

# Modelling Thirty-day Mortality in the Acute Respiratory Distress Syndrome (ARDS) in an Adult ICU

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## SUMMARY

Variables predicting thirty-day outcome from Acute Respiratory Distress Syndrome (ARDS) were analysed using Cox regression structured for time-varying covariates. Over a three-year period, 1996-1998, consecutive patients with ARDS (bilateral chest X-ray opacities,  $P_aO_2/FiO_2$  ratio of  $<200$  and an acute precipitating event) were identified using a prospective computerized data base in a university teaching hospital ICU.

The cohort, 106 mechanically ventilated patients, was of mean (SD) age 63.5 (15.5) years and 37% were female. Primary lung injury occurred in 45% and 24% were postoperative. ICU-admission day APACHE II score was 25 (8); ARDS onset time from ICU admission was 1 day (median: range 0-16) and 30 day mortality was 41% (95% CI: 33%-51%). At ARDS onset,  $P_aO_2/FiO_2$  ratio was 92 (31), 81% had four-quadrant chest X-ray opacification and lung injury score was 2.75 (0.45). Average mechanical ventilator tidal volume was 10.3 ml/predicted kg weight. Cox model mortality predictors (hazard ratio, 95% CI) were: APACHE II score, 1.15 (1.09-1.21); ARDS lag time (days), 0.72 (0.58-0.89); direct versus indirect injury, 2.89 (1.45-5.76);  $P_aO_2/FiO_2$  ratio, 0.98 (0.97-0.99); operative versus non-operative category, 0.24 (0.09-0.63). Time-varying effects were evident for  $P_aO_2/FiO_2$  ratio, operative versus non-operative category and ventilator tidal volume assessed as a categorical predictor with a cut-point of 8 ml/kg predicted weight (mean tidal volumes, 7.1 (1.9) vs 10.7 (1.6) ml/kg predicted weight). Thirty-day survival was improved for patients ventilated with lower tidal volumes.

Survival predictors in ARDS were multifactorial and related to patient-injury-time interaction and level of mechanical ventilator tidal volume.

Key Words: ACUTE RESPIRATORY DISTRESS SYNDROME: mechanical ventilation, 30 day mortality, Cox model, time-varying covariates, multiple imputation

Despite doubts about the utility of randomized controlled trials in Acute Respiratory Distress Syndrome (ARDS)<sup>1</sup>, the impact of the recent large multicentre ARDS Network trial<sup>2</sup> would appear to have validated the ventilatory approach of "lung protection". The ARDS Network trial<sup>2</sup> reported an overall mortality of 35.4% at 180 days in a total trial population composed of 83.5% ARDS patients. The review of Kraft and co-workers<sup>3</sup> in 1995 of 101 studies over the period 1967-1994, in 3264 patients, had pre-

viously suggested a stable mortality of ARDS of 50%, although Luce<sup>4</sup>, three years later, perceived an improved outcome albeit for "unclear" reasons. We report our experience with ARDS in an adult intensive care unit (ICU) of a university teaching hospital over the years 1997-1999. The focus of the current study was twofold. Firstly, to investigate the mortality impact, at thirty days after onset of ARDS, of various patient variables: pulmonary versus non-pulmonary disease mechanisms<sup>5</sup>; severity of illness, as measured by the APACHE II algorithm<sup>6</sup>, given that some studies reported patient series with surprisingly low severity of illness<sup>5,7,8</sup>; indices of lung dysfunction, in particular the  $P_aO_2/FiO_2$  ratio<sup>9</sup> and the lung injury score<sup>10</sup>; the time-delay of ARDS onset from ICU admission<sup>11</sup>; and of most interest, the prescription of "low" ventilator tidal volume, albeit such may have been subject to selection bias. Secondly, we sought to explore the utility of the Cox model, given recent interest in its performance<sup>12</sup>, and the effect of missing data<sup>13</sup> upon the analysis.

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## METHODS

Consecutive admissions to The Queen Elizabeth Hospital (TQEH) ICU of mechanically ventilated patients with ARDS over a three-year period (1996-98) were identified using a prospective ICU computerized database incorporating the APACHE II scoring system, hospital information systems and case notes. Access to these records was obtained under extant guidelines of the TQEH Ethics of Research Committee. ARDS was defined after Bernard and co-workers<sup>14</sup> as acute respiratory distress following a defined acute precipitating event (primary or secondary injury), in the absence of pre-existing chronic lung disease and cardiogenic pulmonary oedema, with onset heralded by bilateral chest X-ray (CXR) opacities and  $P_{aO_2}/FiO_2$  ratio  $\leq 200$ .

Initially, patients with a  $P_{aO_2}/FiO_2$  ratio  $\leq 200$  at any time of their ICU admission were identified from electronic records of the ICU ABL 620 (Radiometer, Copenhagen) blood gas machine. These patients and their initial  $P_{aO_2}/FiO_2$  ratios were subsequently cross-indexed with ICU electronic database records, ICU discharge summaries, ICU daily flow-charts and case note records to identify ARDS study patients and precipitating events. Hospital information systems were also interrogated to identify recorded ICD 9 codes 518.4 and 518.5 (non-cardiogenic pulmonary oedema) from all patients admitted to ICU in the study period. Sequential CXRs of all patients suspected of having ARDS were reviewed by two investigators; particular attention was directed to excluding those patients with CXR signs of bi-basal collapse and/or pleural effusion.

Patient data from the ICU electronic database was supplemented by further minimum data recorded for the ICU admission day and on each of days 1 (that is, first day), 2, 3 and 7 of ARDS: (i) initial data: relevant demographics; initiating mechanism(s) of ARDS, in particular direct versus indirect injury and patient type (operative versus non-operative admission to ICU, where operative was defined as immediate postoperative admission to ICU from the operating theatre or recovery room)<sup>5,7,11</sup>; Charlson comorbidity score<sup>15</sup>; ICU admission day severity scores (APACHE II and III, SAPS II); body weight, recorded as either hospital and ICU admission measured weights or ICU staff estimated weights, and ICU admission measured height, (ii) day-by-day data (days 1, 2, 3 and 7 of ARDS): severity score (APACHE II); lung injury score<sup>10</sup>; sepsis state, as systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, septic shock<sup>16</sup>; non-respiratory organ failures as defined by Knaus and co-workers<sup>17</sup>; ventilation and arterial

blood gas variables (averaged over 24 hour period for each of the days, 1, 2, 3 and 7, of ARDS), including mechanical ventilator tidal volume as ml/kg body weight and ml/kg predicted body weight, the latter being calculated according to the ARDS Network formula<sup>2</sup>, and (iii) ICU and hospital length of stay and outcome. Thirty-day outcome was assessed from ICU and hospital records, or, when hospital discharge had occurred, by contact with local medical officers. Categorical variables were scored 0/1.

## STATISTICAL ANALYSIS

Variables are reported as mean (SD) unless otherwise indicated. Interval data were analysed by t-test and categorical by Fisher's exact test, where appropriate. Stata<sup>®</sup> statistical software (Version 8.0 SE; 2003 Stata Corp, College Station, TX) was used.

Mortality outcome of patients was assessed at 30 days post onset of ARDS, using Kaplan-Meier and Cox model estimates. Predictor variables for a final parsimonious model were defined by a backward selection from a full model using minimization of the Akaike information criterion (AIC)<sup>18</sup>. Attention was directed to the question of model selection with correlated variables; the potential effect of multicollinearity was carefully assessed and non-linearity of covariate effect was also explored. Overall Cox model fit was assessed by residual plots<sup>19</sup>. Time-varying covariates, where these were recorded over days 1, 2, 3 and 7 of ARDS, 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. Graphical display of parameter change over time was performed using the Stata<sup>®</sup> module "stgtcalc"<sup>20</sup>. Data set-up was for multiple (daily) records per patient (411 instances within 106 patients)<sup>21</sup> and to adjust for clustering of patients, robust standard errors were used. Smoothed (kernel density) hazard estimates with 95% CI were computed after the method of Klein and Moeschberger<sup>22</sup>.

Evidence was also sought for a "mechanical tidal volume" effect, as per the ARDS Network trial protocols<sup>2</sup>. Patients whose initial mechanical tidal volumes (on at least day 1 and 2 of ARDS) were  $< 8$ , 9 or 10 ml/predicted kg were identified and categorized and these (0/1) categorical variables were used as indicators of treatment efficacy within a revised Cox model. These values were chosen as being the most approximated to ARDS Network trial protocols, given data-set size limitations.

As height and weight were incompletely recorded and the effect of mechanical tidal volume per predicted kg was of interest, values were imputed using

multiple imputation, both deterministic (expectation maximization (EM) algorithm) and stochastic imputation (iterative data augmentation (DA)); full details are provided in the Appendix, section 1. Little's test (Systat Version 10, SPSS Inc, Chicago IL) assessed that the "missingness" was completely at random (MCAR)<sup>23</sup>.

RESULTS

Over the period December 1995 to December 1998, a total of 1829 patients were admitted to the ICU and 1361 were mechanically ventilated. Of the latter group, 220 patients were initially considered for the diagnosis of ARDS and 106 were identified as having had ARDS. Reasons for exclusion were: 39, diagnosis of acute lung injury, not ARDS; 23, cardiogenic pulmonary oedema; 44, CXR interpretation not consistent with ARDS; and 8, pre-existing chronic lung disease.

The ARDS cohort was composed of 106 ventilated patients: key variables are shown in Table 1. The patients were elderly, with a moderate comorbidity load: of note ARDS was diagnosed in 12% (13/106) of cases at, or beyond, two days after ICU admission. Secondary causes of ARDS, males and non-operative patients predominated within the cohort. ICU admission severity of illness was severe with mean (SD) APACHE II score of 25 (8); ICU mortality was 40% and 30 day mortality was 41%. Compared with the 114 excluded patients from the ARDS cohort, there was no difference in APACHE II score (non-ARDS 24 (9) vs 25 (8), *P*=0.36) or ICU outcome (non-ARDS 27% vs ARDS 40% mortality, *P*=0.06), but both ICU length of stay (non-ARDS 7 (1-45) vs ARDS 12 (1-96) days, *P*=0.0001) and total mechanical ventilation time (non-ARDS 5.3 (0.25-45) vs ARDS 9.4 (0.4-94) days, *P*=0.0001) differed significantly.

At onset of ARDS (day 1), the calculated APACHE II score was 23 (6) and the *P*<sub>a</sub>O<sub>2</sub>/FiO<sub>2</sub> ratio was 92 (30), with 84% showing four quadrant opacification on CXR; the mean positive airway pressure (PEEP level) was 6.2 (2.2) cmH<sub>2</sub>O and the lung injury score was 2.75 (0.45). Ventilator details, arterial gas values and the percentage of patients with non-respiratory organ system failures over days 1, 2, 3 and 7 of ARDS are shown in Table 2. Initial management in early ARDS was with synchronized intermittent mandatory ventilation (SIMV; volume controlled); Puritan-Bennett PB 7200ae ventilators were used. Average mechanical ventilator tidal volume, as recorded over the days 1, 2, 3 and 7, was 9.1 ml/kg and 10.7 ml/predicted kg weight, although this was avail-

TABLE 1  
ARDS: key patient variables

Age (years)	63.5 (15.5)
Sex: female	37%
Height (cm)	172 (10)
Weight (kg)	75.6 (14.5)
CCI	1 (0-14)*
APACHE II score	25 (8)
SAPS II score	51 (17)
APACHE III score	94 (31)
ARDS aetiology	
Primary lung injury	48 (45%)
pneumonia	26 (25%)
aspiration	17 (15%)
trauma	5 (5%)
Secondary lung injury	58 (55%)
sepsis	40 (38%)
reperfusion syndrome	13 (12%)
other (transfusion, pancreatitis)	5 (5%)
Non-operative	81 (76%)
Operative	25 (24%)
ARDS lag time (days)	1 (0-16)*
Ventilation on ICU admission	95 (90%)
Dialysis in ICU	29 (27%)
ICU length of stay (days)	12 (6-19)**
	16.8 (17.7)
Total MV time (days)	9.4 (5.4-15.3)**
	14.9 (17.1)
Adjusted MV time (days)	8.6 (4.4-14.3)**
	13.9 (16.3)
Adjusted MV time (days): ICU survivors	8.5 (4.1-14)**
Adjusted MV time (days): ICU deaths	8.7 (4.9-18.2)**
ICU mortality	42 (40%)
30 day mortality	43 (41%)

Values as mean (SD) unless otherwise indicated. \*median and range. \*\*median, lower and upper quartiles. For categories; number (% of total cases).

CCI: Charlson comorbidity index. Reperfusion syndrome: reperfusion syndrome after abdominal aortic aneurysm surgery. Transfusion: massive transfusion. ARDS lag time: time from ICU admission to onset of ARDS. MV: mechanical ventilation. Adjusted MV time: mechanical ventilation time adjusted for ARDS lag time.

able directly in only 38% of patients due to missing patient weight and height data. Barotrauma occurred in five patients, with one death; tracheotomy was performed during ICU stay in 21% of patients and ICU dialysis, as continuous veno-venous haemodiafiltration, occurred in 27%. Cause of death (thirty-day outcome) was respiratory failure in 7 patients, multi-system organ failure in 31 patients (where withdrawal of therapy occurred in 15) and other (cardiovascular and cerebro-vascular) in 5 patients.

Figure 1 shows Kaplan-Meier survival estimates over 30 days with 95% CIs (top panel) and non-parametric estimates of the smoothed hazard rate (middle panel). The mortality hazard demonstrated an initial delayed rise, with peak mortality hazard at day 8, and subsequent fall. The effect of removing from consideration the patients where withdrawal

TABLE 2

Ventilation and blood gas variables and non-respiratory organ failures for days 1, 2, 3 and 7 of ARDS (averaged over 24 hours); data as mean(SD) except where indicated

	Day 1	Day 2	Day 3	Day 7
Patients in ICU	106	103	103	95
Mechanical ventilation	95	94	95	74
SIMV (number [%])	81 [85]	66 [70]	56 [59]	29 [39]
PCV or IVR (number [%])	5 [5]	6 [6]	8 [8]	8 [11]
PS+CPAP alone (number [%])	9 [10]	22 [24]	31 [33]	37 [50]
SIMV total MV l/min	16.64	18.32	16.39	17.47
CPAP MV l/min	10	11.02	12.22	11.81
P <sub>a</sub> O <sub>2</sub> /FiO <sub>2</sub> ratio	92 (30)	104 (35)	112 (38)	134 (63)
P <sub>a</sub> O <sub>2</sub> mmHg	64 (16)	64 (12)	63 (12)	63 (9)
P <sub>a</sub> CO <sub>2</sub> mmHg	42 (14)	40 (8.6)	40 (9.9)	41 (9.1)
Arterial pH	7.35 (0.13)	7.39 (0.01)	7.40 (0.11)	7.42 (0.09)
Peak airway pressure (cm H <sub>2</sub> O)	30 (7)	31 (6.5)	32 (6.4)	33 (6.2)
Mean airway pressure (cm H <sub>2</sub> O)	14.5 (5.4)	15.5 (5.4)	14.8 (5.9)	15.1 (7.1)
PEEP cmH <sub>2</sub> O	6 (2.2)	6.5 (2.3)	6.5 (2.4)	6.2 (2.6)
NR organ failures (1) %	32	26	20	28
NR organ failures (2) %	9	7	10	6
NR organ failures (3) %	5	5	4	3
NR organ failures (4) %	1	6	2	0

SIMV: synchronised intermittent mandatory ventilation. PCV: pressure controlled ventilation. IVR: inverse ratio ventilation. PS: pressure support. CPAP: continuous positive airway pressure. PEEP: positive end expiratory pressure. MV: minute ventilation. l/min; litres per minute. SIMV total MV: sum of set ventilator minute volume and patient initiated minute volume. NR organ failures; percentage of patients with 1, 2, 3 and 4 non-respiratory organ system failures (as defined in METHODS). PS+CPAP alone; patient on ventilator but not on mandatory breaths.

of therapy had occurred was to (not surprisingly) moderate the peak of the hazard, which, however, still occurred at day 8 (bottom panel). Cox model predictors of 30 day survival are shown in Table 3: the hazard increased per unit increase in APACHE II score, decreased with unit increase in ARDS lag time (days) and P<sub>a</sub>O<sub>2</sub>/FiO<sub>2</sub> ratio; was decreased in operative versus non-operative patients and was increased in direct versus indirect ARDS injury processes. Of note, no effect of dialysis requirement was apparent ( $P=0.89$ ) and the Charlson comorbidity index was not predictive ( $P=0.18$ ). The total number of non-respiratory organ failures achieved significance as a predictor (HR: 1.91, 95% CI: 1.33-2.76;  $P=0.001$ ). However, there were significant correlations between individual organ failures; the total number of non-respiratory organ failures was highly correlated with the APACHE II score ( $r=0.55$ ,  $P=0.0001$ ); parameter instability occurred when the variable was removed from the model (more so when time-varying covariates were used, see below); and organ failure(s), as a categorical variable, may be more properly considered as an (competing) outcome in itself. Therefore, the total number of non-respiratory organ failures was not retained in the final model. Figure 2 shows the survival probabilities of the four groupings; surgical versus medical and direct versus indirect lung injury at an APACHE II score of 27, P<sub>a</sub>O<sub>2</sub>/FiO<sub>2</sub> ratio of 100 and ARDS lag time of two days (that is, elevated severity of illness).

For the variables operative versus non-operative

patient status (categorical) and P<sub>a</sub>O<sub>2</sub>/FiO<sub>2</sub> ratio (continuous), time-varying effects were demonstrated (that is, significant interaction,  $P<0.05$ , of the covariate with failure-times (time to death) over 30 days). Parameter change (as hazard ratio) over time for the predictor variables is seen in Figure 3; although time "variation" occurred in all these estimates (not surprisingly), this was adjudged significant only for the above two variables. No significant interactions, nor non-linear effect of ARDS lag time, APACHE II score or P<sub>a</sub>O<sub>2</sub>/FiO<sub>2</sub> ratio were demonstrated. Further exposition of interpretation of these time-varying effects is given in the Appendix, section 2 and displayed (as model 2) in the accompanying Table A.

Of interest was the potential survival effect of "low" mechanical tidal volumes, as per the ARDS Network trial<sup>2</sup>. As height (mean 172 (14) cm) and weight (mean 75.6 (14.5) kg) were stable demographic variables, but recorded in only 38% and 32% of patients respectively, imputation of these variables was undertaken. Little's test ( $P=0.28$ ) suggested that height and weight were missing completely at random; that is, the values recorded were a random subset of the total patient cohort. Mean imputed values (EM) for height and weight were 170 (9.5) cm and 73.7 (12.8) kg respectively and did not differ significantly from those of DA values (170.5 (8.3) cm and 73.3 (12.3) kg respectively,  $P$  always  $>0.2$ ) and those initially recorded ( $P$  always  $>0.2$ ). Mean mechanical ventilator tidal volume (over days 1,2 3 and 7) using

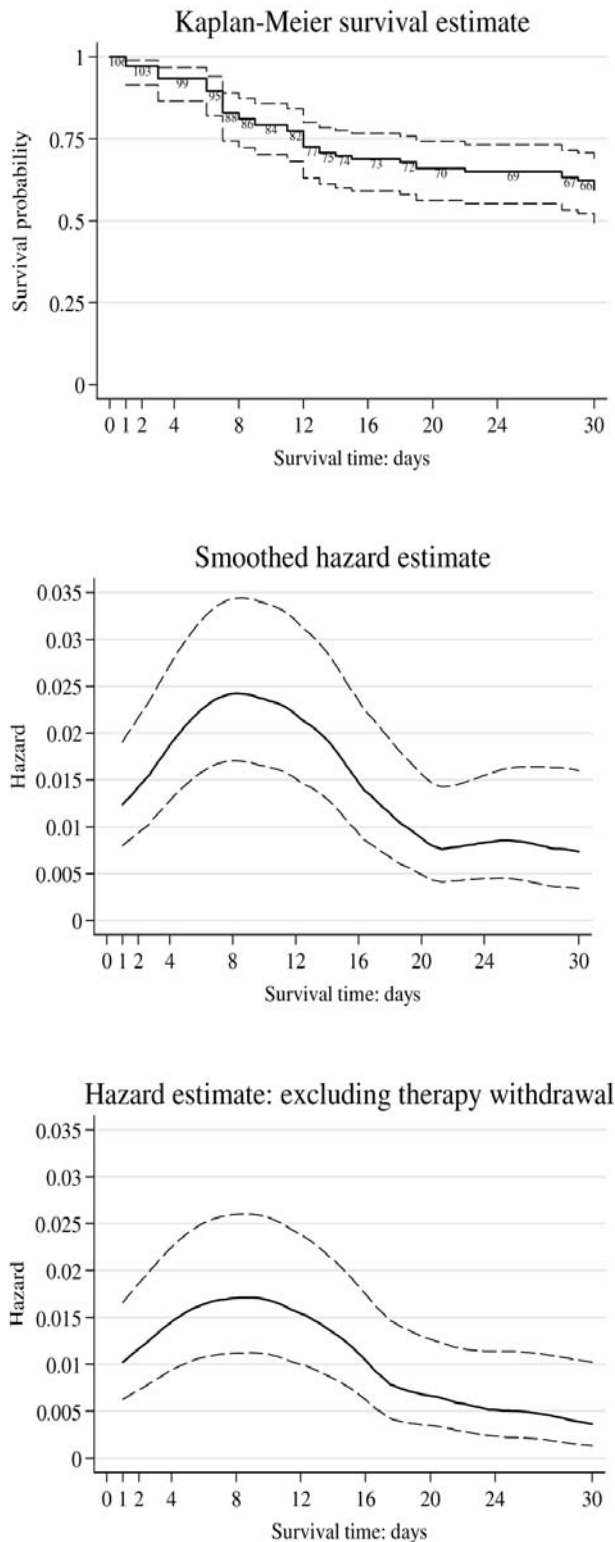


FIGURE 1: Kaplan-Meier (top panel, with number at risk at each interval shown below the point estimate solid line) and smoothed non-parametric mortality hazard (middle panel) estimates (solid line) with 95% CI (dashed lines). Lower panel: smoothed non-parametric mortality hazard with patients dying and having therapy withdrawn being excluded from analysis (see RESULTS).

these imputed mean values were 9.0 ml/kg and 10.7 ml/predicted kg weight and the progression of tidal volume over time is displayed in Figure 4 (left panel).

In a revised Cox analysis, using the EM imputed data-set, significant time-dependent effects were demonstrated for patients classified as ventilated with an initial (day 1 and 2 of ARDS) mechanical tidal volume <8 ml/predicted kg (n=7) versus those not so ventilated (model 3, Table A in Appendix). No difference in parameter point estimates, CIs and P values was demonstrated for DA data, where uncertainty estimates (variance of point values) were incorporated into the analysis. Figure 4 (right panel) displays the mechanical tidal volume over days 1, 2, 3 and 7 of ARDS as box-plots for patients ventilated with tidal volume < and >8 ml/kg predicted kg. No difference in initial (day 1 of ARDS) characteristics (age, sex, APACHE II score, P<sub>a</sub>O<sub>2</sub>/FiO<sub>2</sub> ratio) was apparent between the two groups of patients; at day 7 of ARDS, two of the seven patients with initial mechanical tidal volume <8 ml/predicted kg were still receiving mechanical ventilation (as SIMV). No consistent application of mechanical tidal volume <9 or 10 ml/predicted kg was apparent and estimation demonstrated no effect.

Figure 5 shows these tidal volume effects as (unadjusted) Kaplan-Meier estimates (left panel) and as predicted by the Cox model in two subsets of patients: non-operative direct and indirect lung injury (right panel). Crossing of the survival curves was noted at days 8 to 9 such that the survival for patients ventilated with tidal volumes <8 ml/ predicted kg weight was improved compared with those not so ventilated. In the (non-imputed) original data set, these tidal volume effects were not demonstrated (see Appendix, section 3).

DISCUSSION

The current study, in a cohort of elderly patients with high severity of illness as measured by the APACHE II and other severity scores, would appear to be comparable with reported survival rates<sup>5,8,11,24,25</sup>, average mechanical tidal volumes used in ARDS<sup>11,26,27</sup> and both time of mechanical ventilation and ICU length of stay. Of interest was the relatively low mean level of positive end expiratory pressure (PEEP) over days 1 to 7 of ARDS (6.2 to 6.5 cmH<sub>2</sub>O), albeit approximated the mean levels in the recent report of Bersten et al<sup>24</sup>. PEEP levels in the ARDS Network trial<sup>2</sup> were on average 3 cmH<sub>2</sub>O higher than the current study over days 1 to 7, but mean P<sub>a</sub>O<sub>2</sub> levels were also approximately 10 mm Hg higher over this time,

TABLE 3  
Cox models, parameter (hazard ratio) point estimates and 95% CI, for 30-day outcome

Variable	APACHE II	Direct vs Indirect	P <sub>a</sub> O <sub>2</sub> /FiO <sub>2</sub> ratio	Operative vs Non-operative	ARDS lag time
HR estimate	1.15	2.89	0.98	0.24	0.72
Lower 95% CI	1.10	1.45	0.97	0.09	0.58
Upper 95% CI	1.21	5.76	0.99	0.63	0.89
P	0.001	0.003	0.009	0.004	0.003

Operative vs non-operative; categorical variable, scored 1/0, indicating patient immediately transferred from surgery or not so.

ARDS lag time; time in days, from ICU admission to development of ARDS.

Direct vs Indirect; mechanism of lung injury associated with ARDS.

Parameters are shown as point estimates with 95% CI. P: P value.

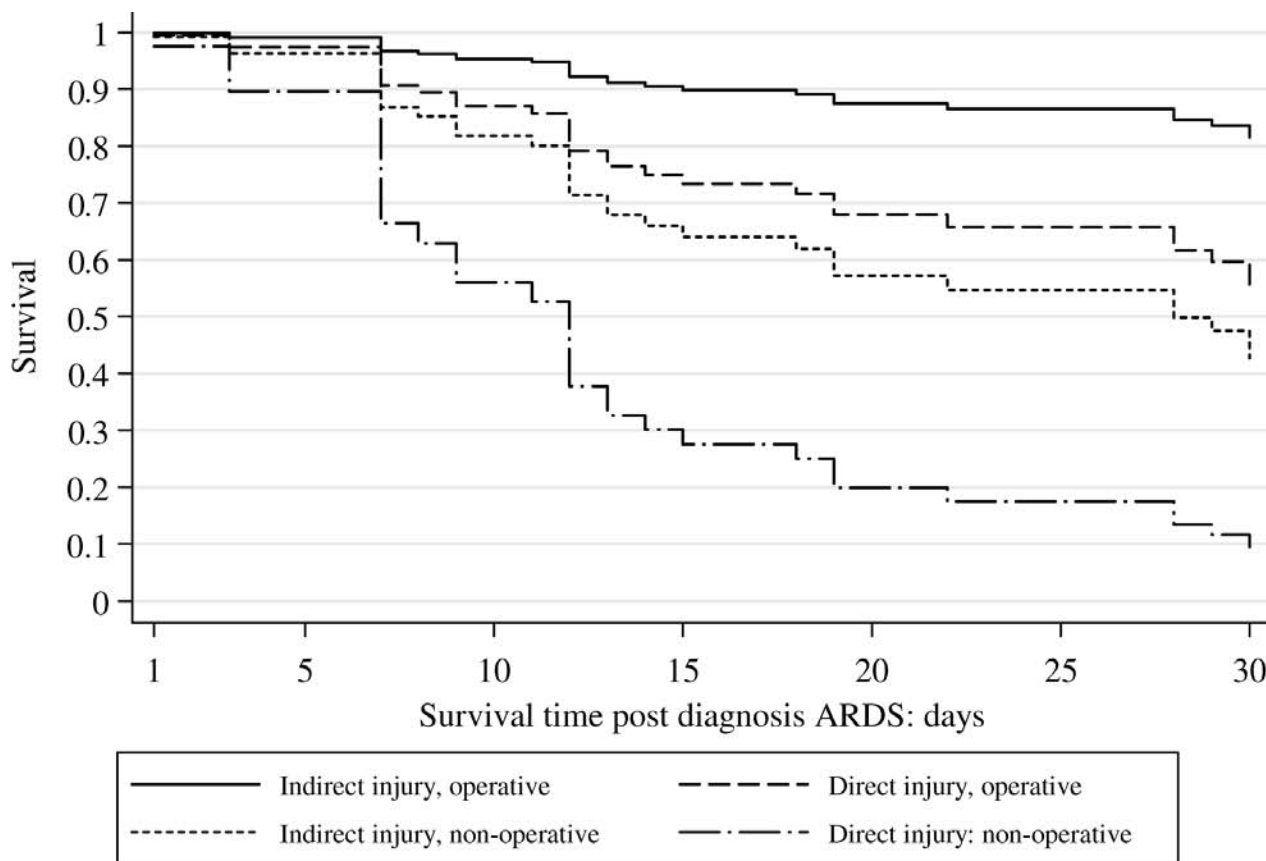


FIGURE 2: Cox model with covariate effect of operative versus non-operative category and additional effect of direct versus indirect injury (4 groups), adjusted to various levels of continuous variables (APACHE II score=27, P<sub>a</sub>O<sub>2</sub>/FiO<sub>2</sub>=100, ARDS lag time=2 days). Vertical axis: survival probability; horizontal axis: survival time in days. Indirect injury, operative group, n=21; direct injury, operative group, n=4; indirect injury, non-operative group, n=37; direct injury, non-operative, n=44.

suggesting differential clinician tolerance of patient P<sub>a</sub>O<sub>2</sub> as the most likely explanation.

One of the key cohort studies using a lung protective ventilatory strategy<sup>28</sup> reported a 26.4% hospital mortality compared with a 53.3% predicted mortality via the APACHE II algorithm. In the two randomized trials allowing permissive hypercapnia and most closely comparable with this cohort study, treatment group mortalities were 46.6% (at 60 days<sup>29</sup>) and 50%

(in hospital<sup>30</sup>) respectively. Although prospective, the results of Hickling and co-workers' study<sup>28</sup> may be interpreted as pertaining to a "pilot" study for future controlled clinical trials. Confidence intervals in pilot studies, by virtue of their small size and unrepresentative samples, are known to be wide; in this case 16-39%. The use of the 75th percentile of the population variance has been recommended<sup>31</sup> as an appropriate "benchmark" point estimate for the purpose of

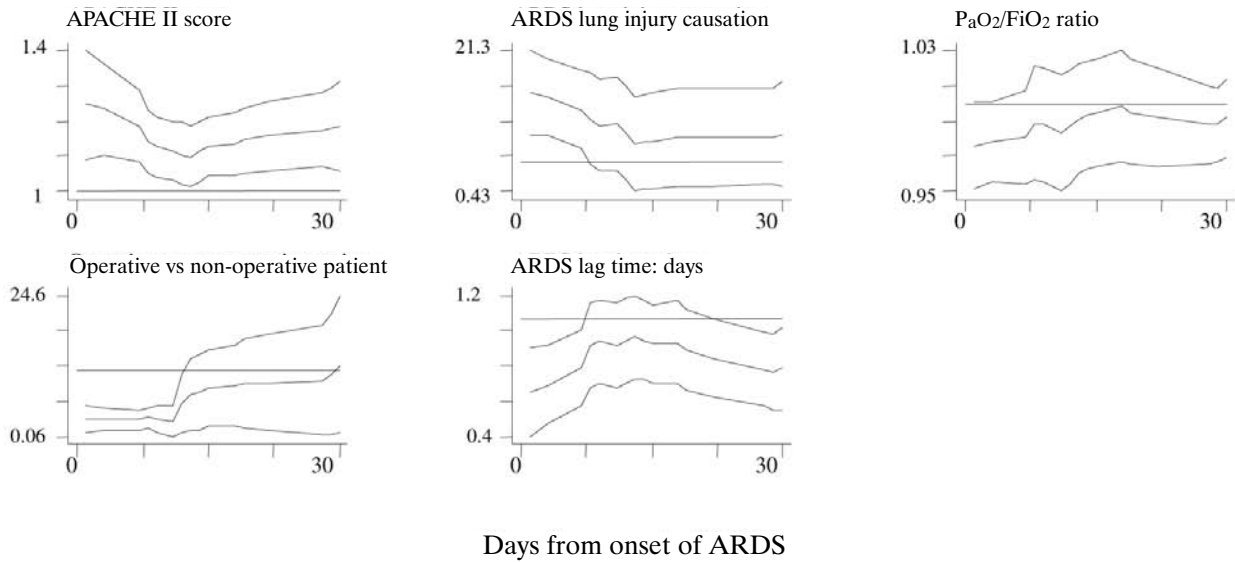


FIGURE 3: Time variation of coefficients of the five predictor variables in the initial Cox model. Vertical axis: parameter estimate ( $\beta$  coefficients, exponentiated as HR). Horizontal axis, Days from onset of ARDS. Horizontal line: HR=1. The variables APACHE II score,  $\text{PaO}_2/\text{FiO}_2$  and ARDS lag time in days were modelled as continuous variables; the categorical variables ARDS lung causation (direct vs indirect injury) and operative vs non-operative patient were modelled as 1/0 variables, such that the effect expresses the HR of the first vs second mentioned category.

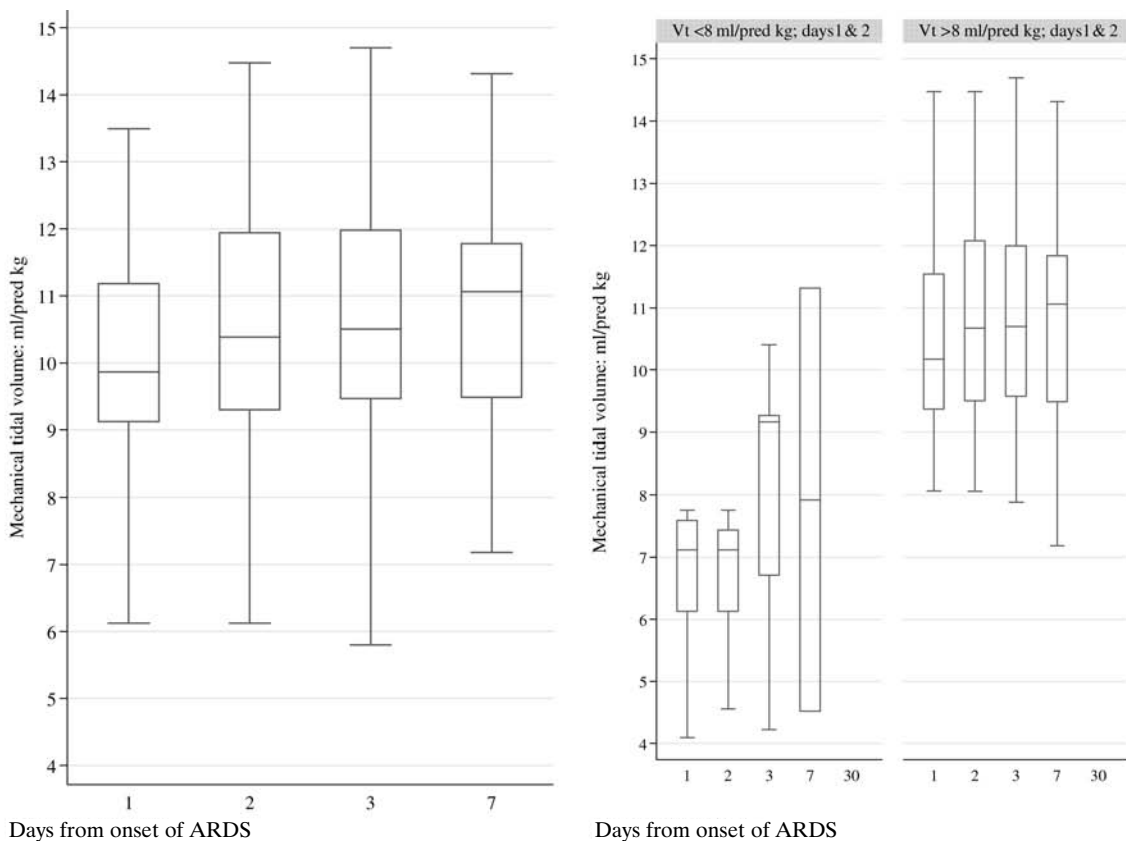


FIGURE 4: Vertical axis: mechanical tidal volumes (ml/predicted kg). Horizontal axis: days of ARDS. Left panel: All patients; box-plots as median, inter-quartile range and upper and lower adjacent values. Right panel: “treatment groups” defined as mechanical tidal volume < and >8 ml/predicted kg on days 1 and 2 of ARDS; box-plots as median, inter-quartile range and upper and lower adjacent values.

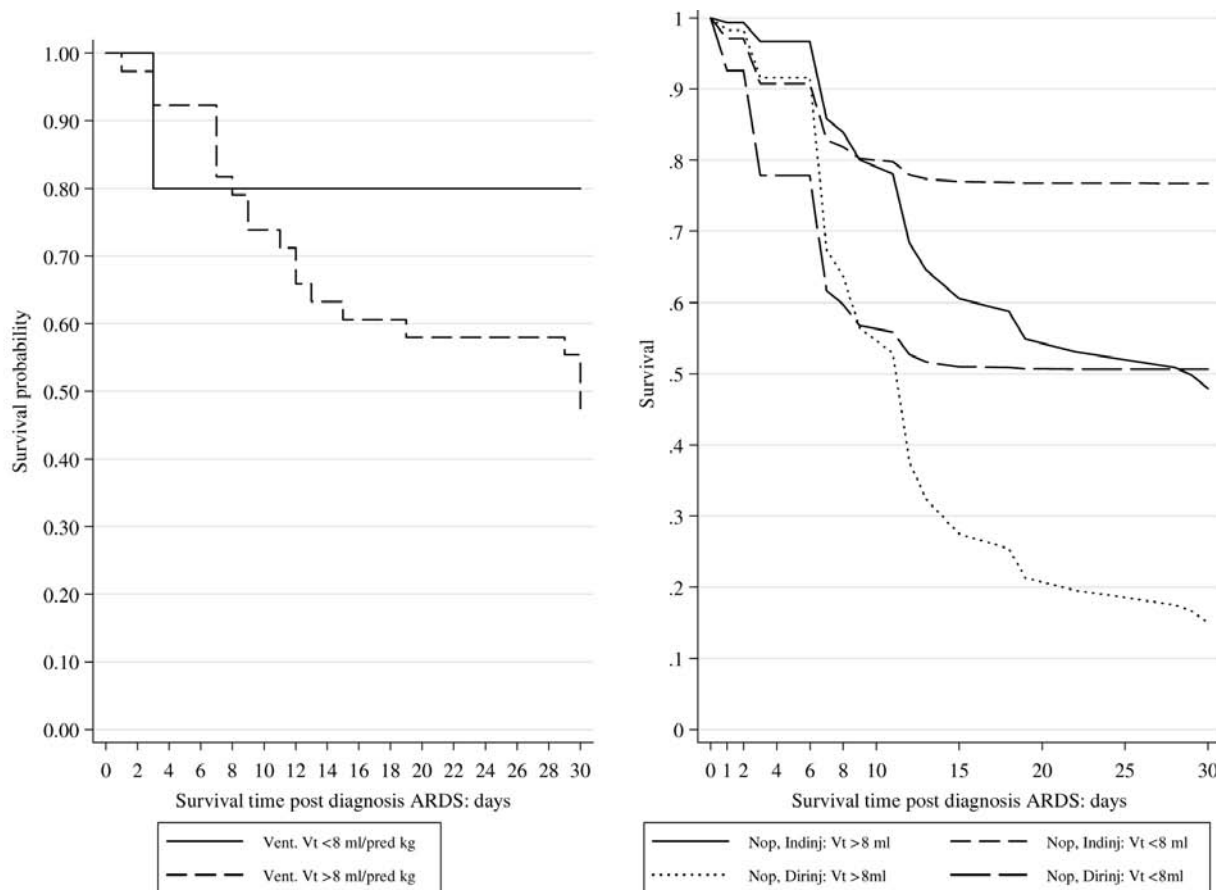


FIGURE 5: Left panel: Kaplan-Meier estimates; Wilcoxon test (stratified over quartiles of APACHE II, ARDS lag time and  $P_{aO_2}/F_{iO_2}$  ratio),  $P=0.15$ . Right panel: Cox model: effect of ventilator tidal volume  $< > 8 \text{ ml/}$  predicted kg weight, in subsets of non-operative patient (Nop) with indirect injury (Indinj) and non-operative patient (Nop) with direct injury (Dirinj) and continuous variables set to various values (APACHE II score=27,  $P_{aO_2}/F_{iO_2}=100$ , ARDS lag time=2 days). Vertical axis: survival probability; horizontal axis: survival time in days.

sample size calculations; which would correspond to a “revised” mortality rate of 35% instead of 26.4%. Such a mortality rate is consonant with recent studies such as the ARDS Net trial<sup>2</sup>.

*Severity of Illness and Outcome*

A relation between general ICU severity of illness scores and outcome in ARDS has been frequently demonstrated<sup>11,26,27</sup>. Given that the largest trial in ALI/ARDS<sup>2</sup>, with 861 patients and a mean APACHE III score of 83, yielded an overall (180 day) mortality of 35%, caution must be exercised in interpretation of therapies and subsequent outcomes attendant upon low severity of illness scores<sup>5,7,8</sup>. Knaus et al<sup>26</sup> pointed out the seeming paradox of wide individual risk of mortality (10-90%) when patients admitted with res-

piratory failure and  $P_{aO_2}/F_{iO_2}$  ratio  $< 300$  were grouped according to a  $P_{aO_2}/F_{iO_2}$  ratio cut-off of 150. In the current study there was a significant distributional difference of the APACHE II score and risk of death ( $P=0.004$  and  $P=0.007$ , respectively) about the median admission day  $P_{aO_2}/F_{iO_2}$  ratio (=110), and the APACHE II risk of death showed wide distribution (3% to 95%) above and below this level.

*Effect of Ventilator Tidal Volume*

The ability to demonstrate a mortality effect of ventilator tidal volume, the thrust of the lung protection thesis<sup>32</sup>, was an additional feature of this analysis. Some cautions, however, need to be observed regarding these conclusions. Firstly, the number of patients who were prescribed “low” tidal volumes was small



(see Results, above); given the calendar time of the study (1996-1998), this was not surprising<sup>33</sup>. Secondly, tidal volumes in the “low” volume group were seen to increase beyond day 2 of ARDS although they remained less than those of the “high” volume group (Figure 4, left panel). Thirdly, analysis was dependent upon the process of imputation (of patient height, but not of tidal volume), no general linear or non-linear relationship of tidal volume/kg predicted weight was obvious and cut-point analysis (that is, tidal volumes greater or less than 8 ml/predicted kg) is known to exaggerate treatment effects in cohort studies<sup>34</sup>; and despite controlling for other covariates in the model, selection bias in terms of physician choice of tidal volume may have occurred. Tidal volumes in this study were selected by individual clinicians. Thus the treatment effect demonstration in this cohort study should be properly viewed as suggestive, although consistent with current perspectives<sup>32</sup>.

#### *Other Risk Factors*

Of note in this study were the adverse effects on mortality of direct lung injury, the onset of ARDS proximal to ICU admission and non-surgical disease processes. Direct lung injury has been previously associated with increased mortality in ARDS<sup>5,35</sup> and a hazard ratio of 2.82 is in agreement with these observations. That delayed onset of ARDS with respect to ICU admission was associated with better outcome is perhaps somewhat surprising, although other studies have reported no<sup>36</sup>, increased<sup>37</sup> or decreased<sup>11</sup> mortality when mechanical ventilation precedes ARDS onset. Surgical patients have also been noted to have a reduced mortality compared with medical<sup>11,35</sup>, although reasons for the current covariate effect were not immediately apparent. As expected, the comorbidity load of operative patients was less than non-operative, mean Charlson comorbidity index 2.6 versus 1.6, one-sided  $P=0.04$ , but neither the index, nor its interaction with operative/non-operative status was a significant predictor ( $P=0.28$  and  $P=0.16$ , respectively). No difference was noted in the ARDS lag time between operative versus non-operative groups (mean difference =  $-0.35$  days,  $P=0.35$ ) and the interaction between these two predictors was also non-significant ( $P=0.92$ ). If ARDS lag time in post-operative patients was a surrogate for a delay in recognition of ARDS due to, say, a search for post-operative sequelae, the expectation might reasonably be that such a “delay” would prejudice outcome, but this was not the case. Although not included as a predictor in the final Cox model, the impact of increased

non-respiratory acute organ failure was adverse, again consistent with other reports<sup>35</sup>.

#### *Modelling issues*

The retrospective nature of this study may have engendered problems of patient selection in terms of major definitional categories and bias in parameter estimates consequent upon this potential misclassification<sup>38</sup>, but we were at pains to reduce these to a minimum, with careful attention being addressed to inclusion criteria for ARDS, especially in those where onset (12%) was removed from ICU admission and risk factors or initiating events of ARDS. Furthermore, “operative” was strictly defined as immediate transfer to the ICU from the operating theatre or recovery room. That retrospective chart review can yield consistent estimates of the effect of interest has been previously demonstrated<sup>39</sup>.

In the ARDS literature the variables predicting survival have usually been selected at baseline and where analysis has included covariates recorded over time<sup>11,27,35</sup>, specific attention has not been addressed to the correlation between such measurements (by default an independent correlation structure has been assumed) and the integration of repeated observations into an outcome analysis. Thus the full impact of time-varying covariates has not been developed; such a failure leads to bias in estimation of covariate parameters<sup>40</sup>. Moreover, there is statistical advantage in using such “maximal” information, to the extent that information loss due to censoring is compensated by repeated subject observation<sup>41</sup>. Precise specification of this time course may also illuminate underlying patho-physiological events, as with the coincidence of the peak mortality hazard at day 8 (Figure 1) and the beginning of the separation of survival curves for the ventilation tidal volume effect (Figure 5).

Some caution must be also exercised in the interpretation of the effect of variables such as mechanical ventilation and  $P_aO_2/FiO_2$  ratio which produce change, or are subject to change, with therapy. Wolfe and Strawderman documented the bias consequent upon simultaneously adjusting for baseline and time-dependent covariates when the effect of the baseline factor may manifest itself through its effect on the time-dependent covariate<sup>42</sup>. Instability of Cox regression point parameter estimates and CIs were noted with inclusion of total number of non-respiratory organ failures as a predictor; this instability indicating potential collinearity and/or a mis-specified model. The same phenomenon was presumably evident in two ARDS studies<sup>8,35</sup>, where reported (without com-

ment) upper 95% CI of odds ratios varied from 30 to 121, values suggesting an implausible covariate effect.

#### Missing data

Recent recommendations on the conduct of multi-variable analysis<sup>43</sup> have been silent on appropriate statistical procedures to handle missing values, but strategies such as normal value replacement or mean substitution are not recommended<sup>13</sup>. Multivariable analysis is usually accompanied by complete-case analysis; only complete observations are considered across variables, resulting in a decrease in the total *n* and potential bias and/or loss of efficiency in estimation. Such was demonstrable in the current study where significant time-dependent effects of ventilator tidal volume were not present in the non-imputed data set. The imputation focus in this study was narrow; to generate weight and height estimates in the presence of substantial missing data. Analysis based upon the two imputation methods yielded almost identical point estimates and SEs, but EM imputation had the advantage of being a less data intensive process. The presumption in the current study, supported by a non-significant Little's test, albeit a test of low power, was that height and weight were missing from the initial data set completely at random. Under these conditions, it was reasonable to assume that final parameter estimates and inferences deriving from the imputation process itself were robust.

#### CONCLUSIONS

The predictors of survival in ARDS are multifactorial and relate to patient-injury-time interaction. The time-change of hazard for particular covariates must be appropriately addressed in analysis, as must the effect of missing data, the disregarding of which may lead to inefficient estimation of covariate effects. Peak mortality hazard for patients with ARDS is apparent at day 8 post development. Mechanical ventilator tidal volume appears a risk factor for survival, but the therapeutic tidal volume level was not clearly defined.

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**APPENDIX**

1. Two multiple imputation (MI)<sup>1</sup> processes were used:

- (a) "deterministic" whereby single values of the missing data points were produced and no variance estimates were incorporated into the replacement process, via the expectation maximisation (EM) algorithm<sup>2</sup> (Systat Version 10, SPSS Inc, Chicago Il)
- (b) iterative data augmentation (DA), a stochastic (incorporating variance of the point estimates) multiple imputation process where variables were determined over multiple (20) individual data sets<sup>3</sup>. The number of data sets required to produce effective multiple imputation is usually relatively small (5-10); the efficiency of an estimate based upon *m* imputations is

$$\left(1 + \frac{\gamma}{m}\right)^{-1}$$

where  $\gamma$  is the rate of missing information (a function of the variance between and within-imputed data sets). In this study, where height and weight were measured in only 38% and 32% of patients respectively, a conservative approach to the number of data sets (that is, *m*=20) was used. The variables used in the production of the multiple data sets were: height and weight; age, APACHE II score, Charlson comorbidity score, gender, patient type (operative versus non-operative), direct versus indirect injury and 30-day outcome<sup>4</sup>. The set of mean values of the imputed variables were compared between imputation mechanisms and with the original data; for computation of Cox regression parameter estimates, specific Stata<sup>®</sup> routines were used for this purpose<sup>5</sup>.

As pointed out by a referee, analysis of EM-

imputed data would be expected to yield SE biased downwards compared with DA; however, this was not found in the current study (see RESULTS) and the results for both imputation regimens were therefore presented. Similarly, Little’s test (which computes Mahalanobis distance between parameter estimates based upon list-wise complete data and estimates resulting from the EM algorithm) has low power to detect MCAR and there is no specific test for MAR (missing at random, or ignorable missing data where missing values may depend upon the value of other observed variables, but not upon values of unobserved variables). The assumption in the current study of MCAR may have been unrealistic; for instance, height and weight may not have been measured in the severely ill or morbidly obese patient. However, analysis based upon an MI regimen is still consistent with an MAR assumption.

Whether a more complete missing value replacement regimen would have been of value is an empirical question, but a more complete imputation scheme would have required specification of both an analytic and an imputation model, involving an understanding of the “missingness” mechanism. Moreover, the multivariate normal assumptions of the MI process used, those of additive linear regression, may be unsuitable for

the non-linear Cox model with time-varying covariates<sup>6</sup>.

- Table A shows coefficients for the variables and models (1-3) as hazard ratios with 95% CI. Construing time-varying coefficients in the Cox model may be somewhat exigent<sup>7,8</sup>. The interpretation of the dual constant-within-time and time-varying coefficients is: log hazard ratio,  $LHR = \beta_1x_1 + \beta_2x_2 + \beta_3x_2 * t$ , where  $x_1$  and  $x_2$  are observed covariates,  $\beta_s$  are the coefficients and  $t$  is the time, in appropriate scale. The marginal effect (ME) of  $x_2$  (derivative of LRH with respect to  $x_2$ ) is:  $ME(x_2) = \beta_2 + \beta_3 * t$  and the effect increases or decreases with time according to the sign of  $\beta_3$ . Thus from Table A, model 2, the time-constant coefficient (non-hazard metric) for  $P_aO_2/FiO_2$  ratio is  $-0.024$  (SE, 0.008) and the time-varying is  $+0.0008$  (SE, 0.003); the effect is one of increase over time (according to the scale) of the hazard, per unit increase of  $P_aO_2/FiO_2$ .

For a (continuous) covariate repeatedly measured over time, where no statistically “significant” time varying effect is demonstrated (see “Statistical analysis”), the coefficients are interpreted as an “average” over all days for which failures occurred; that is the coefficients representing covariate effect are “time-invariant”.

- As mentioned in the text (RESULTS: final para-

TABLE A  
Cox models, parameter (hazard ratio) point estimates and 95% CI, for 30 day outcome

Model Variable	1	2	3
APACHE II	1.15 (1.10-1.21)	1.15 (1.1-1.21)	1.15 (1.09-1.20)
P	0.001	0.001	0.001
Operative vs Non-operative	0.24 (0.09-0.63)	rh:0.016 (0.001-0.246) t: 1.162 (1.036-1.303)	rh: 0.016 (0.001-0.251) t: 1.16 (1.034-1.303)
P	0.003	rh: 0.003 t: 0.01	rh: 0.003 t: 0.01
Direct vs Indirect Injury	2.89 (1.45-5.76)	2.55 (1.33-4.119036)	2.58 (1.34-4.95)
P	0.003	0.005	0.008
$P_aO_2/FiO_2$	0.985 (0.975-0.996)	rh: 0.976 (0.962-0.991) t: 1.001 (1.0002-1.0014)	rh: 0.975 (0.960-0.991) t: 1.001 (1.0003-1.002)
P	0.009	rh:0.001 t: 0.006	rh: 0.002 t: 0.004
ARDS lag time	0.72 (0.58-0.89)	0.72 (0.58-0.88)	0.72 (0.59-0.88)
P	0.003	0.001	0.001
Biv Vt			rh: 0.167 (0.069-0.399) t: 1.344 (1.094-1.651)
P			rh: 0.001 t: 0.005

Operative vs Non-operative; categorical variable, scored 1/0.

ARDS lag time; time in days, from ICU admission to development of ARDS.

Biv Vt; categorical variable, scored 1/0, indicating ventilator mechanical tidal volume of greater or less than 8 ml / predicted kg weight.

Model 1: initial model with 5 predictors. Model 2: initial model with time-varying effect of operative vs non-operative categorical variable and the continuous  $P_aO_2/FiO_2$  ratio. Model 3: full model using EM imputed data.

rh; constant within time coefficient. t: time varying coefficient.

Parameters are shown as point estimates with 95% CI. P: P value.

graph), the time-varying effects of the “tidal-volume effect” were not seen in the non-imputed data set. The coefficients (HR metric) in the non-imputed data set were: time-constant 0.68 (SE, 0.73;  $P=0.72$ ) and time-varying 0.98(SE, 0.05;  $P= 0.77$ ). Notable was the opposite effect of the time-varying coefficient compared with that in Table A, model 3.

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