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## **Inotropes and vasopressors are associated with increased short-term mortality but not long-term survival in critically ill patients**

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## ABSTRACT

**Objective:** Limited information is currently available on the impact of vasoactive medications in intensive care (ICU) and long-term outcomes. The main objective of our study was to describe the association between the use of inotropes and/or vasopressors and ICU mortality. Secondary objectives were to evaluate the association between the use of vasoactive drugs and in-hospital as well as 1-year all-cause mortality in ICU survivors.

**Methods:** FROG-ICU was a prospective, observational, multi-centre cohort designed to investigate long-term mortality of critically ill adult patients. Cox proportional hazards models were used to evaluate the association between the use of inotropes and/or vasopressors and ICU mortality, as well as in-hospital and 1-year all-cause mortality in a propensity-score matched cohort.

**Results:** The study included 2087 patients, 939 of whom received inotropes and/or vasopressors during the initial ICU stay. Patients treated with vasoactive medications were older and had a more severe clinical presentation. In a propensity score-matched cohort of 1201 patients, ICU mortality was higher in patients who received vasoactive medications (HR of 1.40 [1.10 – 1.78],  $p = 0.007$ ). One thousand six hundred thirty-five patients survived the index ICU hospitalisation. There was no significant difference according to the use of inotropes and/or vasopressors in the propensity-score matched cohort on in-hospital mortality (HR of 0.94 [0.60 - 1.49],  $p = 0.808$ ) as well as one-year all-cause mortality (HR 0.94 [0.71 – 1.24],  $p = 0.643$ ).

**Conclusion:** Inotropic and/or vasopressor therapy is a strong predictor of in-ICU death. However, the use of inotropes and/or vasopressors during ICU admission was not associated with a worse prognosis after ICU discharge.

**Keywords:** inotropes, vasopressors, mortality, long-term outcomes, propensity score matching

**Abbreviations:**

CAD – coronary artery disease

CCI – Charlson Comorbidity Index

CHF – chronic heart failure

CI – confidence interval

CKD – chronic kidney disease

COPD – chronic obstructive pulmonary disease

GCS – Glasgow Coma Scale

HR – hazard ratio

ICU – intensive care unit

IQR – interquartile range

MICE – multiple imputation by chained equations

SAPS II - simplified acute physiology score

SBP – systolic blood pressure

SOFA – sequential organ failure assessment score

## 1. INTRODUCTION

Adequate fluid resuscitation and timely initiation of the use of vasoactive medications are the cornerstone of haemodynamic management of critically ill patients (1-3). Inotropes are used to increase myocardial contractility and cardiac output, whereas vasopressors induce vasoconstriction and thereby elevate mean arterial pressure. Several guidelines for different types of shock give different recommendations for the use of inotropic and vasopressor agents (4-6). Despite different recommendations and the apparent lack of evidence, these vasoactive drugs are used in daily clinical practice. Although these medications effectively improve haemodynamic parameters, they are also associated with important side effects such as increased myocardial oxygen consumption, myocardial ischaemia and arrhythmias (7, 8). There is growing evidence that excessive adrenergic stimulation might be detrimental during critical illness (9, 10). Evidence from trials mostly in heart failure settings show that the use of inotropes and vasopressors is associated with reduced short and long-term survival (11-15). However, it must be acknowledged that inotropes and vasopressors are only given to the most severely ill patients and randomisation is practically impossible in such situations. Thus, the association of the use of vasoactive medications with increased mortality could simply reflect the severity of initial illness. How the use of vasoactive medications during intensive care impacts long-term survival is unclear. Very limited information is currently available concerning the risk factors for long-term survival after a stay in the intensive care unit (ICU) (16).

The main objective of our study was to describe the association between the use of inotropes and/or vasopressors and ICU mortality. The secondary objectives were to

evaluate the association between the use of vasoactive drugs and in-hospital as well as 1-year all-cause mortality in all cohorts, as well as the subgroup of ICU survivors.

## **2. METHODS**

### **2.1 Study design and population**

FROG-ICU was a prospective, observational, multicentre cohort study of ICU survivors followed 1 year after discharge, including 21 medical, surgical or mixed ICUs in France and Belgium (registered on ClinicalTrials.gov, NCT01367093). Inclusion criteria for the FROG-ICU registry were: all consecutive patients admitted to intensive care with a requirement for invasive mechanical ventilation and/or vasoactive drug support for more than 24 h following ICU admission. Non-inclusion criteria were: age younger than 18 years old; severe head injury (initial Glasgow Coma Scale  $\leq 8$ ), brain death or a persistent vegetative state; pregnancy or breastfeeding; transplantation in the past 12 months; moribund patient; and/or no social security coverage. Patients were recruited from August 2011 to June 2013. Details of design and methods have been published previously (16-18). The Ethical Committees waived the need for written consent; all patients and/or next of kin were informed and oral consent was documented in the patients' medical records by the investigator.

Clinical and biological data were recorded at admission, during the ICU stay and at discharge. At the time of inclusion, the following data were collected: demographics, data on past medical history, ICU admitting diagnosis, haemodynamic and respiratory parameters, severity of disease classification systems (SOFA, SAPS II and GCS scores) as well as laboratory parameters. All patients included in the study who survived to ICU discharge were followed up for one year by telephone contact and information about vital status was

recorded. For patients who could not be contacted by telephone, vital status was obtained via a national data registry.

## **2.2 Statistical analysis**

In this post-hoc analysis of the FROG-ICU registry, we compared a cohort of patients who received inotropes and/or vasopressors during the first 3 days of ICU stay *versus* those who did not receive any vasoactive medication during the first 3 days of their ICU stay (see **Supplementary Figure 1**).

Results are expressed as median (interquartile range (IQR)) or count (percentage) as appropriate. Associations between single variables and inotrope/ vasopressor use as well as ICU mortality were assessed by a Wilcoxon rank-sum test for quantitative variables and the Chi-square test for qualitative variables. Survival was plotted with the Kaplan–Meier curve, and differences between groups were tested with the log-rank test. Unadjusted and covariate-adjusted Cox proportional hazards models were used to evaluate the association between the use of inotropes and/or vasopressors and ICU mortality, as well as in-hospital and 1-year all-cause mortality in patients who survived the initial ICU stay. The relative hazard is expressed as hazard ratio (HR) with 95% confidence interval (CI). Adjustments were performed for gender, age, SAPS II score, systolic blood pressure, lactate, haemoglobin, sodium, creatinine at inclusion, history of heart failure, coronary artery disease, diabetes, chronic obstructive pulmonary disease (COPD), chronic kidney disease. Missing values were handled by multiple imputation by chained equations (MICE).

To reduce the bias related to the difference in baseline characteristics, the primary and secondary endpoints were investigated in a propensity score-matched cohort. The propensity score is the probability that a patient with specific baseline characteristics would

receive the treatment evaluated conditionally on individual characteristics (19). We estimated the propensity score using logistic regression, where the dependent variable was the treatment under study. Variables with a potential association with the treatment assignment and/or the outcome were used to create a propensity score, including age, gender, weight, systolic blood pressure (SBP) and heart rate on admission, endotracheal intubation and mechanical ventilation, partial oxygen pressure (PO<sub>2</sub>), partial CO<sub>2</sub> pressure (PCO<sub>2</sub>), fraction of inspired oxygen (FiO<sub>2</sub>), lactate, haemoglobin, sodium, potassium and creatinine concentration on admission, diagnosis at inclusion (cardiogenic shock/cardiac arrest/acute respiratory failure/acute renal failure/acute pancreatitis/neurological disease/haemorrhagic shock/anaphylactic choc/trauma/postoperative care), SAPS II and SOFA clinical score, history of chronic heart failure (CHF), coronary artery disease (CAD), arterial hypertension, diabetes mellitus, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), active or recent malignant tumours.

Propensity-based matching was used to create samples of patients treated by inotropes and/or vasopressors and not treated patients who were similar in terms of propensity score, *i.e.*, in terms of probability of receiving the therapy under study. Unmatched observations were discarded, thus leading to possibly non-representative samples of the original database. Ratio for matching was to 1 for 1 (one man associated with one women) with a calliper of 10%, using the “nearest neighbour” method. Matching was accepted when all standardised differences were smaller than 10%. The matching process significantly reduced differences in baseline characteristics (see **Supplementary Table 1**).

Subgroup analyses were performed for age (below vs. above the median), diagnosis at ICU admission, Charlson Comorbidity Index (CCI) groups, systolic blood pressure (below



and above 120 mmHg), serum lactate concentration on admission (below and above 2 mmol/l).

$P < 0.05$  was considered statistically significant. All statistical analyses were performed using R statistical software version 4.0.3 (The “R” Foundation for Statistical Computing, Vienna, Austria).

### 3. RESULTS

The study included 2087 patients, with 939 patients receiving inotropes and/or vasopressors during the first 3 days of their ICU stay. Patient characteristics are summarised in **Table 1**. Patients treated with vasoactive medications were older and had a more severe initial clinical presentation (*i.e.*, lower blood pressure, higher SOFA and SAPS II scores, lower pH and a higher concentration of lactate). Significant differences between the two groups were found with respect to some pre-existing diseases and the ICU referral diagnosis, as shown in **Table 1**. Unadjusted ICU mortality was significantly higher in patients who required inotrope and/or vasopressor treatment in comparison to those who did not (32 vs. 13%,  $p < 0.001$ ). Both in-hospital and 1-year all-cause mortality rates were also higher in patients treated with inotropes and/or vasopressors during the initial ICU stay (39 vs. 18% and 49 vs. 28% respectively).

#### 3.1 Primary end-point: ICU mortality

The unadjusted hazard ratio (HR) of ICU death in patients treated with vasoactive drugs was 2.05 (95% CI 1.68 – 2.49),  $p < 0.001$ . The difference persisted after multivariable adjustment with a HR of 1.58 [1.27 - 1.96],  $p < 0.001$ . In a propensity score-matched patient

cohort of 1202 patients, ICU mortality was higher in patients who received vasoactive medications during the first 3 days of their index ICU hospitalisation, with a HR of 1.40 [1.10 – 1.78],  $p = 0.007$  (see **Figure 1**).

### **3.2 Secondary endpoints: in-hospital and one-year mortality in all cohorts**

The analysis of in-hospital mortality of all patients included in this study demonstrated a negative association with the use of vasoactive medications before and after adjustment for confounders (HR 2.07 [1.75 - 2.46],  $p < 0.001$  and HR 1.62 [1.35 - 1.94],  $p = 0.001$ ) as well as after propensity-score matching (HR 1.41 [1.14 - 1.75],  $p = 0.001$ ).

One-year all-cause mortality was higher in patients who received inotropes and/or vasopressors during their ICU stay, with an unadjusted HR 2.08 [1.81 – 2.40],  $p < 0.001$ , HR 1.55 [1.31 – 1.86],  $p = 0.001$  after adjustment for confounders, HR 1.34 [1.12 - 1.61],  $p = 0.001$  after propensity-score matching (see **Figure 2**).

### **3.3 Secondary endpoints in the subgroup of ICU survivors**

A subgroup analysis was performed in 1635 patients who survived the initial ICU hospitalisation. Concerning in-hospital mortality of ICU survivors, there was no significant difference according to the use of inotropes and/or vasopressors before and after adjustment for confounding factors (HR 1.38 [0.97 - 1.98],  $p = 0.075$  and 1.19 [0.80 - 1.75],  $p = 0.391$  respectively). Propensity-score matching confirmed these results with a HR of 0.94 [0.60 - 1.49],  $p = 0.808$  (see **Figure 3**).

Concerning one-year all-cause mortality of ICU survivors, the unadjusted hazard of death at one year was 1.51 [1.22 - 1.80],  $p = 0.0002$  and 1.28 [1.02 - 1.62],  $p = 0.036$  after adjustment for confounders. In a propensity-score matched cohort there was no significant

difference in one-year all-cause mortality according to the use of vasoactive medications during the index ICU hospitalisation (HR0.94 [0.71 – 1.24],  $p = 0.645$ ).

### **3.4 Subgroup analysis of the primary endpoint**

As depicted in **Figure 4**, consistent results were found independently of age, diagnosis on admission and Charlson comorbidity index. The use of inotropes and/or vasopressors on ICU admission was associated with increased ICU mortality in all subgroups. The negative association of inotropes and/or vasopressors and ICU death was most pronounced in the subgroup of patients admitted for postoperative care with the HR of 2.90 [1.50 - 5.63]. This association was stronger in the subgroup of patients with low systolic blood pressure on admission (HR 1.71 [1.21 - 2.41],  $p=0.002$ ) and low concentration of serum lactate (HR 1.57 [1.19 - 2.06],  $p = 0.001$ ). Subgroup analysis according to the presence of comorbidities confirmed the persistent deleterious association of the use of inotropes and/or vasopressors and ICU mortality (see **Supplementary Figure 2**).

## **4. DISCUSSION**

### **4.1 Key findings**

This study aimed to test the hypothesis that the use of inotropes and/or vasopressors is independently associated with worse ICU survival as well as long-term outcomes in a large, prospective, multi-centric cohort of critically ill patients. We found that patients receiving vasoactive medications in initial days of their ICU stay had a higher risk of ICU death. However, administration of vasoactive medications was not associated with excess mortality after ICU discharge both during hospital stay and the following year.

## 4.2 Relationship to previous literature

Inotropic and vasopressor agents are among the most used therapies in the management of haemodynamic instability in intensive care. However, despite the fundamental importance of appropriate vasoactive drug use in the treatment of critically ill patients, the clinical evidence base is surprisingly limited. Poor short-term outcomes in patients exposed to inotropes and/or vasopressors in our study are consistent with the results demonstrated in several previous reports (9, 10, 12, 14, 20). However, it must be taken into account that most evidence concerning the deleterious effects of inotropes and/or vasopressors arise from trials conducted in acute heart failure and cardiogenic shock. In our study, the proportion of patients with cardiogenic shock was low (7%) and even less patients were included in the propensity score-matched analysis, as the overall majority needed inotropic support. Subgroup analysis demonstrated that the negative association of inotropes and/or vasopressors and ICU mortality was most pronounced in the subgroup of patients admitted for post-operative care.

Several mechanisms may explain the increased short-term mortality observed in patients exposed to inotropes and/or vasopressors. Common side effects of vasoactive medications include increased myocardial oxygen consumption and cardiac arrhythmia (21). Both of these side effects may lead to poor cardiac performance. A recent clinical trial of beta-adrenergic receptor blockade in the settings of septic shock demonstrated an unexpected large mortality benefit, potentially unmasking the harms of excessive beta-receptor stimulation with vasoactive therapy (22). Furthermore, catecholamine use has been associated with reduced metabolic efficiency by promoting fatty acid oxidation over that of glucose (23). This may be a further impediment to optimal cardiac performance.

Catecholamine use has also been associated with immunosuppression, bacterial growth, increased bacterial virulence, biofilm formation, insulin resistance and hyperglycaemia, all of which may contribute to poor outcomes in intensive care settings (23-25). Vasopressor induced excessive vasoconstriction can play a detrimental role in ICU survival due to impaired microcirculation, tissue hypoxia and organ ischemia (8).

Despite the initial severity of patients receiving vasoactive medications in our cohort, our subgroup analysis demonstrated that the negative association of inotrope and/or vasopressor use and ICU mortality was independent of the presence of comorbidities. These results confirm that the administration of vasoactive medications is an independent predictor of ICU mortality. The subgroup analysis also showed that patients presenting with lower systolic blood pressure on admission had a higher hazard of ICU death when receiving inotropes and/or vasopressors. Our study was underpowered to identify and compare the effects of different vasoactive drugs. However, based on previous literature (1), it is possible to assume that the most commonly used vasopressor in our registry was norepinephrine. Moreover, as only 7% of patients in this study were admitted for cardiogenic shock, it is likely that only this small subgroup of patients received inotropes such as dobutamine. According to earlier studies, there is evidence to suggest that deleterious association of vasopressors such as norepinephrine and mortality might be dose-dependent. Higher doses of vasoactive medications are needed to stabilise haemodynamics, thus increasing the risk of cardiac arrhythmia and excessive vasoconstriction (8). Unfortunately, our data does not allow for detection of the dose-related effect of vasopressors and ICU mortality. Further research comparing different vasoactive agents as well as dose selection is needed. It seems likely that the optimal approach should involve the use of vasoactive agents in the lowest effective dose and for the shortest period of time that is necessary.

There is limited data concerning factors related to long-term survival after ICU discharge. A recent European registry of nearly 7000 patients with acute heart failure demonstrated a detrimental association between the use of i.v. inotrope and/or vasopressor and long-term all-cause mortality in a propensity-score matched cohort (11). Discordant results have been found in a recent meta-analysis of 28,280 patients, which showed no difference in long-term mortality among patients receiving inotropes and/or vasopressors in a variety of clinical settings (26). However, it must be taken into account that only 5.6% of the studies included in this meta-analysis reported 1-year outcomes. Moreover, the authors found no randomised trial comparing treatment with an inotropic/vasopressor drug to placebo. Naturally, such randomisation would be unethical in critically ill unstable patients. The propensity score matching that we used in our study allowed us to balance groups according to a number of baseline variables that were recorded in the FROG-ICU registry, creating comparable sets of patients and reflecting the experience of daily clinical practice. Our results suggest that the deleterious association of vasoactive medications and excess mortality does not persist after ICU discharge.

### **4.3 Limitations of the study**

Several limitations of our study must to be acknowledged. First of all, it is an observational study, thus the associations could be due to residual confounding. Specifically, we may not have fully adjusted the data for confounding by indication and confounding due to severity of illness. To minimise confounding, we performed multiple different analyses, including propensity score matching. Secondly, we analysed a highly heterogeneous patient population, with various types and degrees of organ dysfunction, and their response to different types of vasoactive medication might be varied. However, subgroup analysis

according to the initial diagnosis showed the deleterious effect of inotropes and vasopressors throughout the different spectrum of critical illness. Our study was underpowered to evaluate the association of inotropes/vasopressors and all-cause mortality in specific patient populations such as cardiogenic shock. By definition, all patients presenting with cardiogenic shock received an inotrope or a vasopressor and propensity score matching was not possible in this subgroup of patients. What is more, our study did not investigate the effect of each vasoactive or inotropic agent on clinical outcome in ICU patients. Clearly, different vasoactive drugs are not identical and some catecholamines can be superior to others under specific conditions such as cardiogenic (27) or septic (28) shock. Moreover, the doses of vasoactive medications used were not recorded. It is possible that excessive mortality observed with the use of inotropes and/or vasopressors might be dose-related.

#### **4.4 Clinical implications**

Our study has important implications for daily clinical practice. Despite widespread use, the evidence for administration of inotropes and vasopressors in critically ill patients is limited. Our findings suggest that accurate evaluation of benefits and risks is required when prescribing a vasoactive agent in critical care settings. The use of inotropes and/or vasopressors in intensive care is an independent factor of early mortality and calls for close monitoring of the patient, as suggested by previous studies (29, 30). However, the administration of vasoactive agents does not seem to have a prolonged deleterious impact on patients who survive the initial ICU hospitalisation.

## **5. CONCLUSIONS**

We found that inotropic and/or vasopressor therapy was associated with increased ICU mortality. However, in our cohort, the use of inotropes and/or vasopressors during ICU admission was not associated with a worse prognosis after ICU discharge. Importantly, in the subgroup of ICU survivors, no association was found between in-hospital as well as 1-year all-cause mortality and the use of vasoactive medications during the initial ICU hospitalisation, within the limitations of the study design.



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**Table 1:** Comparison of baseline characteristics and outcomes in FROG ICU patients according to the use of vasopressors during the first 3 days after admission

|   | Available data,<br>n (%) | Total cohort<br>n = 2087 | No inotropes/<br>vasopressors<br>n = 1148 | Inotropes/<br>vasopressors<br>n = 939 | p value |
|---|--------------------------|--------------------------|---|---------------------------------------|---------|
| Age, years  | 2087 (100)               | 63 [51 – 74]             | 62 [48 – 72]                              | 65 [54 – 76]                          | < 0.001 |
| Female sex, n (%)   | 2087 (100)               | 726 (35)                 | 404 (35)                                  | 322 (34)                              | 0.264   |
| BMI, kg/m <sup>2</sup>                                    | 1295 (62)                | 26.5 [23.2 – 30.8]       | 26.1 [23.0– 30.5]                         | 26.9 [23.4 – 30.1]                    | 0.066   |
| <b>Clinical parameters on admission</b>                   |                          |                          |   |                                       |         |
| SOFA clinical score                                       | 1518 (73)                | 8 [5 – 10]               | 7 [4 – 10]                                | 9 [6 – 11]                            | < 0.001 |
| SAPS II clinical score                                    | 2086 (100)               | 49 [36 – 63]             | 45 [33 – 60]                              | 52 [39 – 65]                          | < 0.001 |
| Systolic blood pressure (mmHg)                            | 2037 (98)                | 122 [108 – 139]          | 128 [113 – 144]                           | 115 [102 – 130]                       | < 0.001 |
| Heart rate (bpm)  | 2009 (96)                | 92 [78 – 106]            | 92 [77 – 105]                             | 92 [79 – 107]                         | 0.335   |
| Respiratory rate/min                                      | 1546 (74)                | 20 [16 – 25]             | 20 [16 – 25]                              | 21 [16 – 26]                          | 0.005   |
| Blood oxygen saturation, SpO <sub>2</sub> (%)             | 1978 (95)                | 98 [96 – 100]            | 98 [96 – 100]                             | 98 [96 – 100]                         | 0.012   |
| Body temperature (°C)                                     | 2040 (98)                | 37.2 [36.7 – 37.8]       | 37.3 [36.9 – 37.9]                        | 37.1 [36.5 – 37.7]                    | < 0.001 |
| Diuresis of the first 24 h after admission                | 1718 (82)                | 1350 [800 – 2200]        | 1550 [968 – 2400]                         | 1100 [580 – 1800]                     | < 0.001 |
| Endotracheal intubation and mechanical ventilation, n (%) | 2087 (100)               | 1948 (93)                | 1148 (100)                                | 845 (90)                              | < 0.001 |
| FiO <sub>2</sub>  | 1920 (99)                | 40 [30 – 50]             | 40 [30 – 45]                              | 40 [30 – 55]                          | < 0.001 |
| PEEP, cmH <sub>2</sub> O                                  | 1704 (87)                | 5 [5 – 8]                | 5 [5 – 7]                                 | 6 [5 – 8]                             | < 0.001 |
| Expired volume, ml  | 1419 (73)                | 470 [410 – 534]          | 480 [420 – 547]                           | 453 [401 – 519]                       | 0.051   |
| Plateau pressure, cmH <sub>2</sub> O                      | 735 (38)                 | 20 [16 – 26]             | 19 [15 – 24]                              | 21 [17 – 27]                          | 0.001   |
| <b>Laboratory tests on admission</b>                      |                          |                          |   |                                       |         |
| pH  | 1905 (91)                | 7.24 [7.36 – 7.46]       | 7.43 [7.38 – 7.46]                        | 7.39 [7.35 – 7.45]                    | <0.001  |
| pO <sub>2</sub> (mmol/l)                                  | 1912 (92)                | 92 [75 – 120]            | 93 [76 – 121]                             | 90 [74 – 118]                         | 0.072   |
| pCO <sub>2</sub> (mmol/l)                                 | 1894 (91)                | 38 [34 – 43]             | 38 [34 – 43]                              | 38 [34 – 43]                          | 0.163   |
| HCO <sub>3</sub> <sup>-</sup> (mmol/l)                    | 1758 (84)                | 24 [21 – 26]             | 24 [22 – 27]                              | 23 [20 – 26]                          | < 0.001 |

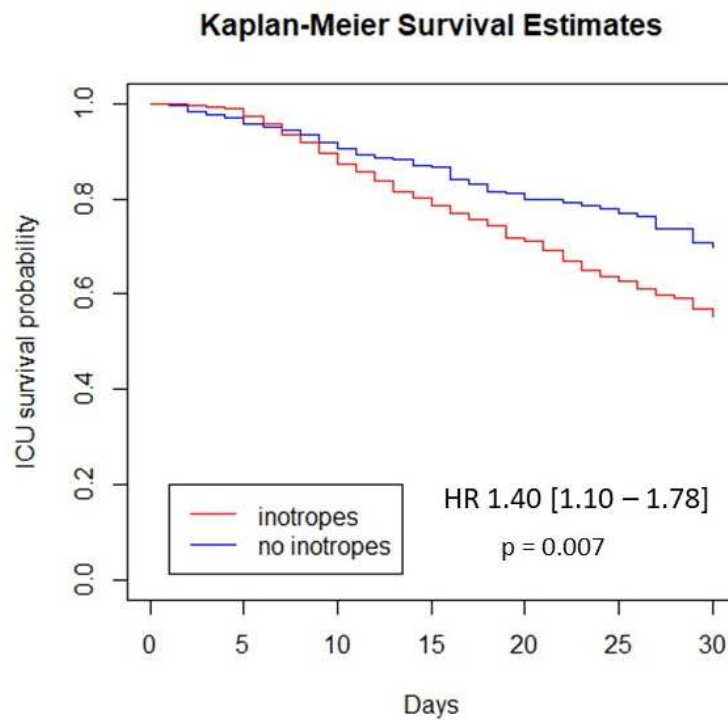
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|---|-----------|--------------------|--------------------|--------------------|---------|
| Lactate (mmol/L)                          | 1647 (79) | 1.39 [1.00 – 1.94] | 1.20 [0.90 – 1.70] | 1.54 [1.10 – 2.34] | < 0.001 |
| Haemoglobin (g/dL)                        | 1984 (95) | 10.0 [8.9 – 11.4]  | 10.2 [9.03 – 11.6] | 9.8 [8.8 – 11.3]   | 0.001   |
| Sodium (mmol/L)                           | 2031 (97) | 140 [137 – 143]    | 140 [137 – 143]    | 140 [137 – 144]    | 0.263   |
| Potassium (mmol/L)                        | 2015 (97) | 3.9 [3.6 – 4.3]    | 3.8 [3.5 – 4.2]    | 4.0 [3.6 – 4.4]    | < 0.001 |
| Creatinine (µmol/L)                       | 1998 (96) | 83 [59 – 150]      | 73 [54 – 116]      | 107 [69 – 184]     | < 0.001 |
| Capillary glycaemia (mmol/L)              | 1828 (88) | 7.4 [6.2 – 9.2]    | 7.3 [6.1 – 9.0]    | 7.5 [6.3 – 9.3]    | 0.030   |
| C-reactive protein (mg/L)                 | 566 (27)  | 127 [57 – 223]     | 108 [53 – 204]     | 145 [66 – 249]     | 0.002   |
| BNP (pg/mL)                               | 1946 (93) | 245 [87 – 991]     | 185 [56 – 551]     | 430 [113 – 1512]   | 0.002   |
| Troponin I (µg/L)                         | 1946 (93) | 0.26 [0.06 – 2.05] | 0.14 [0.05 – 1.42] | 0.37 [0.08 – 3.08] | 0.006   |
| <b>Medical history</b>                    |           |                    |                    |                    |         |
| Previous history of heart failure, n (%)  | 2083 (99) | 153 (7)            | 67 (6)             | 86 (9)             | < 0.001 |
| Coronary artery disease, n (%)            | 2083 (99) | 188 (9)            | 89 (8)             | 99 (11)            | < 0.001 |
| Hypertension, n(%)                        | 2083 (99) | 902 (43)           | 457 (40)           | 445 (47)           | < 0.001 |
| Atrial fibrillation/atrial flutter, n (%) | 2083 (99) | 221 (11)           | 104 (9)            | 117 (12)           | < 0.001 |
| Dyslipidaemia, n (%)                      | 2083 (99) | 412 (20)           | 214 (19)           | 198 (21)           | < 0.001 |
| Obesity, n (%)                            | 2083 (99) | 227 (11)           | 116 (10)           | 111 (12)           | < 0.001 |
| Diabetes mellitus, n (%)                  | 2083 (99) | 384 (18)           | 201 (18)           | 183 (20)           | < 0.001 |
| COPD, n (%)                               | 2083 (99) | 273 (13)           | 139 (12)           | 223 (14)           | < 0.001 |
| Asthma, n (%)                             | 2083 (99) | 93 (4)             | 52 (4)             | 41 (4)             | 0.061   |
| Chronic kidney disease, n (%)             | 2083 (99) | 241 (12)           | 95 (8)             | 146 (16)           | < 0.001 |
| Chronic liver disease, n (%)              | 2083 (99) | 158 (8)            | 76 (7)             | 82 (9)             | < 0.001 |
| Active cancer, n (%)                      | 2083 (99) | 281 (13)           | 151 (13)           | 130 (14)           | < 0.001 |
| Chronic inflammatory disease, n (%)       | 2083 (99) | 77 (4)             | 43 (4)             | 34 (4)             | 0.116   |
| <b>Causes of ICU admission</b>            |           | <b>2086 (100)</b>  |                    |                    |         |
| Septic shock, n (%)                       |           | 536 (26)           | 216 (19)           | 320 (34)           | < 0.001 |
| Acute respiratory distress, n (%)         |           | 394 (19)           | 258 (22)           | 136 (14)           | < 0.001 |
| Coma (neuro), n (%)                       |           | 286 (14)           | 224 (20)           | 62 (7)             | < 0.001 |
| Acute post-operative care, n (%)          |           | 207 (10)           | 113 (10)           | 94 (10)            | 0.068   |
| Cardiac arrest, n (%)                     |           | 179 (9)            | 106 (9)            | 73 (8)             | 0.009   |

|   |            |              |              |              |         |
|---|------------|--------------|--------------|--------------|---------|
| Cardiogenic shock, n (%)                    |            | 146 (7)      | 67 (6)       | 79 (8)       | 0.0003  |
| Haemorrhagic shock, n (%)                   |            | 110 (5)      | 51 (4)       | 59 (6)       | 0.015   |
| Trauma, n (%)                               |            | 89 (4)       | 51 (4)       | 38 (4)       | 0.162   |
| Other, n (%)                                |            | 140 (6)      | 62 (5)       | 78 (8)       | < 0.001 |
| <b>ICU length of stay (days)</b>            | 2087 (100) | 12 [7 – 21]  | 12 [7 – 20]  | 14 [8 – 23]  | < 0.001 |
| <b>Total hospital length of stay (days)</b> | 2085 (99)  | 23 [13 – 39] | 23 [12 – 40] | 23 [13 – 38] | 0.584   |
| <b>Medication at discharge (n=1635)</b>     |            |              |              |              |         |
| Beta blockers, n (%)                        | 1635 (100) | 300 (18)     | 172 (18)     | 128 (19)     | < 0.001 |
| ACEIs or ARBs, n (%)                        | 1635 (100) | 275 (16)     | 174 (18)     | 101 (15)     | < 0.001 |
| Aldosterone receptor antagonists, n (%)     | 1635 (100) | 19 (1)       | 12 (1)       | 7 (1)        | < 0.001 |
| Statin, n (%)                               | 1635 (100) | 301 (18)     | 165 (17)     | 136 (20)     | < 0.001 |
| Antiplatelet agent, n (%)                   | 1635 (100) | 385 (23)     | 226 (23)     | 159 (24)     | 0.273   |
| Vitamin K antagonist, n (%)                 | 1635 (100) | 90 (5)       | 52 (5)       | 38 (6)       | 0.021   |
| Inhaled steroid, n (%)                      | 1635 (100) | 44 (3)       | 30 (3)       | 14 (2)       | < 0.001 |
| <b>Outcome</b>                              |            |              |              |              |         |
| ICU mortality                               | 2087 (100) | 452 (22)     | 152 (13)     | 300 (32)     | < 0.001 |
| In-hospital mortality                       | 2087 (100) | 575 (28)     | 210 (18)     | 365 (39)     | < 0.001 |
| 1-year all-cause mortality                  | 2087 (100) | 785 (38)     | 326 (28)     | 459 (49)     | < 0.001 |

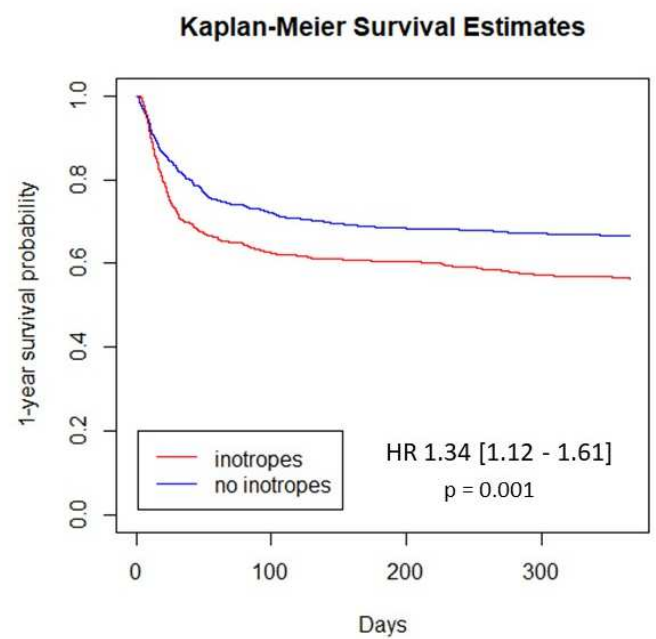
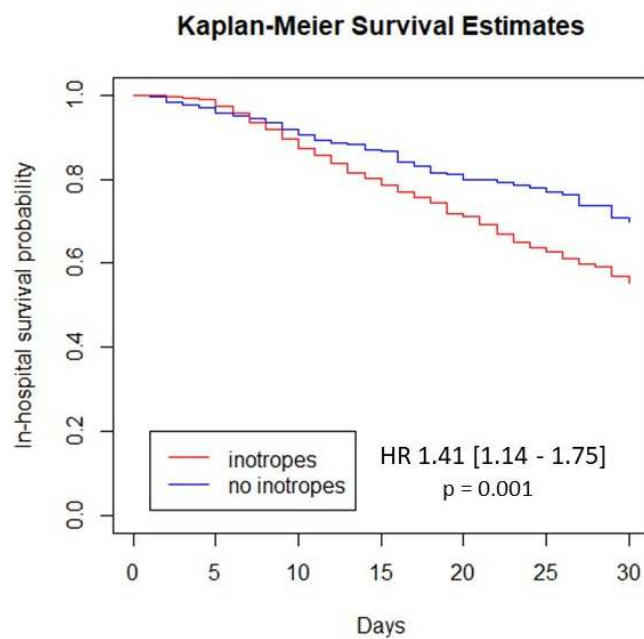
Data are presented as median [1<sup>st</sup> and 3<sup>rd</sup> quartile] or number (percentage).

BMI: body mass index, BNP: B-type natriuretic peptide, NT-proBNP: N-terminal-proBNP, COPD: chronic obstructive pulmonary disease, ACEI: angiotensin converting enzyme inhibitor, BB: beta blocker

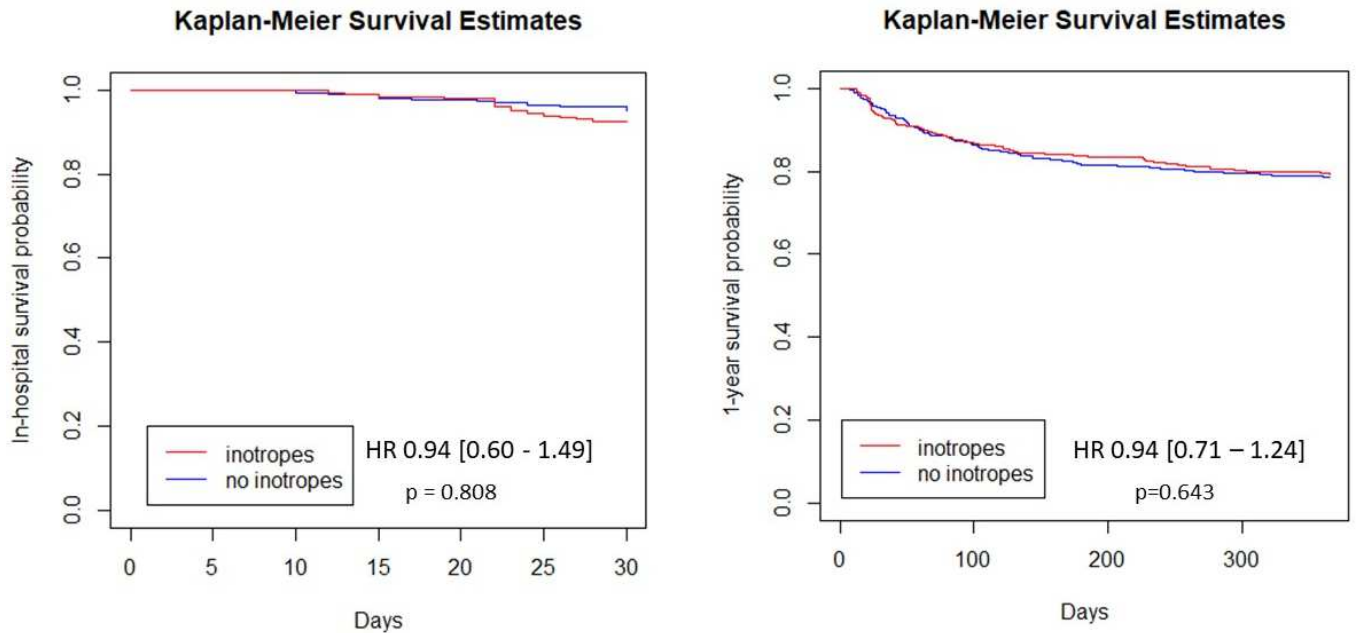
**Figure 1:** Kaplan-Meier survival estimates for ICU mortality according to the use of inotropes and/or vasopressors during the first 3 days of ICU stay in a propensity score matched cohort



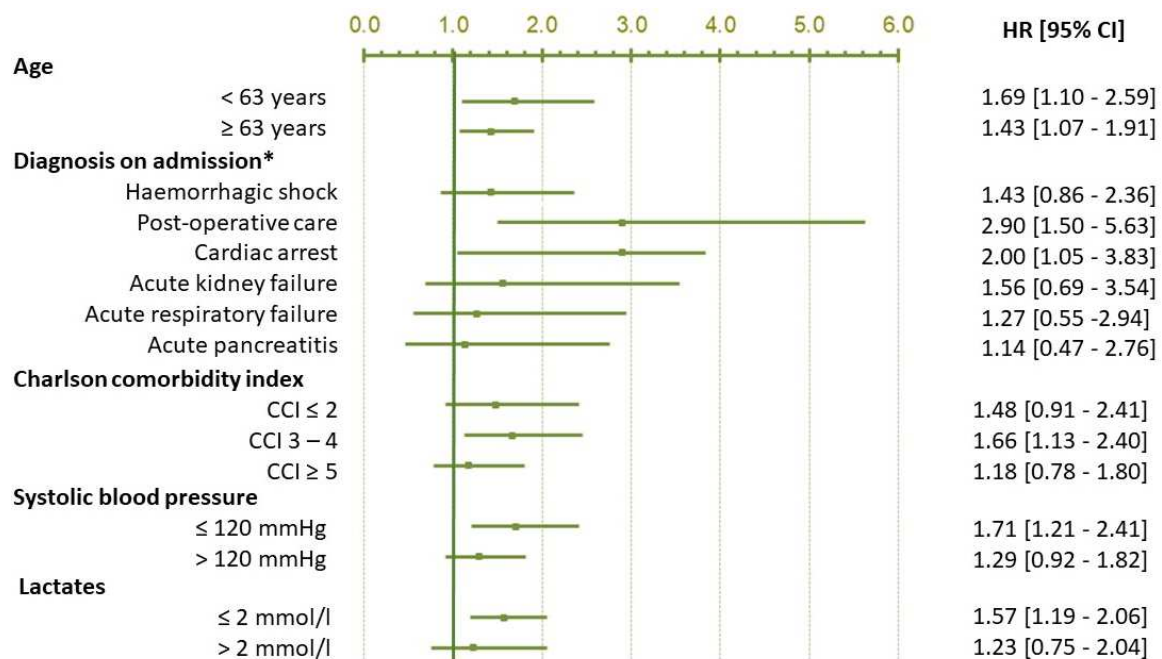
**Figure 2:** Kaplan-Meier survival estimates for in-hospital and 1-year all-cause mortality according to the use of inotropes and/or vasopressors during the first 3 days of ICU stay in all cohort after propensity score matching



**Figure 3:** Kaplan-Meier survival estimates for in-hospital and 1-year all-cause mortality according to the use of inotropes and/or vasopressors during the first 3 days of ICU stay in a propensity score matched cohort of ICU survivors



**Figure 4:** Subgroup analysis of the association between the use of inotropes/vasopressors and ICU mortality in a propensity score matched cohort



\*Sepsis, septic shock as well as cardiogenic shock cannot be represented as the great majority of the patients were treated with inotropes and/or vasopressors and could not be included in the matched analysis.