Published in final edited form as:

Crit Care Med. 2012 June ; 40(6): 1835–1843. doi:10.1097/CCM.0b013e31824e1696.

In the critically ill patient, diabetes predicts mortality independent of statin therapy but is not associated with acute lung injury: a cohort study

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Abstract

Objectives—Patients with diabetes mellitus (DM) form 23–30% of published cohorts of critically ill patients. Conflicting published evidence links DM to both higher and lower mortality. Other cohort studies have suggest that DM protects against acute lung injury (ALI). We hypothesized that DM is an independent risk factor for mortality. We further hypothesized that DM is a risk factor for cardiac overload (CO) and not for ALI.

Design—Retrospective cohort study.

Setting—The intensive care unit (ICU) of a tertiary referral hospital.

Patients—From 1 November 2004 to 1 October 2007, a cohort of patients admitted 48h to the ICU.

Interventions—None

Measurements and Main Results—Of 2,013 patients, 317 had DM. Ninety-day mortality was higher in the DM patients compared to patients without DM (hazard ratio [HR] 1.53, 95% confidence interval 1.29–1.80). This association strengthened after adjusting for confounders and for medication (HR 1.53, 1.07–2.17). We found no association between DM and ALI (relative risk ratio [RRR] 1.01, 0.78–1.32; adjusted RRR 0.99, 0.75–1.31), but DM was a risk factor for CO (RRR 1.91, 1.30–2.81; adjusted RRR 1.45, 0.97–2.18). Statins were associated with both a reduced risk of mortality (HR 0.74, 0.63–0.87; adjusted HR 0.53, 0.44–0.64) and a decreased risk of developing ALI (RRR 0.71, 0.56–0.89; adjusted RRR 0.61, 0.47–0.79).

The authors have no conflicts of interest to declare.

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Conclusions—DM is an independent risk factor for mortality in critically ill patients and failure to adjust for statins underestimates the size of this association. DM is not associated with ALI but is associated with CO. A diagnosis of CO excludes a diagnosis of ALI. Investigators who do not account for CO as a competing alternative outcome may therefore falsely conclude that DM protects from ALI.

Keywords

diabetes mellitus; intensive care; acute lung injury; acute respiratory distress syndrome; mortality; heart failure; hydroxymethylglutaryl-CoA reductase inhibitors; confounding factors (epidemiology); multinomial logistic regression; Cox regression

Introduction

The World Health Organization estimates that diabetes mellitus (DM) affects 220 million people worldwide and that number is projected to double by 2030 (1). DM predisposes to a large number of other diseases, such as cardiovascular disease, infection and renal failure. It is therefore unsurprising that patients with DM form 23–30% of the published cohorts of critically ill patients (2, 3).

The influence of DM on outcomes in the critically ill patient is uncertain. Some studies have reported that DM increases mortality (2, 4), some that DM decreases mortality (5–7), and some that the risk is neutral (3, 8–10). Acute lung injury (ALI) is a common complication on the intensive care unit and occurs in 30% of critically ill patients, with an estimated mortality of up to 60% (11). Of interest, previous studies have shown that patients with DM appear to have a lower incidence of ALI or acute respiratory distress syndrome (ARDS) (12, 13) (a syndrome of hypoxia and lung edema not secondary to left heart failure) (14).

Multiple reasons have been proposed to explain why DM may protect against ALI/ARDS, including the effect of hyperglycemia on the host response (15), and in this study we elected to look specifically at the role of medication prescribed to patients with diabetes. A number of pre-admission drug treatments have also been postulated to influence mortality or the development of ALI in observational human or animal studies, most notably statins (16–18), angiotensin converting enzyme (ACE) inhibitors (19, 20) and angiotensin II receptor (AIIIR) inhibitors (21). We also considered the possibility of biases introduced by analysis techniques: the diagnoses of ALI and cardiac overload (CO) are mutually exclusive, and patients with diabetes are more prone to ischemic heart disease and consequently CO (22). We considered the possibility that patients with diabetes who do not suffer from ALI may die of CO instead.

In this study, we investigated the influence of diabetes on mortality, and hypothesized that any protective effect might be conferred by medication taken by patients with diabetes, and not due to diabetes itself. We examined this question using data from a previously published cohort (23), with 90-day mortality as the primary outcome and ALI as a secondary endpoint. We included CO as a secondary endpoint, the diagnosis of which excludes the diagnosis of ALI.

Materials and methods

Cohort

We examined a cohort of 2,024 intensive care patients (previously described by Vlaar *et al.*) (23). In brief, this is a cohort of consecutive adult patients (aged >18 years) admitted 48

hours to the intensive care unit of the Academic Medical Center, Amsterdam, over the period 1 November 2004 to 1 October 2007. Re-admissions were excluded.

The primary outcome measure was mortality (28-day and 90-day) verified against the national Dutch registry of deaths; this was therefore missing only when subjects had left the country. Secondary outcomes were ALI and CO. ALI was defined using the consensus definition of Bernard et al. (24) (acute onset; bilateral interstitial infiltrates on chest radiography; pulmonary-artery wedge pressure ≥ 18 mmHg or lack of left atrial hypertension; and $\text{PaO}_2:\text{FiO}_2 < 300$). Pulmonary edema was diagnosed as being of cardiogenic origin if the pulmonary arterial occlusion pressure was >18 mmHg. In the absence of pulmonary artery wedge catheter measurements, cardiac failure was diagnosed if two of the following were present: central venous pressure >15 mmHg, a history of heart failure or valve dysfunction, ejection fraction $<45\%$ as estimated by echocardiogram, or a positive fluid balance. The probability of cardiogenic pulmonary edema was scored by two physicians independently on a scale of 1–4 (APIV and NPJ) (25). Chest radiographs were scored by two physicians independently (APIV and NPJ), with disagreements resolved by a radiologist. In the Netherlands, the National Intensive Care Evaluation (NICE) has prospectively collected data on severity, length of stay and mortality for all intensive care patients since 2002 (26, 27). Information was collected on alcohol abuse, liver failure, diabetes, hematological malignancy, chronic obstructive pulmonary disease, autoimmune disease, immune compromise, massive transfusion, surgery, pancreatitis, pneumonia and sepsis. Diabetes was specifically scored as a history of diabetes diagnosed prior to admission.

Details of drug treatment (sulphonylureas, metformin, thiazolidinediones, HMG CoA-reductase antagonists [statins], angiotensin converting enzyme [ACE] inhibitors and angiotensin II receptor [AIIIR] inhibitors) were obtained by review of the patient's notes or by telephoning the patient's general practitioner when this was missing. No drug history was obtained for patients admitted <48 h. Immunosuppression was defined as prednisolone treatment ≥ 30 mg/day (or the equivalent dose of corticosteroid), therapy with azathioprine, methotrexate, cyclosporin or rapamycin; HIV infection with a CD4 count was <200 cells/ mm^3 , or a neutrophil count $<1.0 \times 10^9$ cells/litre prior to admission.

Statistical analysis

Statistical analyses were performed on Stata 11 (StataCorp, College Station, Texas), details of which are contained in the online supplement.

Ninety-day mortality was the primary outcome of interest and survival was analyzed by Kaplan-Meier methods. Mortality was also examined at 28-days and 1-year, but these were of secondary interest. Secondary outcomes examined were ALI, CO, and no ALI/no CO. DM was the main exposure of interest. The effect of DM on mortality was explored using Cox regression models, the effect of DM on ALI, CO and no ALI/no CO were explored using multinomial logistic regression, since no data was available for time of onset. We sought to avoid over adjustment bias and unnecessary adjustment (28) by identifying confounders using a conceptual hierarchical framework/directed acyclic graph (Supplementary Figure 1, laid out using Cytoscape 2.8.1) (29) and not by p -values or likelihood ratio tests (30–32). Further details are presented in the online supplement.

Ethics

The study was approved by the Medical Ethics Committee of the Academic Medical Center, Amsterdam, The Netherlands (reference 08.17.0964), who waived the requirement for individual informed consent in view of the retrospective nature of this research.

Results

Over the course of the study period, 5,208 patients were admitted, of whom 2,013 were included in the final study, with a mean of 1.98 years of follow-up per person (Figure 1). In this cohort, there were a total of 317 patients with diabetes diagnosed prior to admission versus 1,696 without.

The characteristics of study participants are described in Table 1. Patients with diabetes were older than non-diabetic patients (median 68 years versus 61 years, respectively, $p<0.001$), had a higher BMI (27.1 versus 24.6, $p<0.001$). There was no difference in sex ratio between the two groups.

Diabetes patients were more likely to have had a myocardial infarction, present with sepsis or pancreatitis and less likely to present with multiple trauma. They were also more likely to be admitted to ICU electively. Patients with diabetes were also more severely unwell (SAPS II score 48 versus 44, APACHE II score 17 versus 16).

We also compared the characteristics of survivors against non-survivors (Table 2). Patients who died were more likely to have diabetes, were older and had a lower BMI. They were more likely to have sepsis, liver failure, hematological malignancy, pneumonia, immune compromise, and auto-immune disease. They were less likely to present with multiple trauma. Non-survivors were less likely to be planned admissions and less likely to be surgical patients. They also tended to be more unwell at admission (median SAPS II score 48 versus 44; median APACHE II score 17 versus 16). Patients who died were more likely to have had either ALI or cardiac overload.

We compared the patients according to secondary outcomes, acute lung injury (ALI) and cardiac overload (CO), and found multiple differences in risk factors that are described in Table 3.

Effect of diabetes on mortality and ALI

Mortality was higher in patients with diabetes at 28 days, 90 days and at one year (Table 1) and the hazard ratio (HR) for diabetes was 1.53 (Table 4). This dropped slightly to 1.46 after adjustment for confounders, but rose again to 1.53 in an exploratory analysis that adjusted for the effect of medication. Adjusting for APACHE II score (which we argue is incorrect) dropped the HR to 1.43.

DM patients were not at increased risk of ALI (relative risk ratio [RRR] 1.01), but were more likely to have CO (RRR 1.91). Adjustment for confounders did not change the risk for ALI (RRR 0.99), but did reduce slightly the risk of CO (RRR 1.45) (Table 5). If one combined the CO patients with the No ALI/No CO patients, the odds ratio (OR) in DM fell to 0.92 (95%CI, 0.71–1.17).

We performed two further exploratory analyses for ALI and CO. In the first analysis, we found that the effect of diabetes on CO was further reduced after adjustment for the effect of medication and the confidence intervals crossed one (RRR 1.32) (Table 5). In the second analysis, we combined CO patients with No ALI patients, and found that the odds ratio for ALI then fell to 0.92.

Effect of medication on mortality and ALI

Patients with diabetes were more likely to be taking statins, ACE-inhibitors or AIIR-inhibitors (Table 1).

There were also differences in the medication history of non-survivors compared to survivors. Non-survivors were more likely to be on cardiac SUs and less likely to be on statins (Table 2). Further differences were also found in ALI and CO patients (Table 3). In this cohort, ALI patients were less likely to be taking statins, while CO patients were more likely to be on statins and ACE-inhibitors.

In the unadjusted Cox regression analysis (Table 6), insulin, cardiac SUs and metformin were associated with increased mortality. However, these associations disappeared after adjusting for confounders. Use of statins was associated with survival and this effect strengthened after adjustment for confounders.

Use of statins was also protective in the occurrence of ALI in the unadjusted multinomial logistic regression analysis (Table 7), an association which became stronger after adjusting for confounders. Use of metformin and insulin were associated with CO, but this effect disappeared in the multivariable analysis (Table 7).

Discussion

In this cohort of 2013 critically ill patients, we studied the relationship of DM with two outcomes: mortality and ALI. We found that DM was associated with mortality, but was unrelated to ALI. These results diverge from those in the published literature.

DM was associated with increased mortality (HR 1.53) and this effect persisted after adjusting for confounders (HR 1.47). The finding that DM increases the risk of mortality agrees with some studies (2, 4) but not all (3, 5–9). We provide two possible explanations for these contrasting findings: the effect of medication and differences in the identification of confounders.

Our analysis was designed to distinguish between effects of DM and of medications which are often prescribed to diabetics. Adjustment for statin use increased the association between diabetes and mortality: diabetes patients were more likely to be prescribed statins and this can be interpreted to mean the protective effect of statins was ameliorating the apparent detrimental effect of diabetes (HR for DM was 1.47 after adjustment for confounders, but 1.55 after adjusting for medication).

The protective effect of statins on mortality has been shown in multiple previous observational studies (16, 33). Our adjusted estimate for statins on mortality (HR 0.53, 95% CI 0.44–0.64) is comparable to that reported by Janda in a meta-analysis of 20 sepsis studies (30-day mortality odds ratio 0.61, 95% CI 0.48–0.73) (16). However, Christensen's study of 12,483 critically ill patients reported a higher hazard ratio of 0.76 (0.69–0.86) (33) that is consistent with our unadjusted estimate.

Multiple mechanisms have been proposed for the effect of statins, including effects on cell signaling, alteration of leukocyte-endothelial cell interaction and reduced major histocompatibility class II antigen expression (34). We suggest that differences in prescribing practices may account for differences in the published studies of diabetes and mortality.

We have also demonstrated the bias that arises from over adjustment. In our data set, inappropriate adjustment for APACHE II score resulted in an underestimate of the association between diabetes and mortality (the hazard ratio fell from 1.53 to 1.43). In studies of DM and mortality where estimates have been inappropriately adjusted for severity, we propose that the unadjusted estimate may be more reliable.

The second outcome examined was ALI, and we found no association with DM in our study (RRR 1.01, adjusted RRR 0.99, Table 5). The effect of DM on ALI dropped after adjusting for medication (RRR 0.76) but the confidence interval still crossed one. The confidence intervals for the first two estimates were entirely contained within the third, strongly suggesting that the three estimates are consistent with each other, even though the point estimate did drop.

The proportion of DM patients in the CO group (25.0%) was different from the other two groups (14.8% in the No ALI/No CO group and 15.0% in the ALI group, Table 3, $p=0.005$). Combining the CO patients with the No ALI/No CO patients increased the proportion of DM patients in the comparator group and caused the unadjusted estimates for the effect of DM on ALI to fall from 1.01 to 0.92. This demonstrates that combining CO patients with No ALI/No CO does in principle bias the results towards an apparent protective effect. This bias would have been more severe had there been a larger proportion of cardiac failure patients in our cohort.

Two previous studies have shown a protective effect of diabetes on ALI/ARDS (12, 13), but neither study accounted for the effect of medication or considered CO as an alternative outcome.

Our study has a number of limitations. First, Hb A1c measurements were not available, so patients with previously undiagnosed diabetes would be misclassified in the No DM group. The proportion of patients with diabetes in this study (15.7%) was lower than in other published studies (2, 3), and this may be attributed to misclassification. If the misclassification is unrelated to diabetes severity, then our estimate of the effect of diabetes on mortality is closer to zero than the true value. If patients identified with DM have more severe diabetes than patients with diabetes misclassified as having No DM, then we overestimate the association between DM and mortality, but only if such an association already exists. The lack of Hb A1c measurements also means that we have no data on the level of diabetes control in patients known to have diabetes.

Second, we were unable to distinguish type 1 and 2 diabetes in our cohort, the pathogenesis of which are heterogenous. Third, patients were excluded if they stayed less than 48h in the ICU, because the cohort was originally designed to look for transfusion-related ALI, which is rare in patients who stay on the ICU for <48h (35, 36). ALI and CO may develop within 48 of admission, but our study contains no information about these patients. Fourth, the gold standard for distinguishing between hydrostatic pulmonary edema (due to CO) and pulmonary edema secondary to increased vascular permeability (ALI) is to estimate protein leakage in bronchoalveolar lavage fluid, but this is not a routine clinical procedure and therefore not available retrospectively. Fifth, we may not have adjusted for unmeasured confounders, for instance, other common causes of diabetes and differences in pre-admission medication.

The primary criticism of retrospective studies is the potential for recall bias regarding exposures of interest. Our data was not collected from interviews, so recall bias seems unlikely to be an issue. The cohort was originally formed to study transfusion-related ALI, so observer bias in scoring the patients for diabetes and for cardiac risk factors also seems unlikely. Nevertheless, our results need to be validated by investigators using the same methods.

Our study has a number of strengths, one of which is the use of new epidemiological techniques to identify confounding. Observational studies are prone to confounding, and although statistical methods are available to adjust for confounding, inappropriate selection of parameters that are not true confounders may result in biases from over-adjustment

(adjustment for parameters on the causal pathway) or unnecessary adjustment (adjustment for irrelevant parameters) (28).

This study confirms and extends previous observational evidence that statins protect from mortality (16, 17) and from ALI (18). The retrospective nature of this study means that the drugs under study were all started prior to admission and this study cannot provide guidance on whether they might be associated with benefits if given after admission. Evidence is currently awaited from randomized-controlled trials that initiating statins after admission produces similar benefits ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00528580) NCT00528580 and NCT00979121) and the routine use of statins to prevent ALI or mortality in the ICU cannot currently be recommended outside of the research setting.

Conclusions

DM is associated with increased mortality in the critically ill patient and this association is independent of pre-admission drug therapy. We argue that in the context of DM studies, adjusting for severity is inappropriate and produces biased estimates that could be incorrectly interpreted as demonstrating no effect of diabetes on mortality.

We found no effect of DM on the incidence of ALI, even after adjusting for confounders. We demonstrated that CO must be analyzed as an alternative competing outcome for ALI and that failure to do so leads to biased estimates.

Statin therapy may influence estimates for the effect of DM on outcomes and these effects need to be accounted for in studies of the effect of DM.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We wish to thank Allen C. Cheng, Kuik Yishen and Emma Persson for advice on epidemiological and statistical techniques; Tom van der Poll for support and advice. GCKWK is funded by the Wellcome Trust of Great Britain (086532/Z/08/Z). Sharon Peacock is supported by the NIHR Cambridge Biomedical Research Centre. W. Joost Wiersinga is supported by a VENI grant from the Netherlands Organization for Medical Research.

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Figure 1. Flow chart describing patient recruitment
DM, Diabetes mellitus.

Figure 2. Kaplan-Meier survival curves for 2013 ICU patients with and without a pre-admission diagnosis of diabetes

DM, diabetes mellitus (solid line); No DM (interrupted line).

A total of 837 deaths were observed and 35 individuals were censored 90 days (33 in the control group and 2 in the diabetes group). Total time at risk was 1,453,913 person-days (median 715 days per patient).

Table 1

Summary of patient characteristics by diabetes status.

Characteristics	No diabetes (<i>n</i> = 1696)		Diabetes (<i>n</i> = 317)		<i>p</i>	
Demographics						
Age		61 y	(47–72) ^a	68 y	<0.001 ^b	
Male sex	1,044	61.6%	(59.2–63.8)	205	64.7%	0.31
BMI ^c						
<18.5 kg/m ²	52	3.1%		6	1.9%	<0.001 ^d
18.5–24.9	856	50.6%		107	33.9%	
25–29.9	589	43.8%		96	30.4%	
30	196	11.6%		107	33.9%	
Admission glucose ^e						
<4.0 mM	41	2.4%		15	4.7%	<0.001 ^d
4.0–5.6	293	17.3%		25	7.9%	
5.6–6.9	396	23.4%		48	15.1%	
7.0–11.0	703	41.5%		102	32.2%	
11.1	262	15.5%		127	40.1%	
Medication						
Insulin	0	0.0%		136	42.9%	–
Metformin	0	0.0%		141	44.5%	–
Cardiac SU	0	0.0%		41	12.9%	–
Noncardiac SU	0	0.0%		56	17.7%	–
Thiazolidinediones	0	0.0%		14	4.4%	–
Statins	328	19.3%	(17.5–21.3%)	156	49.2%	<0.001
ACE inhibitor	222	13.1%	(11.6–14.8%)	115	36.3%	<0.001
AIIR inhibitor	94	5.5%	(4.6–6.7%)	35	11.0%	0.001
History						
Alcohol abuse	139	8.2%	(7.0–9.6%)	28	8.8%	0.74
Sepsis	252	14.9%	(13.2–16.6%)	63	19.9%	0.028
Liver failure	37	2.2%	(1.6–3.0%)	8	2.5%	0.68

Characteristics	No diabetes (<i>n</i> = 1696)		Diabetes (<i>n</i> = 317)		<i>p</i>
	No.	95% CI	No.	95% CI	
Pancreatitis	21	1.2% (0.8–1.9%)	10	3.2% (1.7–5.7%)	0.021
Myocardial infarction	296	17.5% (15.7–19.3%)	97	30.6% (25.8–35.9%)	<0.001
Hematological malignancy	66	3.9% (3.1–4.9%)	7	2.2% (1.1–4.5%)	0.19
Massive transfusion	121	7.1% (6.0–8.5%)	14	4.4% (2.6–7.3%)	0.086
Aspiration	49	2.9% (2.2–3.8%)	9	2.8% (1.5–5.3%)	1.00
Pneumonia	213	12.6% (11.1–14.2%)	43	13.6% (10.2–17.8%)	0.65
COPD	186	11.0% (9.6–12.5%)	47	14.8% (11.3–19.2%)	0.055
Immune compromise	115	6.8% (5.7–8.1%)	29	9.1% (6.4–12.8%)	0.15
Auto-immune disease	68	4.0% (3.2–5.1%)	19	6.0% (3.9–9.2%)	0.13
Multiple trauma	109	6.4% (5.4–7.7%)	9	2.8% (1.5–5.3%)	0.013
<i>Admission type</i>					
Planned admission	433	25.5% (23.5–27.7%)	100	31.5% (26.7–36.9%)	0.026
Surgery	844	49.8% (47.4–52.1%)	152	47.9% (42.5–53.4%)	0.58
elective	(458)	(27.0%)	(119)	(37.5%)	<0.001
emergency	(386)	(22.8%)	(33)	(10.4%)	
<i>Outcomes</i>					
SAPS II	44	(35–57) ^a	48	(37–60) ^a	0.004 ^b
APACHE II	16	(12–22) ^a	17	(13–23) ^a	0.005 ^b
ALI	612	36.1%	108	34.1%	0.005 ^{d,f}
Cardiac overload	126	7.4%	42	13.3%	
Mortality 28 days	–	19.4% ^g	–	28.7% ^g	<0.001 ⁱ
		(17.6–21.4%) ^h		(24.1–34.0%) ^h	
Mortality 90 days	–	26.4% ^g	–	34.4% ^g	
		(24.4–28.6%) ^h		(29.5–39.9%) ^h	
Mortality 1 year	–	32.3% ^g	–	43.8% ^g	
		(30.1–34.6%) ^h		(38.5–49.5%) ^h	

% per cent; 95% CI, 95 per cent confidence interval; ACE inhibitor, angiotensin converting enzyme inhibitor (e.g., captopril, ramipril); AIIR inhibitor, angiotensin II receptor inhibitor; ALI, acute lung injury; APACHE, acute physiology and chronic health evaluation score; BMI, body mass index; COPD, chronic obstructive pulmonary disease; No., number of patients; SAPS, simplified acute physiology score; SU, sulfonyleureas (cardiac SU: glyburide and tolbutamide; noncardiac SU: glimepiride); y, years.

^aMedian (interquartile range).

^bMann-Whitney U test.

^cBMI was unavailable for 4 patients.

^dFisher exact test.

^eGlucose level was unavailable for 1 patient.

^fThis *p*-value is for ALI and CO in the same 3 by 2 contingency table.

^gKaplan-Meier failure function evaluated over the entire dataset and not a simple mortality ratio.

^hGreenwood pointwise confidence interval.

ⁱMantel-Cox log-rank test over the whole survivor function, not just at the time points listed.

The Fisher exact test was used to compare all categorical variables. Confidence intervals for proportions are those proposed by Wilson.

Table 2

Summary of patient characteristics by 90-day survival.

Characteristics	Survivors (n = 1425)		Non-survivors (n = 553)		p
	No.	95% CI	No.	95% CI	
<i>Demographics</i>					
Diabetes	206	14.5%	109	19.7%	(16.6–23.2%) 0.005
Age	61 y	(48–72 y) ^a	67 y	(55–76 y) ^a	<0.001 ^b
Male sex	884	62.0%	339	61.3%	(57.2–65.3%) 0.80
BMI ^c					
<18.5 kg/m ²	34	2.4%	24	4.4%	0.014 ^d
18.5–24.9	663	46.6%	283	51.3%	
25–29.9	501	35.2%	173	31.3%	
30	225	15.8%	72	13.0%	
<i>Admission glucose^e</i>					
<4.0 mM	37	2.6%	18	3.3%	<0.001 ^d
4.0–5.6	242	17.0%	73	13.2%	
5.6–6.9	336	23.6%	100	18.1%	
7.0–11.0	581	40.8%	209	37.8%	
11.1	228	16.0%	153	27.7%	
<i>Medication</i>					
Insulin	92	6.5%	44	8.0%	(6.0–10.5%) 0.24
Metformin	92	6.5%	48	8.7%	(6.6–11.3%) 0.096
Cardiac SU	19	1.3%	21	3.8%	(2.5–5.7%) 0.001
Noncardiac SU	39	2.7%	16	2.9%	(1.8–4.6%) 0.88
Thiazolidinediones	11	0.8%	3	0.5%	(0.2–1.6%) 0.77
Statins	383	26.9%	99	17.9%	(14.9–21.3%) <0.001
ACE inhibitor	245	17.2%	89	16.1%	(13.3–19.4%) 0.59
AIIR inhibitor	101	7.1%	26	4.7%	(3.2–6.8%) 0.053
<i>History</i>					
Alcohol abuse	123	8.6%	43	7.8%	(5.8–10.3%) 0.59
Sepsis	183	12.8%	128	23.2%	(19.8–26.8%) <0.001

Characteristics	Survivors (<i>n</i> = 1425)		Non-survivors (<i>n</i> = 553)		<i>p</i>
	No.	95% CI	No.	95% CI	
Liver failure	19	1.3% (0.8–2.1%)	25	4.5% (3.1–6.6%)	<0.001
Pancreatitis	23	1.6% (1.1–2.4%)	6	1.1% (0.5–2.3%)	0.53
Myocardial infarction	267	18.7% (16.8–20.8%)	124	22.4% (19.1–26.1%)	0.068
Hematological malignancy	35	2.5% (1.8–3.4%)	38	6.9% (5.0–9.3%)	<0.001
Massive transfusion	94	6.6% (5.4–8.0%)	36	6.5% (4.7–8.9%)	1.0
Aspiration	34	2.4% (1.7–3.3%)	22	4.0% (2.6–5.9%)	0.069
Pneumonia	169	11.9% (10.3–13.6%)	85	15.4% (12.6–18.6%)	0.043
COPD	155	10.9% (9.3–12.6%)	78	14.1% (11.5–17.3%)	0.052
Immune compromise	80	5.6% (4.5–6.9%)	62	11.2% (8.8–14.1%)	<0.001
Auto-immune disease	53	3.7% (2.9–4.8%)	34	6.1% (4.4–8.5%)	0.020
Multiple trauma	96	6.7% (5.5–8.2%)	16	2.9% (1.8–4.6%)	0.001
<i>Admission type</i>					
Planned admission	468	32.8% (30.4–35.3%)	65	11.8% (9.8–14.7%)	<0.001
Surgery	789	55.4% (52.8–57.9%)	186	33.6% (29.8–37.8%)	<0.001
elective	(496)	(34.8%)	(77)	(13.9%)	
emergency	(293)	(20.6%)	(109)	(19.7%)	
<i>Outcomes</i>					
SAPS II	44	(35–57) ^a	48	(37–60) ^a	<0.001 ^b
APACHE II	16	(12–22) ^a	17	(13–23) ^a	<0.001 ^b
ALI	471	33.1%	238	43.0%	<0.001 ^f
Cardiac overload	118	8.3%	50	9.0%	

%, per cent; 95% CI, 95 per cent confidence interval; ACE inhibitor, angiotensin converting enzyme inhibitor (e.g., captopril, ramapril); AIIR inhibitor, angiotensin II receptor inhibitor; ALI, acute lung injury; APACHE, acute physiology and chronic health evaluation score; BMI, body mass index; COPD, chronic obstructive pulmonary disease; No., number of patients; SAPS, simplified acute physiology score; y, years.

^aMedian (interquartile range).

^bMann-Whitney U test.

^cBMI was unavailable for 4 patients.

^d Fisher exact test.

^e Glucose level was unavailable for 1 patient.

^f This *p*-value is for ALI and CO in the same 3 by 2 contingency table.

This table does not include data from 35 patients censored before 90 days (33 in the control group and 2 in the diabetes group). The Fisher exact test was used to compare all categorical variables. Confidence intervals for proportions are those proposed by Wilson.

Table 3

Summary of patient characteristics by acute lung injury/cardiac overload.

Characteristics	No ALI/No CO (n = 1,125)			ALI (n = 720)			CO (n = 168)		
	No.	95% CI	No.	95% CI	No.	95% CI	No.	95% CI	p
<i>Demographics</i>									
Diabetes	167	14.8%	(12.9–17.0%)	108	15.0%	(12.6–17.8%)	42	25.0%	(19.1–32.1%) 0.005
Age	61 y	(48–72) ^a	62	(49–73) ^a	68 y	(59–75) ^a	68 y	(59–75) ^a	<0.001 ^b
Male sex	645	57.3%	(54.4–60.2%)	489	67.9%	(64.4–71.2%)	115	68.5%	(61.1–75.0%) <0.001
BMI ^c									
<18.5 kg/m ²	29	2.6%		26	3.6%		3	1.8%	0.052 ^d
18.5–24.9	534	47.6%		362	50.3%		67	39.9%	
25–29.9	394	35.2%		230	31.9%		61	36.3%	
30	164	14.6%		102	14.2%		37	22.0%	
<i>Admission glucose^e</i>									
<4.0 mM	20	1.8%		33	4.6%		3	1.8%	0.011 ^d
4.0–5.6	176	15.6%		111	15.4%		31	18.5%	
5.6–6.9	259	23.0%		151	21.0%		34	20.2%	
7.0–11.0	469	41.7%		276	38.4%		60	35.7%	
11.1	201	17.9%		148	20.6%		40	23.8%	
<i>Medication</i>									
Insulin	68	6.0%	(4.8–7.6%)	49	6.8%	(5.2–8.9%)	19	11.3%	(7.4–17.0%) 0.049
Metformin	72	6.4%	(5.1–8.0%)	50	6.9%	(5.3–9.0%)	19	11.3%	(7.4–17.0%) 0.080
Cardiac SU	20	1.8%	(1.2–2.7%)	16	2.2%	(1.4–3.6%)	5	3.0%	(1.3–6.8%) 0.48
Noncardiac SU	31	2.8%	(1.9–3.9%)	19	2.6%	(1.7–4.1%)	6	3.6%	(1.6–7.6%) 0.75
Thiazolidinediones	7	0.6%	(0.3–1.3%)	5	0.7%	(0.3–1.6%)	2	1.2%	(0.3–4.3%) 0.65
Statins	278	24.7%	(22.3–27.3%)	136	18.9%	(16.2–21.9%)	70	41.7%	(34.5–49.2%) <0.001
ACE inhibitor	186	16.5%	(14.5–18.8%)	99	13.8%	(11.4–16.5%)	52	31.0%	(24.5–38.3%) <0.001
AIIR inhibitor	65	5.8%	(4.6–7.3%)	50	6.9%	(5.3–9.0%)	14	8.3%	(5.0–13.5%) 0.32
<i>History</i>									
Alcohol abuse	91	8.1%	(6.6–9.8%)	64	8.9%	(7.0–11.2%)	12	7.1%	(4.1–12.1%) 0.74
Sepsis	133	11.8%	(10.1–13.8%)	153	21.3%	(18.4–24.4%)	29	17.3%	(12.3–23.7%) <0.001

Characteristics	No ALI/No CO (n = 1,125)		ALI (n = 720)		CO (n = 168)		p
	No.	95% CI	No.	95% CI	No.	95% CI	
Liver failure	24	2.1% (1.4–3.2%)	18	2.5% (1.6–3.9%)	3	1.8% (0.6–5.1%)	0.85
Pancreatitis	13	1.2% (0.6–2.0%)	16	2.2% (1.4–3.6%)	2	1.2% (0.3–4.2%)	0.18
Myocardial infarction	187	16.6% (14.6–18.9%)	138	19.2% (16.5–22.2%)	68	40.5% (33.3–48.0%)	<0.001
Hematological malignancy	31	2.8% (2.0–4.0%)	38	5.3% (3.9–7.2%)	3	1.8% (0.6–5.1%)	0.012
Massive transfusion	38	3.4% (2.5–4.6%)	97	13.5% (11.2–16.2%)	0	0.0% (0.0–2.2%)	<0.001
Aspiration	25	2.2% (1.5–3.3%)	32	4.4% (3.2–6.2%)	1	0.6% (0.1–3.3%)	0.004
Pneumonia	95	8.4% (7.0–10.2%)	146	20.3% (17.5–23.4%)	15	8.9% (5.5–14.2%)	<0.001
COPD	125	11.1% (9.4–13.1%)	86	11.9% (9.8–14.5%)	22	13.1% (8.8–19.0%)	0.67
Immune compromise	67	6.0% (4.7–7.5%)	71	10.0% (7.9–12.3%)	6	3.6% (1.6–7.6%)	0.001
Auto-immune disease	34	3.0% (2.2–4.2%)	49	6.8% (5.2–8.9%)	4	2.4% (0.9–6.0%)	<0.001
Multiple trauma	68	6.0% (4.8–7.6%)	46	6.4% (4.8–8.4%)	4	2.4% (0.9–6.0%)	0.11
<i>Admission type</i>							
Planned admission	344	30.6% (30.0–33.3%)	131	18.2% (15.5–21.2%)	62	36.9% (30.0–44.4%)	<0.001
Surgery	643	57.2% (54.2–60.0%)	270	37.5% (34.0–41.1%)	83	49.4% (41.9–56.9%)	<0.001
elective	(362)	(32.2%)	(157)	(21.8%)	(58)	(34.5%)	
emergency	(281)	(25.0%)	(113)	(15.7%)	(25)	(14.9%)	
<i>Outcomes</i>							
SAPS II	42	(33–54) ^a	48	(38–61) ^a	47	(37–56) ^a	<0.001 ^b
APACHE II	16	(12–21) ^a	17	(13–23) ^a	16	(13–22) ^a	<0.001 ^b
Mortality day 28	–	18.6% ^f (16.4–21.0%) ^g	–	23.8% ^f (20.9–27.1%) ^g	–	23.8% ^f (18.1–31.0%) ^g	<0.001 ^h
Mortality day 90	–	23.7% ^f (21.4–26.4%) ^g	–	33.3% ^f (30.0–36.9%) ^g	–	29.8% ^f (23.5–37.3%) ^g	

%, per cent; 95% CI, 95 per cent confidence interval; ACE inhibitor, angiotensin converting enzyme inhibitor (e.g., captopril, ramapril); AIIR inhibitor, angiotensin II receptor inhibitor; ALI, acute lung injury; APACHE, acute physiology and chronic health evaluation score; BMI, body mass index; CO, cardiac overload; COPD, chronic obstructive pulmonary disease; No., number of patients; SAPS, simplified acute physiology score; y, years

^aMedian (interquartile range).

^bKruskal-Wallis test.

^cBMI was unavailable for 4 patients.

d Fisher exact test.

e Glucose level was unavailable for 1 patient.

f Kaplan-Meier failure function. This is evaluated over the entire dataset and is not a simple mortality ratio.

g Greenwood pointwise confidence interval.

h Mantel-Cox log-rank test.

The Fisher exact test was used to compare all categorical variables. Confidence intervals for proportions are those proposed by Wilson.

Table 4

Effect of diabetes mellitus on mortality in critically ill patients described using Cox regression.

Effect of diabetes on mortality (hazard ratio)	95% CI	Adjusted for
1.53	(1.29–1.80)	None
1.46	(1.23–1.74)	Age, sex and BMI
1.53	(1.07–2.17)	Age, sex, BMI, MI, medication (insulin, metformin, sulphonylureas, statin ACE inhibitor, AIIR inhibitor)
1.43	(1.21–1.70)	APACHE II score

95% CI, 95 per cent confidence interval; BMI, body mass index; ACE, angiotensin converting enzyme; AIIR, angiotensin II receptor; MI, myocardial infarction.

Table 5

Effect of diabetes mellitus on occurrence of acute lung injury and cardiac overload described using multinomial logistic regression.

Effect of diabetes on				
ALI (RRR)	95% CI	CO (RRR)	95% CI	Adjusted for
1.01	(0.78–1.32)	1.91	(1.30–2.81)	None
0.99	(0.75–1.31)	1.45	(0.97–2.18)	Age, sex, BMI
0.76	(0.43–1.33)	1.31	(0.60–2.88)	Age, sex, BMI, MI, medication (insulin, metformin, sulphonylurea, statin ACE inhibitor, AIIIR inhibitor) ^a

95% CI, 95 per cent confidence interval; ALI, acute lung injury; BMI, body mass index; CO, cardiac overload; MI, myocardial infarction; RRR, relative risk ratio.

^aMedication cannot be a confounder for diabetes because it lies on the causal pathway between diabetes and ALI. This is therefore an exploratory analyses to look for potential mechanisms, and this estimate cannot be interpreted as being adjusted for confounders.

The comparator for all RRRs was the No ALI/No CO group. Relative risk ratios between 0 and 1 indicate association with ALI or CO less than with No ALI/No CO; values above 1 indicate association with ALI or CO greater than in the patients with No ALI/No CO; RRRs close to 1 suggest no difference compared to patients with No ALI/No CO. The Hausman-McFadden test reported $p > 0.99$ for all models.

Table 6

Effect of medication on mortality described using Cox regression.

Drug	Unadjusted		Adjusted ^a	
	HR	95% CI	HR	95% CI
Insulin	1.44	(1.14–1.83)	1.12	(0.78–1.60)
Metformin	1.30	(1.02–1.66)	0.95	(0.69–1.32)
Cardiac SU	1.97	(1.34–2.89)	1.54	(0.98–2.43)
Noncardiac SU	1.40	(0.98–2.01)	1.07	(0.70–1.64)
Statins	0.74	(0.63–0.87)	0.53	(0.44–0.64)
ACE inhibitor	1.06	(0.88–1.26)	0.91	(0.75–1.10)
AIIR inhibitor	0.85	(0.64–1.13)	0.79	(0.59–1.06)

95% CI, 95 per cent confidence interval; ACE, angiotensin converting enzyme; AIIR, angiotensin II receptor; BMI, body mass index; HR=hazard ratio; SU, sulfonylurea (cardiac: glyburide and tolbutamide; noncardiac: gliclazide and glimepiride).

^a Adjusted for age, sex, BMI, diabetes and myocardial infarction.

Table 7

Effect of medication on acute lung injury and cardiac overload described using multinomial logistic regression.

	ALI				CO			
	Unadjusted		Adjusted ^a		Unadjusted		Adjusted ^a	
	RRR	95% CI	RRR	95% CI	RRR	95% CI	RRR	95% CI
Insulin	1.14	(0.78–1.66)	1.45	(0.81–2.60)	1.98	(1.16–3.39)	1.00	(0.44–2.25)
Metformin	1.09	(0.75–1.59)	1.38	(0.82–2.34)	1.86	(1.09–3.18)	0.98	(0.47–2.07)
Cardiac SU	1.26	(0.65–2.44)	1.58	(0.72–3.47)	1.69	(0.63–4.58)	0.68	(0.21–2.17)
Noncardiac SU	0.96	(0.54–1.71)	1.11	(0.55–2.23)	1.31	(0.54–3.18)	0.68	(0.24–1.92)
Statins	0.71	(0.56–0.89)	0.61	(0.47–0.79)	2.18	(1.56–3.04)	1.12	(0.76–1.64)
ACE inhibitor	0.80	(0.62–1.05)	0.82	(0.62–1.09)	2.26	(1.57–3.25)	1.59	(1.07–2.38)
AIIR blocker	1.22	(0.83–1.78)	1.28	(0.86–1.91)	1.48	(0.81–2.71)	1.35	(0.72–2.55)

95% CI, 95 per cent confidence interval; ACE, angiotensin converting enzyme; AIIR, angiotensin II receptor; BMI, body mass index; CO, cardiac overload; RRR, relative risk ratio; SU, sulfonylurea (cardiac: glyburide and tolbutamide; noncardiac: glimepiride and glipizide).

^a Adjusted for age, sex, BMI, diabetes and myocardial infarction.

The comparator for all RRRs was the No ALI/No CO group. RRRs between 0 and 1 indicate association with ALI or CO less than with No ALI/No CO; values above 1 indicate association with ALI or CO greater than in the patients with No ALI/No CO; RRRs close to 1 suggest no difference compared to patients with No ALI/No CO. The Hausman-McFadden test reported $p > 0.99$ for all models.