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► To cite this version:

Alexandre Pharaboz, Antoine Kimmoun, Jan Gunst, Kevin Duarte, Thomas Merklung, et al.. Association between type II diabetes mellitus and 90-day mortality in a large multicenter prospectively collected cohort. A FROG ICU post-hoc study. *Journal of Critical Care*, 2023, 73, pp.154195. 10.1016/j.jcrc.2022.154195 . hal-03901673

HAL Id: hal-03901673

<https://hal.univ-lorraine.fr/hal-03901673>

Submitted on 15 Dec 2022

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2 **Association between type II diabetes mellitus and 90-day mortality in a large**
3 **multicenter prospectively collected cohort. A FROG ICU post-hoc study.**

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19 *Competing interests.*

20 AM reports personal fees from Orion, grants and personal fees from Roche, personal fees
21 from Servier, personal fees from Otsuka, personal fees from Philips, grants and personal fees
22 from Adrenomed, personal fees from Neuro Tronik, grants and personal fees from 4TEEN4,
23 personal fees from Sanofi. Etienne Gayat. EG received research grant from Sphingotec,
24 radiometer and Philips and consultancy fees from Baxter and Edwards Lifescience. BGC

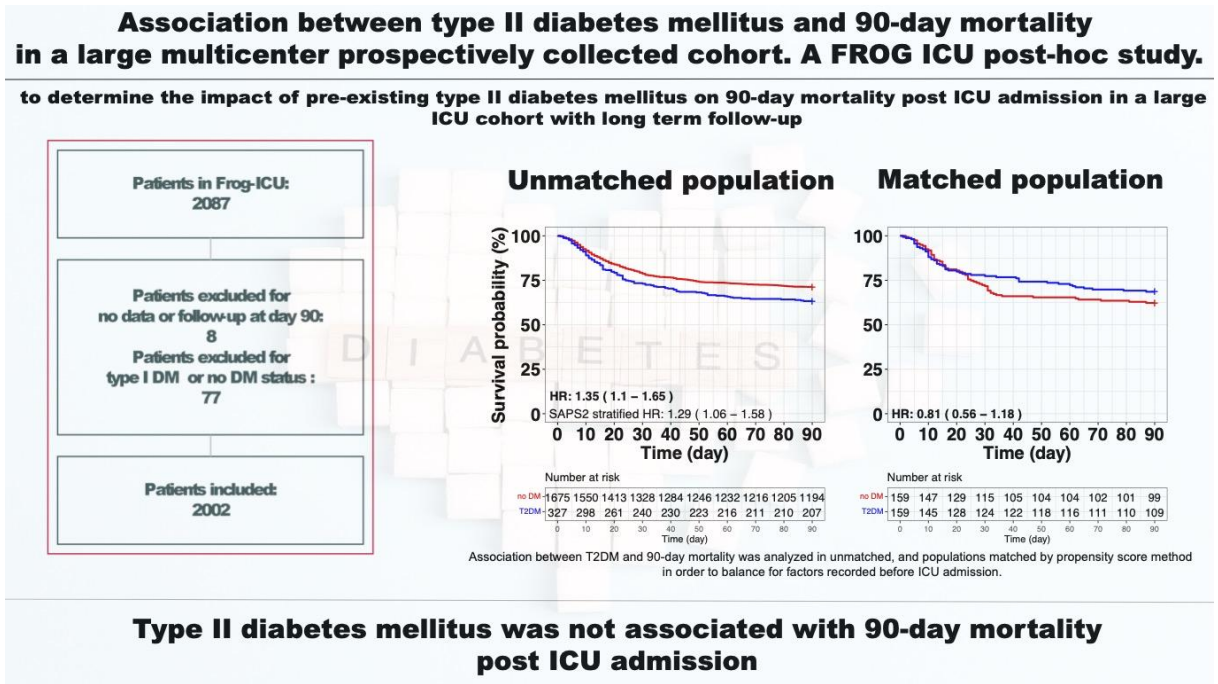
25 received fees as an advisory board member from Roche Diagnostic. All remaining authors

26 have declared no conflicts of interest.

27 Word count: 2904

28

29 Visual abstract



30

31 Abstract

32 **Purpose.** Factors associated with adverse outcomes in ICU patients with type II (T2DM) are
33 poorly defined. The main goal of this study is to determine the impact of pre-existing T2DM
34 on 90-day mortality post ICU admission.

35 **Material.** Post-hoc analysis from the FROG-ICU cohort. All patients admitted to ICU who
36 were ventilated and/or treated by a vasoactive agent for more than 24h were included.

37 Association between T2DM and 90-day mortality was analyzed in unmatched, and
38 populations matched by propensity score (PS) method to balance confounders recorded
39 before ICU admission. Analysis was performed in non-imputed and imputed datasets.

40 **Results.** 2002 patients were included, and 16% had a history of T2DM. The latter were at
41 inclusion more severely ill (SAPSII score 51(39 - 67) vs 48(35 - 61), $p < 0.0001$; Charlson score
42 2(1 - 3) vs 0(0 - 2), $p < 0.0001$). In the unmatched cohort, T2DM patients had a higher 90-day
43 risk of death compared to no-DM patients (HR 1.35(1.1 - 1.65)). The 90-day risk of death was
44 not significantly different T2DM and no T2DM patients after PS matching (HR: 0.81 (0.56-
45 1.18). Results were similar with the analysis performed on imputed datasets (pooled HR:
46 0.95 (0.69 - 1.30)).

47 **Conclusions.** In the present study, T2DM was not associated with 90-day mortality post ICU
48 admission.

49 **Keywords.** Type II diabetes mellitus, outcome, ICU

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54 Introduction

55 Intensive care units are dedicated to high-risk patients with a substantially increased risk of
56 morbidity and mortality. The outcome of intensive care unit (ICU) patient is determined both
57 by disease severity and comorbidities. Type II diabetes mellitus (T2DM) is among the most
58 frequent chronic conditions that are seen in ICU patients [1]. Critically ill patients with
59 T2DM, have been identified as at risk of adverse outcomes [2, 3]. Recently, T2DM has been
60 identified as a major risk factor of increased mortality in COVID-19 [4].

61 Stress induced hyperglycemia was at the origin of an ongoing debate regarding glucose
62 control in the ICU since hyperglycemia was shown to be associated with increased morbidity
63 and mortality. Trials investigating tight glucose control showed divergent results [5-7].

64 The association between T2DM and mortality was almost exclusively studied in retrospective
65 databases [7, 8]. When pooled in a meta-analysis, these studies present discrepant
66 outcomes resulting in high heterogeneity index [9]. For instance, T2DM increases thirty-day
67 mortality in surgical populations while in mixed ICU populations, the estimate is neutral [9].
68 Explanations are unclear as the risk associated with T2DM could be due to concomitant
69 comorbid conditions evoked by long-standing T2DM, such as cardiovascular disease and
70 diabetic nephropathy, and/or high fluctuations of glycaemia [10].

71 Therefore, there is a gap of knowledge regarding the exact impact of T2DM on ICU patients'
72 outcomes.

73 In this article, we aimed at studying the association between T2DM and ICU patients' 90-day
74 mortality with and without adjustment on preadmission medical history confounders using a
75 propensity score matching method.

76

77

79 Methods

80 Study design

81 This study is a post-hoc analysis from the French and euROpean Outcome reGistry in
82 Intensive Care Units (FROG-ICU) cohort. The original study was a prospective, multicenter
83 cohort of 2087 consecutive patients which assessed all-cause one-year mortality after ICU
84 discharge and identified the mortality risk factors during the year following discharge from
85 the ICU. Patients were admitted to the ICU in any of the 21 participating centers (medical,
86 surgical and mixed ICUs) from August 2011 to June 2013 when the following inclusion
87 criteria were met: invasive mechanical ventilation support for at least 24h and/or treatment
88 with a vasoactive agent (norepinephrine, epinephrine, dobutamine, levosimendan,
89 phosphodiesterase inhibitors) for more than 24h. Non-inclusion keys criteria were: < 18
90 years old, severe brain injury or brain death or a persistent vegetative state, pregnancy or
91 breastfeeding, transplantation in the past 12 months, not expected to survive or to leave the
92 hospital and/or no social security coverage.

93 The study was approved by the local ethics committees (Comité de Protection des
94 Personnes, Ile de France IV, IRB n°00003835 and Commission d'éthique biomédicale de
95 l'hôpital de Louvain, IRB n° B403201213352) and registered on
96 <https://clinicaltrials.gov/ct2/show/NCT01367093>. The design and results of the original
97 study have already been published elsewhere [11, 12].

98 Definition of the type II diabetic and non-diabetic populations

99 T2DM patients correspond to patients for whom DM was noted in patient medical history
100 prior to ICU admission and receiving oral antidiabetic treatments. Non-diabetic patients
101 correspond to patients for whom there is no medical history of DM prior to ICU admission.

102 Non-Inclusion Criteria

103 Type I DM and patients without data on DM condition upon admission or follow-up were not
104 included.

105 Endpoints

106 The primary endpoint was to assess the mortality 90 days after ICU admission in T2DM
107 versus non-DM. Secondary endpoints included the association between T2DM and organ
108 failure at admission, the interaction of T2DM condition with the association of upon-
109 admission glycaemia and outcome at 90 days, and the association of T2DM with 90-day
110 mortality in the most prevalent diagnostic subgroups.

111 Data collection

112 Details regarding general data collection have been reported in the original study (11,12).
113 Causes of ICU admission were also recorded and classified in 19 categories. We
114 individualized the most prevalent causes of ICU admission: cardiac arrest, respiratory failure,
115 septic shock, neurological causes, cardiogenic shock, urgent and scheduled post-operative
116 room. The remaining causes were grouped together (trauma, severe sepsis, multiple organ
117 failure, metabolic causes, acute renal failure, acute liver failure, hypovolemic shock,
118 hemorrhagic shock, anaphylactic shock, microangiopathy, unspecified, acute pancreatitis).
119 The time point of baseline characteristics was defined at ICU inclusion. Data on specific
120 antihyperglycaemic treatments were collected retrospectively from the records.

121

122 Statistical method

123 Data expression

124 Data are expressed as median [interquartile range, IQR] or number (%) as appropriate. After
125 visual assumption of non-normality, Wilcoxon rank tests were applied for univariate analysis
126 and the Chi-square test or the Fisher exact test were applied for categorical variables as
127 appropriate.

128 The main goal of the statistical analysis was to balance T2DM with non-DM populations at
129 inclusion with analyses derived from the propensity score performed in the original dataset
130 and in multiple imputed datasets as described below.

131 Management of missing data

132 Number of missing data for variables included in the propensity score were all <1% except
133 BMI which is missing in 38%. Ten copies with five iterations of the initial dataset were
134 created with the missing values replaced by imputed values, based on baseline
135 characteristics. Outcome data were not included.

136 Propensity analysis

137 Propensity scores are used in observational studies to estimate the effect of an intervention
138 by creating a pseudo-randomization to reduce selection bias. In the propensity score model
139 herein, exposure was, in a population of patients admitted ICU, T2DM as cause of initial
140 admission. Model variables included in the propensity score were variables associated with
141 the outcome, selected before ICU admission and determined according to literature
142 research and consensus among authors: centers, demographic data, medical history, chronic
143 medical treatments (excluding antidiabetics treatments). Imbalance between the two groups

144 before and after propensity score matching was assessed using a standardized mean
145 difference for defining the study patients' characteristics as being balanced with respect to
146 the previously described features. This matching was performed in complete cases dataset
147 and in multiple imputed datasets.

148 Survival analysis

149 Kaplan-Meier curves were drawn and overall 90-day mortality was estimated in T2DM and
150 non-DM at admission in non-matched and propensity score matched populations.

151 Stratification on SAPS II was applied on a Cox model for the non-matched population.

152 In the matched population from the imputed datasets, Cox models for 90-day mortality in
153 T2DM and in non-DM populations at admission were created for each dataset. Results were
154 pooled into a final result using Rubin's rules. Hazard ratios (HR) and their respective 95%
155 confidence intervals (CI) were also calculated.

156 Association between glycaemia upon admission and 90-day mortality

157 We assessed association between glycaemia at inclusion on 90-day mortality in a logistic
158 model adjusted on T2DM status using restricted cubic splines. We assessed the interaction
159 between glycaemia at inclusion and T2DM history on 90-day mortality and draw the effects
160 of glycaemia in T2DM and non-DM patients on 90-day mortality. Reference of odds ratio
161 (OR) was set at 8 mmol/l corresponding to the mean targeted glycaemia in ICU (usual
162 considered ranges: 6 to 10.0 mmol/L).

163 Subgroup analysis

164 Analyses, performed in non-imputed dataset, assessed the association between T2DM and
165 90-day mortality according to the most prevalent causes of ICU as specified above.

166 Interactions were calculated between the T2DM status and the cause of admission on 90-
167 day mortality. Odds ratios and their 95% CIs were calculated.

168 All tests were two-sided and a p value < 0.05 was considered statistically significant.

169 All analyses were performed using R 3.6.3 (2020-02-29) statistical software (The R
170 Foundation for Statistical Computing, Vienna, Austria).

171 Results

172 Inclusion population characteristics

173 2002 out of 2087 patients were included in the study (**Figure 1**). Among them 327 (16%) had
174 a history of T2DM. Patient's characteristics are summarized in **Table 1**. Compared to patients
175 without DM (no-DM), patients with T2DM were older (70 (62 - 76) vs 61 (48 - 73) years, p
176 < 0.0001), more severely ill (SAPS II score 51 (39 – 67) vs 48 (35 - 61), p < 0.0001) and had
177 higher Charlson comorbidity scores (2 (1 - 3) vs 0 (0 - 2), p < 0.0001).

178 T2DM and 90-day mortality without and with adjustment

179 Patients with T2DM had a greater 90-day mortality and mortality risk compared to patients
180 with no-DM (37% vs 29%, p = 0.004, HR 1.35 (1.1 - 1.65)). Mortality remained associated to
181 DM after stratifying on the SAPS2 score, which includes vital signs and biological parameters
182 of illness, Glasgow coma score, PaO₂ on FiO₂ ratio, urinary output as well as patient-related
183 features such as age, certain chronic diseases, and type of admission. (stratified HR 1.29 (
184 1.06 - 1.58)) (**Figure 2, panel A**).

185 Similar analyses were performed on propensity-based matched dataset. 159 matched pairs
186 were created from the matching procedure with almost all absolute standardized mean
187 differences on patient characteristics of less than 10%, indicating a successful balance of
188 potential confounders between no-DM and T2DM patients (**See Supplementary, Fig. S1**
189 **online**). Survival analysis performed with the matched cohort found that T2DM didn't
190 remain a 90-day mortality risk factor (HR: 0.81 (0.56 - 1.18)) (**Figure 2, panel B**).

191 As a sensitivity analysis, a propensity score matching on 10 imputed datasets was
192 performed. Absolute standardized mean differences on patient characteristics at inclusion
193 were presented in **Supplementary, Fig. S2 online**. Pooled estimate of the univariate Cox
194 model found that T2DM was still not a 90-day mortality risk factor (HR: 0.95 (0.69 - 1.30)).

195 T2DM and organ failures

196 Three days after inclusion, patients with T2DM compared to no-DM received more renal
197 replacement therapy (18% vs 11%, $p = 0.002$), more vasopressor and/or inotrope (34% vs
198 27%, $p = 0.023$), but received similarly mechanical ventilation (67% vs 70%, $p = 0.43$) (**Table**
199 **2, panel A**). More specifically, biomarkers of acute kidney injury, namely plasma neutrophil
200 gelatinase-associated lipocalin (NGAL), plasma proenkephalin (PenKid), urinary liver-type
201 fatty acid-binding protein (LFABP) were also all increased (**See Supplementary, Fig. S3**
202 **online**). When population were matched, these differences disappeared (**Table 2, panel B;**
203 **See Supplementary, Fig. S4 online**).

204 Association between admission glycaemia and mortality

205 90-day mortality did not vary with inclusion glycaemia ($p = 0.2$). Moreover, there was no
206 interaction between glycaemia at inclusion and T2DM status on 90-day mortality (p for
207 interaction = 0.46, **Figure 3**).

208 Subgroup analysis

209 While T2DM was associated with 90-day mortality in the whole population we did not find
210 any differences in mortality according to the cause of admission (**Figure 4**). Moreover, no
211 interaction was found between T2DM and BMI on 90-day mortality (p -interaction = 0.26).
212 Pre-admission T2DM treatment with dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors) was

213 associated with reduced mortality (OR 0.45 (0.21 - 0.95), $p = 0.04$) as compared with non-
214 diabetics (**See Supplementary, Table S1 online**)

215

216 Discussion

217 In the present study, we observed an association between T2DM and 90-day mortality which
218 disappeared after adjustment for prior chronic medical conditions before ICU admission. Our
219 data suggest that worsened outcome associated with T2DM is mainly due to T2DM-related
220 and associated chronic conditions rather than to T2DM per se.

221 In several fields of critical care medicine T2DM, and hyperglycaemia are associated with
222 complicated clinical course and worsened outcome. During acute heart failure or acute
223 coronary syndrome, T2DM has been shown to increase complications, length of stay and
224 long-term mortality [13, 14]. T2DM patients are also at risk of postoperative infections or
225 new onset atrial fibrillation after cardiac surgery [15-17]. Moreover, during inflammatory
226 disease such as severe pancreatitis, history of T2DM has also a negative impact [18]. Early
227 studies demonstrated that T2DM history was consistently associated with increased, in-ICU,
228 short-term or long-term mortality, specifically in community acquired pneumonia etiology
229 [2, 3]. Later studies report, especially for medical causes of admission, no association
230 between T2DM and ICU-related mortality [8, 19]. Conversely, impact of T2DM on ICU-
231 related mortality is controversial for surgical ICU patients [9]. In almost all subgroup analysis,
232 trauma and surgical ICU patients were more likely to have a worse outcome if they had a
233 history of T2DM.

234 Two factors may explain why T2DM has such impact: first, history of T2DM favors the onset
235 of several chronic organ dysfunctions such as heart failure, peripheral vascular disease,

236 peripheral neuropathy, or chronic kidney disease and promotes metabolic syndrome. Such
237 conditions are together synergistically associated with adverse outcome in T2DM patients.
238 Second, T2DM could be associated with more severe hyper-glycaemia and important
239 fluctuations of glycaemia. Both were shown to be associated with severity and increased
240 mortality, even in patients without T2DM [8]. Moreover, a significant body of literature
241 showed that avoiding both hypo- and hyper-glycaemia, but not necessarily tight, glucose
242 control was beneficial for ICU patients [6]. This could represent a direct link between T2DM
243 and outcome. Nevertheless, intensivists should bear in mind that chronic and acute blood
244 glucose variations have numerous other consequences and implications on T2DM patient
245 outcomes with, to name but a few, chronic hyperglycaemia related tissue glycation, acute
246 hyperglycaemia related immune dysfunction, glycemic variability on oxidative stress and
247 absolute or relative hypoglycaemia [20-23]. Finally, during the two last decades, ICU patient
248 care improved simply because more attention was drawn on glucose control [24]. It is
249 therefore of clinical interest to clarify in our current practice the potential role of T2DM on
250 critical care patient prognosis. Another point that adds to this complex question is related to
251 previous T2DM treatments. Metformin has been shown to have pleiotropic effects that
252 could be beneficial for ICU patients [25]. However, when we tested in a subgroup analysis
253 the role of DM treatment, we found no impact of use of metformin while a significant
254 difference was observed for DPP-4 inhibitors. Inhibition of DPP4 with gliptins stimulate
255 angiogenesis and might help organ repair [26]. Petite et al. found, in a cohort of hospitalized
256 patients with diabetes a significant decrease in mean daily glycaemia and hospital length of
257 stay in patients treated with a basal insulin plus DPP-IV inhibitor regimen compared to
258 patients treated only with a basal plus bolus insulin [27]. While this secondary result should

259 be interpreted with caution, pre-admission inhibition of DPP-4 might play a beneficial role
260 in acute patients in the ICU.

261 Our results primarily show that an increased 90-day mortality is associated with a history of
262 T2DM. However, after adjustment for confounding variables using the propensity score
263 method, this increased 90-day mortality may depend on T2DM-associated comorbidities
264 rather than on T2DM per se. There is a growing body of evidence that, in many clinical
265 settings, pre-admission morbidity is at least equally relevant to the disease considered on
266 the outcome. One example, beside T2DM, is atrial fibrillation which increases the risk of
267 stroke, but this risk is highly influenced on the presence of specific premorbid stroke risk
268 factors. Thus, prevention of thrombo-embolic events is decided on the pre-morbidity
269 CHADVASC2 score (including age sex, diabetes mellitus, stroke hypertension...). Patient
270 despite having atrial fibrillation but with no or one CHADVASC2 criterion doesn't need anti-
271 coagulation [28]. Interestingly, the association between glycaemia and mortality for patients
272 having T2DM or not could be different, one could expect that hyper-glycaemia could be
273 more deleterious in non-DM patients. Indeed, in a post hoc analysis of the Leuven study
274 which included roughly 80% of non-diabetic patients with hyperglycaemia, in-ICU mortality
275 was lower in those with pre-existing diabetes than those without [5, 29]. Moreover, a recent
276 meta-analysis of observational studies including patients with sepsis , demonstrated that
277 high glycaemia at admission, irrespective of the diabetes status, is associated with an
278 increase in in-hospital mortality [30]. We also found no difference in this regard with
279 glycaemia measured at inclusion. Most probably, following the publication of the NICE sugar
280 study, glucose control is now a standard of care in most ICU [31]. We also hypothesized that
281 T2DM could have a different impact according to the admission diagnosis, but again we did

282 not observe any differences. Whether it is about sepsis or ARDS, no direct association has
283 been evidenced between diabetes and clinical outcomes [32].

284 Our study suffers from several limitations. First, this is a post-hoc study of an observational
285 study that could bear several biases and especially reporting bias. Anyway, since it is not
286 possible to randomize a disease, the impact of DM can only be evaluated from observational
287 studies. The design of the FROG-ICU cohort that included consecutive patients limit the risk
288 of bias. Second, the propensity score method cannot consider all the potential confounding
289 factors and is impacted by missing data. We included a very large number of variables in our
290 analysis, and we performed an imputed analysis. Third, the number of patients is limited and
291 reduces the power of subgroup analysis to find any differences. Fourth, we did not collect
292 the glycaemia at admission but according to the inclusion criteria after at least 24h after
293 admission. Thus, patients with hypo or hyper glycaemia between admission and inclusion
294 already received glucose or insulin respectively. Fifth, glucose control protocols in each
295 center were unknown and glycaemia were not recorded throughout the whole ICU stay.
296 Thus, glycemic variability, specifically stress induced hyperglycaemia and hypoglycaemia
297 episodes that might have impacted the outcome were not considered in the analysis. Sixth,
298 as T2DM status at inclusion was only declarative, some patients may have been
299 misclassified. Carpenter et al found in a prospective multicenter study that undiagnosed
300 diabetes account for 9% of the ICU population [33]. Data regarding levels of HbA1c were not
301 recorded but would have been a powerful confounding variable to adjust undiagnosed
302 T2DM in the no-T2DM group with the T2DM group.

303 Conclusion

304

305 In the present study, we observed an association between T2DM and 90-day mortality which
306 was not confirmed after propensity score matching. Our data suggest that worsened
307 outcome associated with DM might be due, in part, to DM-related chronic organ failures
308 rather than to T2DM per se.

309

310 Acknowledgements

311 *Authors' contributions.*

312 AK, AM, BGC: study concept and design. AP: Data acquisition. AK, BGC: Analysis and
313 interpretation of the data. AK, AM, BGC: Drafting of the manuscript. all declared authors:
314 Critical revision of the manuscript. AK, KD, EG: Statistical analysis. AM, EG: Administrative,
315 technical, or material support. AM, BGC: Study supervision.

316 *Competing interests.*

317 AM reports personal fees from Orion, grants and personal fees from Roche, personal fees
318 from Servier, personal fees from Otsuka, personal fees from Philips, grants and personal fees
319 from Adrenomed, personal fees from Neuro Tronik, grants and personal fees from 4TEEN4,
320 personal fees from Sanofi. Etienne Gayat. EG received research grant from Sphingotec,
321 radiometer and Philips and consultancy fees from Baxter and Edwards Lifescience. BGC
322 received fees as an advisory board member from Roche Diagnostic. All remaining authors
323 have declared no conflicts of interest.

324 *Availability of supporting data.*

325 AM had full access to all data in the study and take responsibility for the integrity of the data
326 and the accuracy of the data analysis. R code and Data are available from the corresponding
327 author on reasonable request.

328 *Ethics approval and consent to participate.*

329 The study was approved by the local ethics committees (Comité de Protection des
330 Personnes, Ile de France IV, IRB n°00003835 and Commission d'éthique biomédicale de
331 l'hôpital de Louvain, IRB n° B403201213352) and registered on
332 <https://clinicaltrials.gov/ct2/show/NCT01367093>.

333 *Consent for publication.*

334 All authors read and approved the final manuscript.

335 *Funding.*

336 FROG ICU (ClinicalTrials.gov Identifier NCT01367093) was funded by the Programme

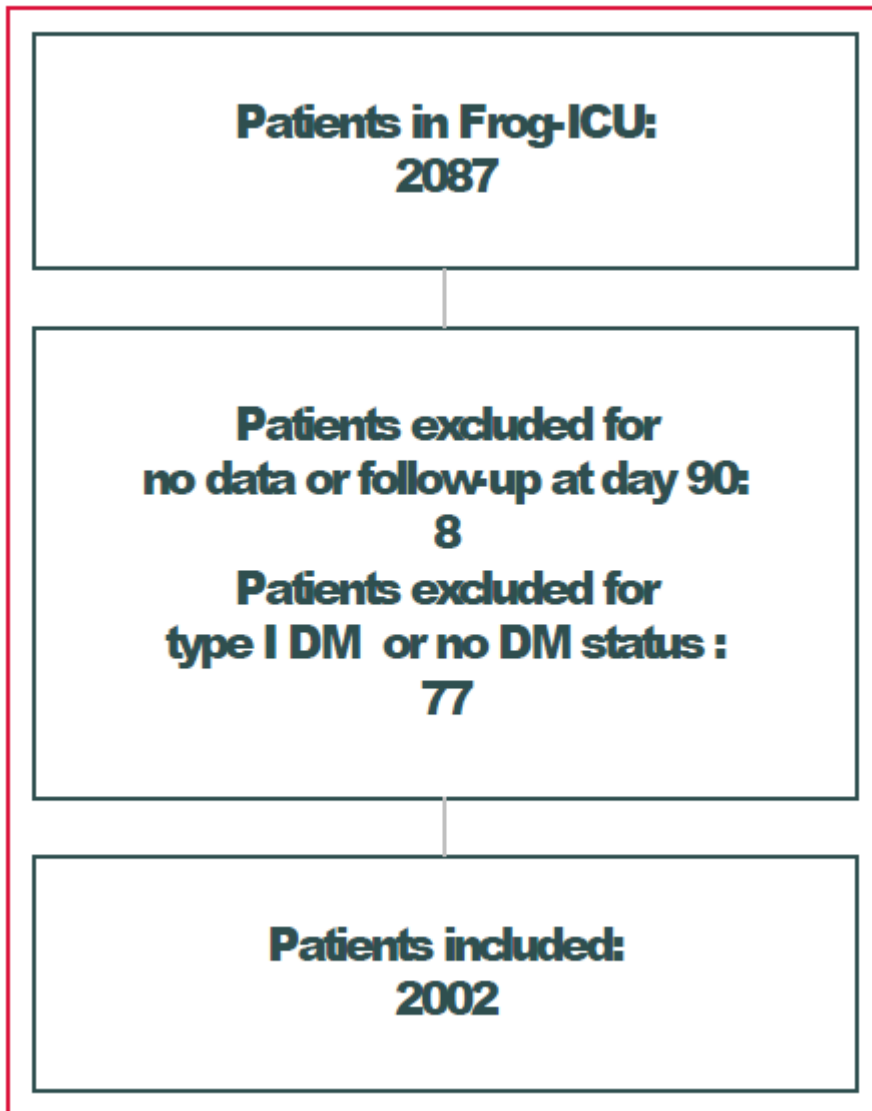
337 Hospitalier de la Recherche Clinique (AON 10-216) and by a research grant from the Société

338 Française d'Anesthésie Réanimation.

339

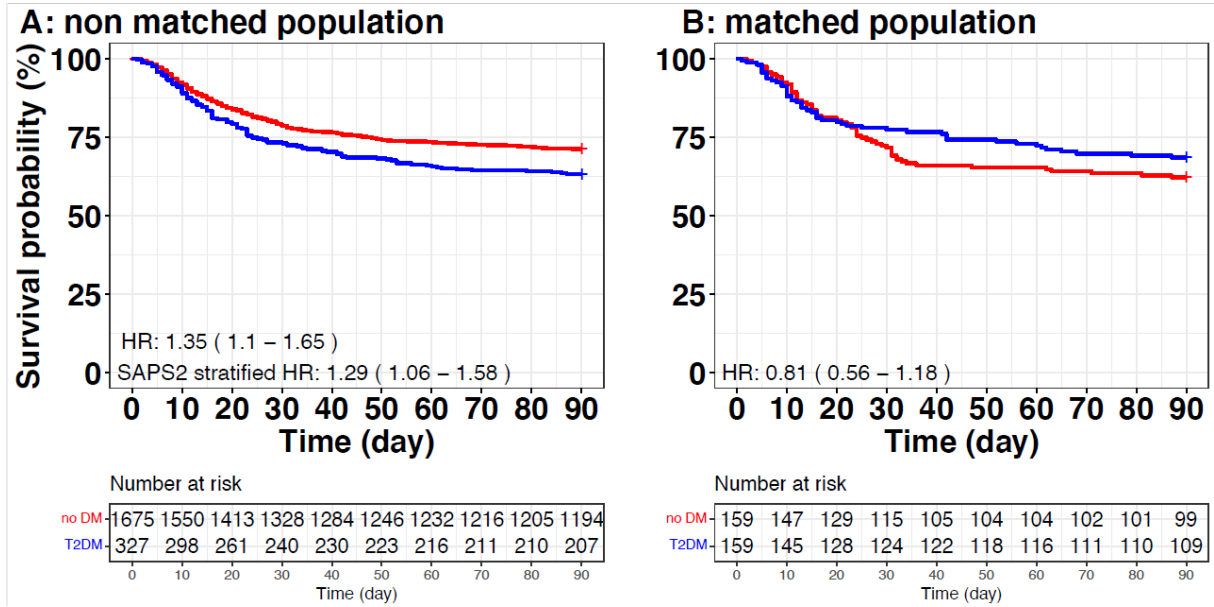
340 Figure legends

341 **Figure 1:** Flow chart



342
343

344 **Figure 2:** Kaplan Meier curves for 90-day mortality in unmatched (Panel A) and matched
 345 population (Panel B) according to DM status. HR values with 95%CI are provided. For panel
 346 A, Cox stratification was performed with SAPS II categorized on the median (Panel A). There
 347 is no loss of follow-up.



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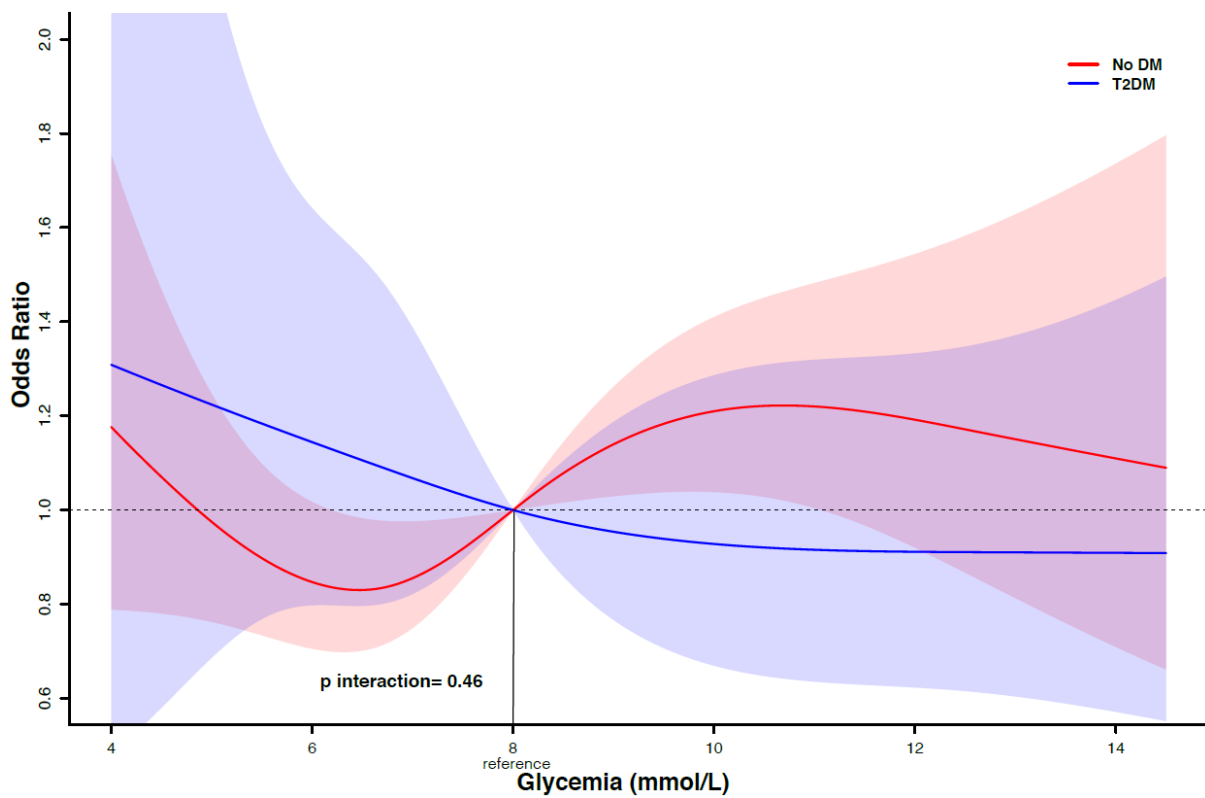
351 **Figure 3:** Interaction between blood glucose at inclusion and DM status on 90-day mortality.

352 The figure shows the evolution of mortality Odds Ratios according to increasing glycaemia

353 levels. No interaction was found between glycaemia levels at inclusion and T2DM status on

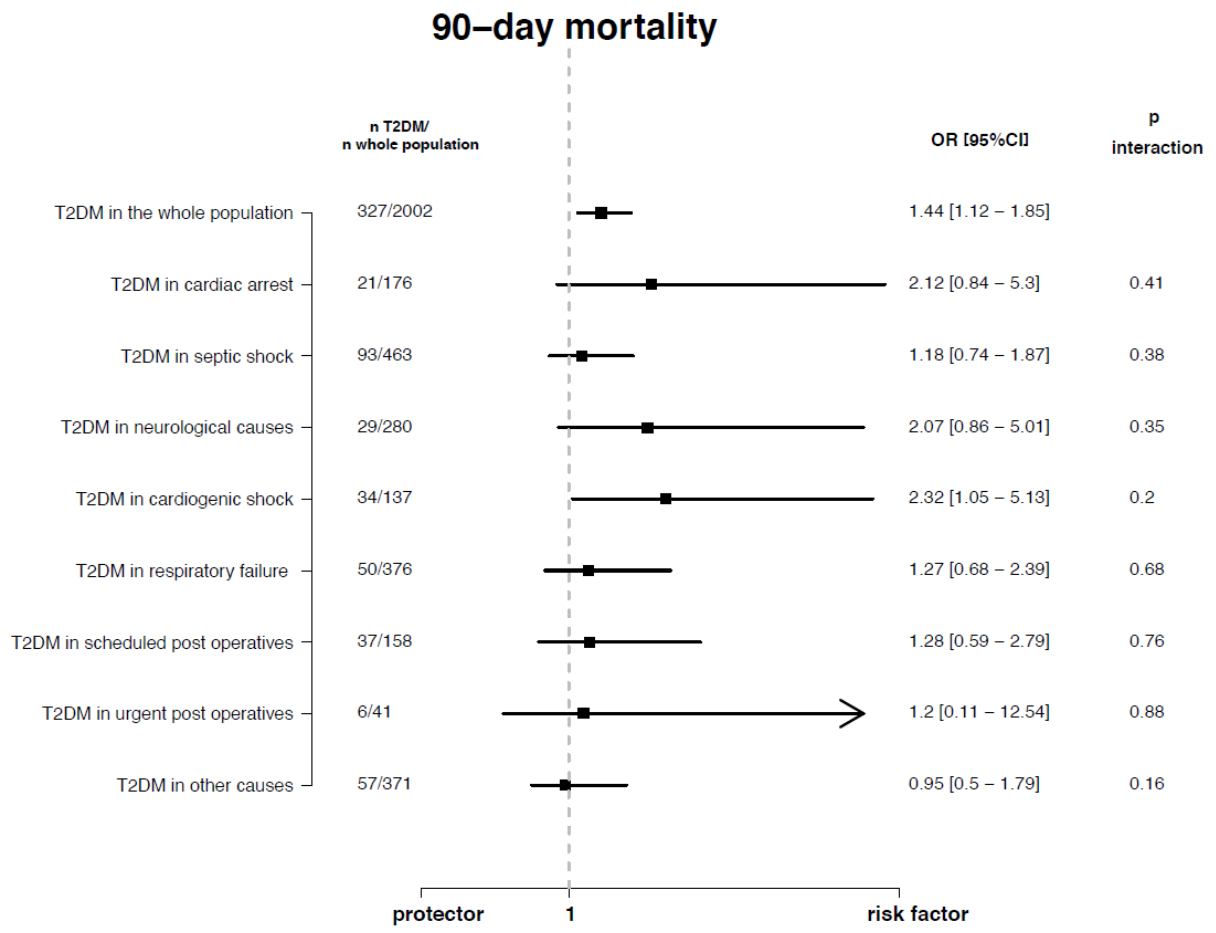
354 90-day mortality. Reference glycaemia is set at 8 mmol/l. y axis is odds ratio of 90-day

355 mortality with a reference at 1. X axis is the glycaemia at inclusion.



356
357

358 **Figure 4:** Subgroup analysis: Impact of DM status according to most prevalent causes of ICU
 359 admissions on 90-day mortality in non-imputed dataset. Reference is non-DM.



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471 **Table 1:** Non-imputed clinical characteristic at baseline in the global population and
 472 according to type II diabetes mellitus (T2DM) status at admission.

variable	n	Global (N=2002)	n	No DM	n	T2DM	p-value
Age (years)	2002	63 (51 - 74)	1675	61 (48 - 73)	327	70 (62 - 76)	<0.0001
BMI (kg/m ²)	1238	26.3 (23.1 - 30.6)	1048	25.8 (22.8 - 29.7)	190	30.1 (26.3 - 35.8)	<0.0001
Male gender (%)	2002	696 (35 %)	1675	597 (36 %)	327	99 (30 %)	0.062
Charlson score	2002	1 (0 - 2)	1675	0 (0 - 2)	327	2 (1 - 3)	<0.0001
Medical history							
Peripheral vascular disease	2000	182 (9 %)	1673	141 (8 %)	327	41 (13 %)	0.018
Hypertension	2000	839 (42 %)	1673	597 (36 %)	327	242 (74 %)	<0.0001
Stroke	2000	84 (4 %)	1673	59 (4 %)	327	25 (8 %)	0.0007
Chronic heart disease	2000	143 (7 %)	1673	104 (6 %)	327	39 (12 %)	0.0002
Chronic respiratory disease	2000	255 (13 %)	1673	198 (12 %)	327	57 (17 %)	0.006
Chronic liver disease	2000	152 (8 %)	1673	125 (7 %)	327	27 (8 %)	0.62
Chronic renal disease	2000	215 (11 %)	1673	142 (8 %)	327	73 (22 %)	<0.0001
Recent malignant tumors	2000	275 (14 %)	1673	243 (15 %)	327	32 (10 %)	0.023
Disability	2000	70 (4 %)	1673	58 (3 %)	327	12 (4 %)	0.86
Smoking	2000	549 (27 %)	1673	464 (28 %)	327	85 (26 %)	0.52
Alcohol	2000	352 (18 %)	1673	295 (18 %)	327	57 (17 %)	0.93
Main chronic treatments							
Diuretics	1988	418 (21 %)	1662	282 (17 %)	326	136 (42 %)	<0.0001
ACE inhibitors and/or ARBs*	1988	522 (26 %)	1662	360 (22 %)	326	162 (50 %)	<0.0001
Beta-blockers	1988	487 (24 %)	1662	354 (21 %)	326	133 (41 %)	<0.0001
Antihyperglycemics	2002	220 (11 %)	1675	0 (0 %)	327	220 (67 %)	<0.0001
Insulin	1988	42 (2 %)	1662	2 (0 %)	326	40 (12 %)	<0.0001
None	1988	612 (31 %)	1662	594 (36 %)	326	18 (6 %)	<0.0001
Causes of admission							
Septic Shock	2002	463 (23 %)	1675	370 (22 %)	327	93 (28 %)	0.013
Cardiac arrest	2002	176 (9 %)	1675	155 (9 %)	327	21 (6 %)	0.098
Acute respiratory failure	2002	376 (19 %)	1675	326 (19 %)	327	50 (15 %)	0.077
Acute neurological failure	2002	280 (14 %)	1675	251 (15 %)	327	29 (9 %)	0.004
Post-operative room	2002	199 (10 %)	1675	156 (9 %)	327	43 (13 %)	0.034
Cardiogenic shock	2002	137 (7 %)	1675	103 (6 %)	327	34 (10 %)	0.005
Others	2002	371 (19 %)	1675	314 (19 %)	327	57 (17 %)	0.58
Clinical/biological parameters							
Heart rate (bpm)	1929	92 (78 - 106)	1618	92 (78 - 106)	311	90 (77 - 105)	0.44
Mean blood pressure (mmHg)	1888	81 (72 - 92)	1578	82 (73 - 93)	310	80 (71 - 89)	0.021
Respiratory rate (breaths /min)	1487	20 (16 - 25)	1244	20 (16 - 25)	243	20 (17 - 26)	0.54
Glasgow coma score	1636	14 (5 - 15)	1407	14 (4 - 15)	229	14 (9 - 15)	0.068
Diuresis for the first 24 hours (mL)	1649	1350 (800 - 2200)	1382	1400 (830 - 2200)	267	1225 (600 - 2200)	0.066
SAPS II score*	2001	49 (36 - 63)	1674	48 (35 - 61)	327	51 (39 - 67)	<0.0001
SOFA score*	1465	8 (5 - 10)	1246	8 (5 - 10)	219	8 (5 - 11)	0.21
Glycemia (mmol/L)	1879	7.3 (6.2 - 9.0)	1578	7.2 (6.1 - 8.5)	301	8.7 (7.1 - 11.2)	<0.0001
Lactate (mmol/L)	2000	1.4 (1.0 - 2.0)	1674	1.4 (1.0 - 2.0)	326	1.4 (1.0 - 2.0)	0.22
Creatinin (micromol/L)	2002	83 (58 - 145)	1675	78 (56 - 133)	327	118 (75 - 192)	<0.0001

variable	n	Global (N=2002)	n	No DM	n	T2DM	p-value
PT (%)*	1098	69 (54 - 80)	919	69 (54 - 80)	179	69 (55 - 80)	0.72
Management							
Renal replacement therapy	2002	450 (22 %)	1675	338 (20 %)	327	112 (34 %)	<0.0001
Red blood transfusion	2002	930 (46 %)	1675	769 (46 %)	327	161 (49 %)	0.27
Inotrope and/or vasopressors	2002	1541 (77 %)	1675	1283 (77 %)	327	258 (79 %)	0.37
Ventilation	2002	1871 (93 %)	1675	1573 (94 %)	327	298 (91 %)	0.063
Outcomes							
In-ICU length of stay (days)	2002	12 (7 - 21)	1675	13 (7 - 21)	327	12 (7 - 21)	0.52
In-ICU mortality	2002	432 (22 %)	1675	352 (21 %)	327	80 (24 %)	0.17
90-day mortality	2002	601 (30 %)	1675	481 (29 %)	327	120 (37 %)	0.004

* ACE inhibitors and/or ARBs: angiotensin-converting enzyme inhibitors / angiotensin receptor blockers, SOFA: sequential organ failure assessment, SAPS II: Simplified Acute physiology score II, PT: Prothrombin time

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476 Table 2: Association between DM and organ failures at day 3 in unmatched (panel A) and
 477 matched cohorts (panel B)
 478
 479 *panel A*

variable	n	Global (N=2002)	n	No type II DM	n DM	type II DM	p-value
Renal replacement therapy	1586	190 (12 %)	1338	146 (11 %)	248	44 (18 %)	0.002
Vasopressor and/or inotrope	1517	426 (28 %)	1280	345 (27 %)	237	81 (34 %)	0.023
mechanical ventilation	1584	1096 (69 %)	1335	929 (70 %)	249	167 (67 %)	0.43

480 *panel B*

variable	n	Global (N=338)	n	No type II DM	n	type II DM	p-value
Renal replacement therapy	269	47 (17 %)	138	25 (18 %)	131	22 (17 %)	0.78
Vasopressor and/or inotrope	260	85 (33 %)	133	45 (34 %)	127	40 (31 %)	0.69
mechanical ventilation	269	188 (70 %)	140	106 (76 %)	129	82 (64 %)	0.030

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