (Figure1). Many patients with clear life-threatening conditions, managed by experienced staff, were admitted to the ICU in a timely manner, and apparent "delays" were simply an inevitable consequence of essential investigations (e.g. CT scan), interventions (e.g. endoscopy) or therapy (e.g. intubation) prior to ICU admission. Conversely patients with an obscure diagnosis or multiple complex issues, managed by inexperienced or over-worked staff may experience a considerable delay prior to definitive treatment and admission to ICU.

Thirdly, more seriously ill patients are likely to take longer to assess, resuscitate and stabilise, and this may create an apparent link between lead-time and mortality-risk. We did not measure illness severity on arrival at hospital and cannot exclude the possibility that lead-time may simply be a surrogate marker of unmeasured

illness severity. However, risk adjustment (using APACHE II) did not negate the association between lead-time and outcome (Table 4).

It should be acknowledged that the APACHE II methodology is itself subject to lead-time bias – improvement in physiological and biochemical variables in response to resuscitation over time reduces the predicted mortality-risk (p_m), which is not calculated until after admission to ICU.[17] Consequently, our risk adjustment may have been incomplete.

We have previously measured the magnitude of lead-time bias (e.g. fall in p_m during resuscitation) for critically ill patients in our ED,[11] and repeating our analysis using a predicted 'arrival in hospital' p_m did not negate our conclusions (chiefly because lead-time bias has a similar effect on survivors and non-survivors). However, if physiological and biochemical variables (and predicted mortality-risk) consistently improve with on-going resuscitation, how is it possible for lead-time to increase mortality-risk? This question is fundamental to our findings: By what possible mechanism could lead-time increase mortality-risk?

The ED is designed to provide acute resuscitation services for critically ill patients with life-threatening conditions. It therefore contains a sophisticated level of equipment and monitoring and is staffed by qualified emergency physicians and nurses. Thus, it is argued, the level of care available is of a similar standard to that in an ICU,[8] and therefore a short-term delay in ICU admission should not be harmful. However the ED, by design, does not have the high staff:patient ratios, nor the specialised equipment (e.g. haemodialysis and complex ventilation) available in an ICU.[9] Thus, a delay in admission to ICU may result in a delay in definitive care that is crucial to the outcome of high-risk patients. Furthermore, 'normalisation' of biochemical and physiological variables during resuscitation is not synonymous with reversal of the underlying pathological process, or with improved survival. We have previously documented[11] that this early 'normalisation' in response to resuscitative measures occurs even in non-survivors and is *per se* not predictive of survival. Even though the aim of resuscitation is to correct abnormal biochemical and physiological variables, any delay in definitive therapy may slow the rate of this process. In support of this we have previously identified[11] that a delay in ICU admission (arising from inter-hospital transfer) is associated with a deceleration of this 'normalisation' process.

Therefore, it is conceivable that 'normalisation' of biochemical and physiological variables (and p_m) during resuscitation of critically ill patients creates a false sense of security by obscuring the mortality-risk associated with any delay in definitive care.

Even if we conclude from the results of this study that lead-time is associated with mortality-risk this would not be unexpected – it concurs with clinical experience and existing research.[10-12] However, if there is a causal link between the two then this has implications for the priority afforded these patients within the emergency medical services, and for hospital bed management and staffing policies. Timely admission to ICU may favour survival and have a similar impact on critically ill medical patients as early coronary intervention has in acute coronary syndromes,[6,7] or Level I trauma centres have in the management of severe trauma.[4,5] If a similar degree of urgency was directed toward critically ill medical patients then significant preventable mortality may be averted.

In conclusion, increasing lead-time (i.e. ICU admission delay) is associated with an increased mortality-risk for patients with acute respiratory or renal failure. Further investigation is required to confirm these findings and to identify which components cause preventable delays.

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REFERENCES

1. McQuillain P, Pilkington S, Allan A, et al. Confidential inquiry into quality of care before admission to intensive care. BMJ 1998;316:1853-1858.
2. Hillman KM. Reducing preventable deaths and containing costs: the expanding role of the intensive care medicine. MJA 1996;164:308-309.
3. Pearse RM, Dana EC, Lanigan CJ, et al. Organisational failures in urgent and emergency surgery. A potential peri-operative risk factor. Anaesthesia 2001;56:684-689.
4. Cooper DJ, McDermott FT, Cordner SM, et al. Quality assessment of the management of road traffic fatalities at a level I trauma center compared with other hospitals in Victoria, Australia. Consultative Committee on Road Traffic Fatalities in Victoria. J Trauma 1998;45:772-779.
5. Sampalis JS, Denis R, Frechette P, et al. Direct transport to tertiary trauma centers versus transfer from lower level facilities: impact on mortality and morbidity among patients with major trauma. J Trauma 1997;43:288-295.
6. Aversano T, Aversano LT, Passamani E, et al. Atlantic Cardiovascular Patient Outcomes Research Team (C-PORT). Thrombolytic therapy vs. primary percutaneous coronary intervention for myocardial infarction in patients presenting to hospitals without on-site cardiac

surgery: a randomized controlled trial. JAMA. 2002;287:1943-1951.
7. Terkelsen CJ, Lassen JF, Norgaard BL, et al. Are we underestimating the full potential of early thrombolytic treatment in patients with acute myocardial infarction? Heart 2003;89:483-484.
8. Fromm RE, Gibbs LR, McCallum WGB, et al. Critical Care in the emergency department: a time based study. Crit Care Med 1993;21:970-976.
9. Richardson DB. Reducing patient time in the emergency department. MJA 2003;179:516-517.
10. Parkhe M, Myles PS, Leach DS, et al. Outcome of emergency department patients with delayed admission to an intensive care unit. Emerg Med (Fremantle) 2002;14:50-57.
11. Duke GJ, Green JV. Outcome of critically ill patients undergoing interhospital transfer. MJA 2001;174:122-125.
12. Bellingham G, Olivier T, Batson S, et al. Comparison of specialist retrieval team with current United Kingdom practice for the transport of critically ill patients. Intensive Care Med 2000;26:740-744.
13. Knaus WA, Draper EA, Wagner DP, et al. APACHE II: a severity of disease classification system. Crit Care Med 1985;13:818-829.
14. ANZICS, Adult Patient Database; http://www.anzics.com.au/admc
15. SPSS v10 statistical software, (2002; http://www.spss.com)
16. Graph-Pad PRISM v3 statistical software (1995; http://www.graphpad.com).
17. Dragsted L, Jorgensen J, Jensen NH, et al. Interhospital comparisons of patient outcome from intensive care: importance of lead-time bias. Crit Care Med 1989;17:418-22.