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ORIGINAL ARTICLE

Type 2 diabetes and 1-year mortality in intensive care unit patients

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ABSTRACT

Background Data on the prognostic impact of diabetes and diabetic complications in intensive care unit (ICU) patients are limited and inconsistent. We, therefore, examined mortality in ICU patients with type 2 diabetes with and without pre-existing heart and kidney diseases compared with nondiabetic patients.

Design We conducted this population-based cohort study in Northern Denmark during 2005–2011. We included all ICU patients aged 40 years or older from the 17 ICUs in the area and identified type 2 diabetes by either a filled prescription for an antidiabetic drug, a previous diagnosis of diabetes, or an elevated glycosylated haemoglobin level. Diabetic patients were disaggregated according to pre-existing diagnoses of heart disease (myocardial infarction or heart failure) and kidney disease.We estimated 1-year mortality by the Kaplan–Meier method and hazard ratios of death (HRs) during follow-up using Cox regression, controlling for confounding factors and stratified by relevant subgroups.

Results Among 45 018 ICU patients, 7219 (16·0%) had type 2 diabetes. Overall, 1-year mortality was 36·0% in ICU patients with type 2 diabetes, rising to 54·6% in patients with pre-existing heart and kidney diseases, compared with 29·1% in nondiabetic patients. Comparing diabetic with nondiabetic patients, the adjusted 0- to 30-day HR was 1·20 (95% confidence interval (CI): 1·13–1·26) and 1·19 (95% CI: 1·10–1·28) during the 31- to 365-day follow-up period. Pre-existing kidney disease further increased the impact of diabetes, while heart disease alone had no such effect.

Conclusions ICU patients with type 2 diabetes had higher 1-year mortality compared with nondiabetic ICU patients, particularly those with pre-existing kidney disease.

Keywords Cohort study, diabetes mellitus type 2, heart disease, intensive care, kidney disease, mortality.

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Introduction

The prevalence of type 2 diabetes is increasing, with about 9% of the world's population affected [1]. Diabetes is a primary cause of chronic kidney disease and cardiovascular disease [2–4]. Diabetes increases the risk of acute renal failure [5], cardiovascular events [3,6,7] and infections [8–10], all of which may lead to intensive care unit (ICU) admission.

The prevalence of diabetes in ICU patients has been reported as high as 19% [11]. While knowledge about the prognosis of ICU patients with type 2 diabetes is important for understanding their clinical course, existing research is limited to four cohort studies. These studies had conflicting findings. Three reported that diabetes was not associated with in-hospital or 90-day mortality [12–14], while one found a 50% increase in 1-year mortality [15]. The four studies were limited by the lack of data on diabetes type, complications and antidiabetic drug prescriptions and haemoglobin A1c (HbA1c) levels as indicators of diabetes [12–15], as well as by potential uncontrolled confounding arising from other chronic diseases and use of in-hospital mortality as the only outcome [13,14]. Methods of selecting study participants [12,14] and settings in heterogeneous healthcare systems may have further biased the studies' results and reduced their generalizability [13].

A large population-based study based on valid diabetes data and complete 1-year follow-up is needed to clarify the clinical course of patients with type 2 diabetes after ICU admission and potentially prevent post-ICU deaths.

We, therefore, undertook a large population-based cohort study to examine in detail whether type 2 diabetes, including pre-existing heart and kidney diseases, was associated with increased mortality for up to 1 year after ICU admission. We further examined differential impacts of diabetes in subgroups of ICU patients.

Materials and methods

Setting

We conducted this cohort study among patients living in Northern Denmark, a region with a population of 1·8 million (33% of the Danish population).

Denmark has a tax-supported healthcare system that guarantees unfettered access to medical care for all residents, as well as partial reimbursement of prescribed drugs. There are 17 ICUs in Northern Denmark (eight units at university hospitals and nine at regional hospitals). All Danish citizens receive a unique civil registration number at birth or upon immigration that allows unambiguous linkage among all Danish medical databases.

Identification of patients in intensive care units

We identified all patients aged 40 years or older with at least one admission to an ICU in the study area between 1 January 2005 and 31 December 2011, using the Danish National Registry of Patients (DNRP) [16].

The DNRP contains data on all nonpsychiatric hospital admissions in Denmark since 1977 and on outpatient clinic and emergency room visits since 1995 [17]. Reporting to the DNRP is mandatory for all Danish hospitals. Data in the registry include dates of hospital admission and discharge, acute/elective admission type, one primary diagnosis (the main reason for hospitalization) and up to 19 secondary diagnoses, as well as treatments, procedures and admissions to intensive care units [16]. Diagnoses are coded according to the *International Classification of Diseases,* 10th revision (ICD-10), since 1994. Patients were considered admitted for surgical reasons if they had a surgical procedure on the day of or within 7 days before ICU admission [18]. Data regarding mechanical ventilation, renal replacement therapy and treatment with inotropes or vasopressors were also obtained from the DNRP.

Diabetes data

We used a previously validated algorithm to identify diabetic patients. According to this algorithm, diabetes was defined as any previous outpatient or inpatient diagnosis of diabetes in the DNRP or any filled prescription for an oral antidiabetic drug, identified in a population-based prescription database [19,20]. Patients were considered to have type 2 diabetes if they had their first-time diabetes diagnosis at or after age 30 or had the diagnosis before age 30 with no insulin prescription in the year before the current admission. We also defined patients as having diabetes if their HbA1C level had reached the diagnostic level for diabetes, that is, 6·5% or more, within a year before admission, as identified through a clinical laboratory database that includes test results from both hospitals and general practitioners [21,22]. Metformin users with polycystic ovarian syndrome and no diabetes diagnoses were considered nondiabetic (n = 5) [23].

To study the influence of major chronic microvascular and macrovascular complications of diabetes [24], we further disaggregated type 2 diabetes patients according to pre-existing diagnoses of chronic kidney disease and/or heart disease, including myocardial infarction and heart failure. Pre-existing heart and kidney diseases were identified by inpatient and outpatient clinic diagnoses registered in the DNRP from 1 year before the first diabetes detection until the current admission date, because both heart and kidney diseases may precede diabetes detection [25]. (ICD codes are provided in Appendix S1.)

Mortality

Data regarding vital status, including the exact date of death or emigration, were obtained from the Danish Civil Registration System, which includes information, updated daily, on vital status (dead or alive), marital status and place of residence for all Danish citizens [26].

Other chronic diseases

We used all inpatient and outpatient diagnoses in the DNRP within 5 years before ICU admission to identify other pre-existing chronic diseases, including chronic pulmonary disease, connective tissue disease, liver disease, cancer, metastatic cancer, obesity and alcoholism. Most of these diagnoses are included in the Charlson comorbidity index and are all known to have prognostic impacts [27–29]. (See Appendix S1 and S2 for ICD-10 and ATC codes).

Statistical analyses

We followed patients for up to 1 year, from the day of first ICU admission during the study period until death, emigration or 1 January 2012, whichever came first. Covariates were tabulated by diabetes status.

The Kaplan–Meier method was used to estimate 30-day, 31- to 365-day and cumulative 1-year mortality.

To compare mortality rates, we used a Cox proportional hazards regression analysis to compute age- and sex-adjusted 30-day and 31- to 365-day hazard ratios of death for patients with type 2 diabetes with and without heart and kidney diseases, compared with nondiabetic ICU patients. The assumption of proportional hazards, including linearity of age, was

checked graphically and found appropriate. In type 2 diabetes patients, we also examined mortality according to duration of diabetes and last HbA1c measurement on or within a year before hospital admission, as markers of severity of diabetes and chronic glycemic control, respectively.

We conducted a second analysis further adjusted for marital status and for other pre-existing chronic diseases, including dementia, chronic pulmonary disease, connective tissue disease, liver disease, cancer, metastatic cancer, alcoholism and obesity. We also repeated the analyses excluding the patients identified solely by an elevated HbA1c level (n = 754), because they may have milder diabetes.

To address the potential differential impact of type 2 diabetes in subgroups of ICU patients, we stratified the analyses by age group, sex, diagnostic category (primary diagnosis during hospitalization), treatment with mechanical ventilation and admission type. (See Appendix S1 for diagnostic codes.) We also stratified by the year of study inclusion.

All analyses were conducted using the software package STATA, version 10.1 (StataCorp, College Station, TX, USA). The study was approved by the Danish Data Protection Agency. Informed consent was not required. Reporting of the study conforms to the STROBE statement [30].

Results

Descriptive data

The study cohort consisted of 45 018 ICU patients aged 40 years or older, with a total follow-up time of 31 761 person-years. Among these patients, 7219 (16·0%) had type 2 diabetes. Diabetes was complicated by pre-existing heart disease in 1269 patients (17·6%), by kidney disease in 313 patients (4·3%) and by both in 171 patients (2·4%).

The median age was 70 years in patients with type 2 diabetes and 67 years in nondiabetic ICU patients. There were slightly more men among the type 2 diabetes patients (60·1%) than among nondiabetic ICU patients (56·6%) (Table 1). Patients with type 2 diabetes were more likely to have chronic pulmonary disease, liver disease and obesity. Cancer was slightly more frequent in nondiabetic ICU patients (Table 1).

Type 2 diabetic patients with pre-existing heart disease were older (median age: 72 years), and many had chronic pulmonary disease than ICU patients without diabetes. More than 90% of diabetes patients with kidney disease also had chronic pulmonary disease (Table 1). Mechanical ventilation was provided to approximately 40% of both uncomplicated type 2 diabetes patients and nondiabetic ICU patients, and renal replacement therapy was provided to almost six per cent of patients with uncomplicated type 2 diabetes and to more than 20% of patients with chronic kidney disease, compared with four per cent of nondiabetic ICU patients. Treatment with inotropes or vasopressors was also more frequent among type 2 diabetes patients with chronic heart or kidney disease compared with nondiabetic ICU patients (Table 1).

Mortality

Thirty-day mortality. Thirty-day mortality was 23·0% (95% CI: 22·0–24·0%) in type 2 diabetes patients and 18·2% (95% CI: 17·8–18·6%) in nondiabetic ICU patients (Table 2). The corresponding age- and sex-adjusted HR was 1·20 (95% CI: 1·13–1·26), comparing ICU patients with type 2 diabetes with nondiabetic ICU patients (Table 2). Thirty-day mortality in type 2 diabetes patients ranged from 22·2% among those without pre-existing heart and kidney diseases to 36·9% among those with diabetes complicated by both heart and kidney diseases.

Type 2 diabetes with pre-existing heart disease was also associated with a slight mortality increase compared with nondiabetic ICU patients [adjusted HR = 1·13 (95% CI: 1·01–1·27)]. Type 2 diabetes patients with pre-existing kidney disease had markedly increased mortality compared with other patients. This was a consistent finding among patients with diabetes with pre-existing kidney disease, both without [adjusted HR = 1·57 (95% CI: 1·28–1·93)] and with pre-existing heart disease [HR = 1·83 (95% CI: 1·43–2·35)] (Table 2). We found virtually the same associations across admission years (data not shown). Diabetes duration and HbA1c level had no impact on mortality in patients with diabetes. However, lack of an HbA1c measurement was associated with an increased mortality in patients with diabetes (Table 2).

Additional adjustment for other chronic diseases and marital status decreased HR estimates further towards one [adjusted HR = 1·14 (95% CI: 1·07–1·21) for diabetes without pre-existing heart and kidney diseases, 1·10 (95% CI: 0·98–1·24) for diabetes with pre-existing heart disease, 1·13 (95% CI: 0·90–1·42) for diabetes with pre-existing kidney disease and 1·33 (95% CI: 1·02–1·73) for diabetes with both pre-existing heart and kidney diseases].

One-year mortality. The cumulative 1-year mortality was 36·0% (95% CI: 34·9–37·2%) in ICU patients with type 2 diabetes and 29·1% (95% CI: 28·7–29·6%) in nondiabetic patients. One-year mortality in type 2 diabetic patients ranged from 34·5% (95% CI: 33·2–35·8%) in patients with uncomplicated diabetes to 54·6% (95% CI: 47·1–62·3%) in diabetic patients with both heart and kidney diseases (Fig. 1 and Table 2).

Among ICU patients surviving the first 30 days, mortality from day 31 to day 365 following ICU admission was 17·0% (95% CI: 16·0–18·0%) in type 2 diabetic patients and 13·4% (95% CI: 13·0–13·8%) in nondiabetic ICU patients. Mortality increased to almost 30% in type 2 diabetes patients with kidney disease (Table 2). The adjusted 31- to 365-day HR was 1·19

Table 1 Characteristics of intensive care unit (ICU) patients with and without type 2 diabetes and among type 2 diabetic patients according to pre-existing diagnoses of heart and kidney diseases

		Type 2 diabetes				
			Pre-existing diabetes-related diseases*			
	No diabetes *n* = 37,799 (%)	All *n* = 7,219 (%)	No *n* = 5,466 (%)	Heart disease *n* = 1,269 (%)	Kidney disease *n* = 313 (%)	Heart+kidney disease *n* = 171 (%)
Age group						
40–59 years	11 345 (30·0)	1279 (17·7)	1065 (19·5)	148 (11·7)	50 (16·0)	16 (9·4)
60–79 years	20 035 (53·0)	4635 (64·2)	3468 (63·5)	848 (66·8)	203 (64·9)	116 (67·8)
80+ years	6419 (17·0)	1305 (18·1)	933 (17·1)	273 (21·5)	60 (19·2)	39 (22·8)
Age, median (IQR†)	67 (57–76)	70 (62–77)	69 (62–77)	72 (65–78)	71 (63–78)	74 (67–78)
Sex						
Female	16 390 (43·4)	2878 (39·9)	2239 (41·0)	463 (36·5)	118 (37·7)	58 (33·9)
Male	21,409 (56·6)	4,341 (60·1)	3,227 (59·0)	806 (63·5)	195 (62·3)	113 (66·1)
Marital status						
Married	20 731 (54·9)	3689 (51·1)	2793 (51·1)	652 (51·4)	153 (48·9)	91 (53·2)
Never married	4171 (11·0)	749 (10·4)	574 (10·5)	113 (8·9)	45 (14·4)	17 (9·9)
Divorced	5,231 (13·8)	1,090 (15·1)	850 (15·6)	174 (13·7)	39 (12·5)	27 (15·8)
Widowed	7577 (20·1)	1684 (23·3)	1242 (22·7)	330 (26·0)	76 (24·3)	36 (21·1)
Unknown	89 (0·2)	7 (0·1)	7 (0·1)	0 (0·0)	0 (0·0)	0 (0·0)
Other preadmission morbidity‡						
Dementia	375 (1·0)	88 (1·2)	60 (1·1)	16 (1·3)	5 (1·6)	7 (4·1)
Chronic pulmonary disease	1054 (2·8)	755 (10·5)	213 (3·9)	93 (7·3)	287 (91·7)	162 (94·7)
Connective tissue disease	1098 (2·9)	286 (4·0)	178 (3·3)	70 (5·5)	26 (8·3)	12 (7·0)
Liver disease	877 (2·3)	242 (3·4)	200 (3·7)	28 (2·2)	10 (3·2)	4 (2·3)
Cancer	5942 (15·7)	975 (13·5)	795 (14·5)	130 (10·2)	39 (12·5)	11 (6·4)
Metastatic cancer	1001 (2·7)	132 (1·8)	110 (2·0)	16 (1·3)	4 (1·3)	2 (1·2)
Alcoholism	2810 (7·4)	473 (6·6)	385 (7·0)	53 (4·2)	25 (8·0)	10 (5·9)
Obesity	733 (1·9)	727 (10·1)	490 (9·0)	169 (13·3)	43 (13·7)	25 (14·6)
ICU admission type						
Medical	13 421 (35·5)	2897 (40·1)	2190 (40·1)	470 (37·0)	150 (47·9)	87 (50·9)
Surgical, acute noncardiac	11 796 (31·2)	2023 (28·0)	1594 (29·2)	273 (21·5)	106 (33·9)	50 (29·2)
Surgical, acute cardiac	1436 (3·8)	268 (3·7)	169 (3·1)	81 (6·4)	12 (3·8)	6 (3·5)
Surgical, elective noncardiac	6660 (17·6)	1011 (14·0)	859 (15·7)	107 (8·4)	31 (9·9)	14 (8·2)

Table 1 *Continued*

		Type 2 diabetes				
			Pre-existing diabetes-related diseases*			
	No diabetes *n* = 37,799 (%)	All *n* = 7,219 (%)	No *n* = 5,466 (%)	Heart disease *n* = 1,269 (%)	Kidney disease *n* = 313 (%)	Heart+kidney disease *n* = 171 (%)
Surgical, elective cardiac	4486 (11·9)	1020 (14·1)	654 (12·0)	338 (26·6)	14 (4·5)	14 (8·2)
Intensive care treatments						
Mechanical ventilation	14 989 (39·7)	3062 (42·2)	2277 (41·6)	619 (48·8)	118 (37·7)	48 (28·1)
Renal replacement therapy	1429 (3·8)	458 (6·3)	308 (5·6)	51 (4·0)	67 (21·4)	32 (18·7)
Treatment with inotropes/ vasopressors	10 480 (27·7)	2362 (32·7)	1745 (31·9)	449 (35·4)	117 (37·4)	51 (29·8)

*First diagnosed from 1 year before first diabetes diagnosis/antidiabetic prescription until the current hospital admission.
†IQR, interquartile range.
‡Any diagnosis within 5 years before the current hospital admission.

(95% CI: 1·10–1·28), peaking at 2·18 (95% CI: 1·69–2·82) in type 2 diabetes patients with kidney disease (Table 2).

Among the 7219 type 2 diabetes patients, 754 (10·4%) were considered to have diabetes based only on an elevated HbA1c test result. Excluding these patients did not affect the estimates [30-day adjusted HR = 1·18 (95% CI: 1·11–1·25) and 31- to 365-day adjusted HR = 1·17 (95% CI: 1·08–1·26)].

Subgroups of intensive care patients

The effect of type 2 diabetes on mortality was most pronounced in patients aged 60 years or older. There were no sex-associated differences (Fig. 2). Type 2 diabetes had no impact on mortality in ICU patients with a primary diagnosis of septicaemia or of pneumonia (Fig. 2).

Overall, there were no major differences in the mortality impact of type 2 diabetes among medical ICU patients and surgical patients, although the impact may be slightly higher in patients admitted after noncardiac surgery (Fig. 2). The association was less pronounced in patients treated with mechanical ventilation [adjusted HR = 1·10 (95% CI: 1·02–1·18)] than in patients not receiving mechanical ventilation [adjusted HR = 1·29 (95% CI: 1·19–1·39)] (Fig. 2). A similar pattern was found in patients who received treatment with inotropes or vasopressors during their ICU admission [adjusted HR = 1·09 (95% CI: 1·01–1·18)] and in those who did not [adjusted HR = 1·22 (1·13–1·32)] (data not shown).

Discussion

Diabetes, including diabetic complications, is a mounting public health challenge and a clinical problem with substantial impact on healthcare costs. Our study is the first to report the impact of type 2 diabetes on 1-year mortality among intensive care patients according to pre-existing heart and kidney diseases. During the entire follow-up period, the mortality rate was 20% higher among ICU patients with type 2 diabetes than among nondiabetic ICU patients. The excess risk was more pronounced in diabetic patients with kidney disease.

Our study extends the current literature by identifying diabetic patients with a pre-existing kidney diagnosis as a subgroup at particular risk. Our results also confirm results from a single-centre cohort study of 2013 patients, which found an even more pronounced effect of diabetes [age- and sex-adjusted hazard ratio = 1·53 (95% CI: 1·29–1·80)] [15]. In addition, a recent systematic review, including a meta-analysis of 141 ICU studies containing data on both diabetes status and mortality, reported an unadjusted pooled odds ratio of 1·19 (95% CI: 0·96–1·47) of death within 30 days, while no such association was found for in-hospital mortality [11].

In contrast to our findings, three previous studies reported no increased short-term mortality among ICU patients with diabetes compared with ICU patients without diabetes [12–14]. A US cohort study of more than 1·5 million ICU patients identified from an administrative database reported an age-adjusted odds ratio of 0·79 (95% CI: 0·78–0·80) for in-hospital mortality, while the odds ratio was 1·01 (95% CI: 0·92–1·11) in a subset of 36 414 patients with additional clinical data and for whom diabetes history was obtained by nurses at ICU admission [13]. In an European study of 3147 patients from 198 ICUs, patients with insulin-treated diabetes had higher in-hospital mortality compared with nondiabetic ICU patients (28% vs. 24%), while the hazard ratio was 0·78 (95% CI: 0·58–1·07) after adjustment for age, liver cirrhosis, SAPS II score and mechanical ventilation [14]. However, an increased SAPS II score can be a consequence of diabetes, and such adjustments may hide

Table 2 Thirty-day, 31- to 365-day and cumulative 1-year mortality and hazard ratios of death (HR) in ICU patients with type 2 diabetes with/without pre-existing diagnoses of heart and kidney diseases

		30-day			31- to 365-day mortality			1-year mortality (cumulative)
	N	Mortality,% (95% CI)	Crude HR (95% CI)	Adjusted* HR (95% CI)	Mortality,% (95% CI)	Crude HR (95% CI)	Adjusted* HR (95% CI)	Mortality,% (95% CI)
Diabetes status and pre-existing heart and kidney diseases								
No diabetes	37 799	18·2 (17·8–18·6)	1·00 (ref.)	1·00 (ref.)	13·4 (13·0–13·8)	1·00 (ref.)	1·00 (ref.)	29·1 (28·7–29·6)
Type 2 diabetes	7219	23·0 (22·0–24·0)	1·30 (1·23–1·37)	1·20 (1·13–1·26)	17·0 (16·0–18·0)	1·29 (1·20–1·38)	1·19 (1·10–1·28)	36·0 (34·9–37·2)
No heart or kidney disease	5466	22·2 (21·1–23·3)	1·24 (1·17–1·32)	1·17 (1·10–1·24)	15·8 (14·7–17·0)	1·19 (1·09–1·29)	1·12 (1·03–1·21)	34·5 (33·2–35·8)
With heart disease†	1269	23·0 (20·8–25·4)	1·31 (1·17–1·47)	1·13 (1·01–1·27)	17·9 (15·6–20·5)	1·40 (1·20–1·63)	1·21 (1·04–1·41)	36·8 (34·2–39·5)
With kidney disease‡	313	29·4 (24·7–34·8)	1·73 (1·41–2·13)	1·57 (1·28–1·93)	29·7 (23·9–36·6)	2·38 (1·84–3·07)	2·18 (1·69–2·82)	50·4 (44·8–56·2)
With heart† and kidney disease‡	171	36·9 (30·1–44·6)	2·26 (1·76–2·90)	1·83 (1·43–2·35)	28·0 (20·4–37·8)	2·29 (1·59–3·30)	1·83 (1·27–2·64)	54·6 (47·2–62·3)
Diabetes duration								
0–2 years	2258	22·5 (20·8–24·3)	1·00 (ref.)	1·00 (ref.)	17·7 (15·9–19·6)	1·00 (ref.)	1·00 (ref.)	36·2 (34·2–38·2)
3–5 years	1295	21·9 (19·7–24·2)	0·98 (0·85–1·13)	1·01 (0·87–1·17)	15·5 (13·4–18·0)	0·87 (0·71–1·05)	0·87 (0·71–1·06)	34·0 (31·4–36·7)
6–10 years	1634	23·6 (21·6–25·7)	1·05 (0·92–1·20)	1·02 (0·89–1·17)	16·8 (14·7–19·0)	0·95 (0·79–1·14)	0·91 (0·76–1·09)	36·4 (34·1–38·8)
>10 years	2032	23·7 (22·0–25·7)	1·07 (0·94–1·21)	1·03 (0·91–1·17)	17·3 (15·4–19·3)	0·98 (0·83–1·16)	0·94 (0·79–1·11)	36·9 (34·8–39·1)
HbA1c level in type 2 diabetes patients$								
<6·5 mM	1539	23·6 (21·6–25·8)	1·00 (ref.)	1·00 (ref.)	15·9 (13·9–18·2)	1·00 (ref.)	1·00 (ref.)	35·8 (33·4–38·3)
6·5–6·9 mM	1377	21·8 (19·7–24·1)	0·92 (0·79–1·07)	0·91 (0·78–1·06)	17·5 (15·3–20·0)	1·10 (0·89–1·36)	1·08 (0·88–1·34)	35·5 (33·0–38·2)
7–7·9 mM	1447	21·4 (19·4–23·6)	0·90 (0·77–1·05)	0·91 (0·78–1·05)	16·1 (14·0–18·4)	1·00 (0·81–1·24)	1·00 (0·81–1·23)	34·0 (31·6–36·6)
≥8 mM	1325	21·9 (19·7–24·2)	0·91 (0·78–1·07)	1·04 (0·89–1·22)	15·9 (13·8–18·4)	0·99 (0·79–1·22)	1·10 (0·89–1·37)	34·3 (31·8–37·0)
No measurement	1531	25·9 (23·8–28·2)	1·11 (0·96–1·28)	1·16 (1·00–1·34)	19·2 (17·0–21·7)	1·22 (1·00–1·49)	1·28 (1·05–1·56)	40·1 (37·7–42·6)

*Adjusted for age and sex.
†Heart diseases included diagnoses of myocardial infarction and congestive heart failure.
‡Kidney diseases included diagnoses of chronic kidney diseases.
$Last HbA1c measurement at or within a year before current hospital admission.

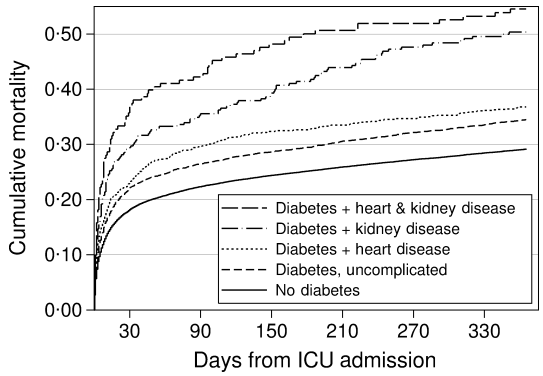

Figure 1 Cumulative 1-year mortality among intensive care patients without diabetes, patients with uncomplicated type 2 diabetes and patients with type 2 diabetes complicated by heart and/or kidney disease.

any true associations [31]. An older cohort study examined 830 ICU patients with severe sepsis identified from the control group of an international multicentre trial [12]. Although 28-day mortality rates were very similar in ICU patients with and without diabetes (31·4% vs. 30·5%), type 2 diabetes patients with severe chronic complications may have been excluded based on one of several exclusion criteria in the trial [32]. The prevalence of diabetes among subjects in the previous studies ranged from 7·2% [14] to 22·7% [12], which may be partly explained by misclassification arising from different definitions of diabetes (insulin treatment, chart review or registration during index hospitalization).

Several pathophysiological mechanisms may underlie our findings. Diabetes is associated with immune dysfunction, endothelial dysfunction and procoagulation [10]. Immune dysfunction in diabetes actually may reduce the risk of acute lung injury [15,33,34]. In contrast to a recent study [35],

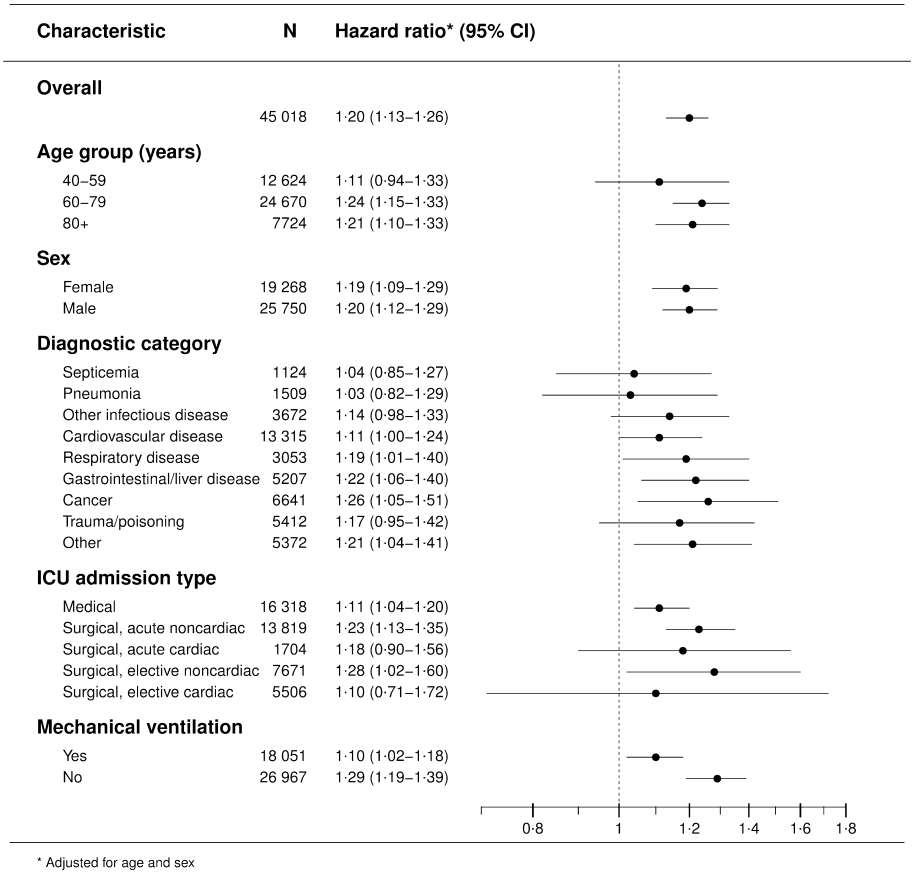

Figure 2 Thirty-day hazard ratios of death (HR) comparing type 2 diabetes patients with nondiabetic ICU patients, stratified by age, sex, diagnostic category (main reason for hospitalization), surgery at or before intensive care unit (ICU) admission and mechanical ventilation.

we found no protective effect of an elevated HbA1c level in patients with diabetes. We found instead that lack of an HbA1c measurement within the past year was associated with increased mortality, probably because of nonadherence to health care including regular diabetes check-ups. Also, the use of antidiabetic and cardioprotective drugs by diabetic patients may be beneficial [36–38], although a previous study found similar results after adjusting for use of such drugs [15].

Some methodological issues may have affected our estimates. We used accurate routine registrations to identify ICU admissions [16] and had virtually complete 1-year follow-up for death. This, together with equal access to health care in Denmark, eliminates selection bias. Undetected diabetic patients would have biased our results towards no association. However, we obtained excellent data on diabetes status by examining hospital diagnoses, prescriptions for antidiabetic drugs and HbA1c measurements. Although diagnostic coding of heart and kidney diseases is valid [28], we did not take into account their severity. We controlled for age and gender and included diabetic complications in the exposure groups. Further adjustment for other chronic diseases slightly decreased the estimates of the association between diabetes and mortality, indicating that the effect of diabetes may be partly mediated through these diseases or associated lifestyle factors. While we lacked individual-level data on in-hospital glycemic control during the study period, we found virtually no difference in the impact of diabetes across study years. To our knowledge, most Danish ICU patients in the study period were treated according to current sepsis guidelines, with a glucose target of a maximum 8 mM [39].

Results from our study may be generalizable to other homogenous healthcare systems with similar ICU cohorts and subgroups. However, comparisons of ICU studies are in general hampered by the heterogeneity of ICU populations with regard to ICU admission and discharge criteria and ICU bed availability [40].

In conclusion, ICU patients with type 2 diabetes experienced higher mortality than nondiabetic ICU patients for up to 1 year after ICU admission. The impact was most pronounced in diabetic patients with a diagnosis of chronic kidney disease. This subgroup may therefore be of particular interest both in the clinical setting and for tertiary preventive initiatives.

Conflicts of interest

The authors have no conflicts of interest to disclose.

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Contributions

CFC, SC and HTS designed the study. MBJ and CFC analysed data. CFC interpreted data and wrote the first draft. SC, HTS, JMO'B, MBJ and ET helped to interpret the results and revised the draft critically. All authors approved the final version.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. International Classification of Diseases, 8th (ICD-8) and 10th revision (ICD-10) diagnosis codes.

Appendix S2. Anatomical Therapeutical Chemical (ATC) codes for included drugs.