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Clinical Characteristics and Day-90 Outcomes of 4,244 critically ill adults with COVID-19: a prospective cohort study

COVID-ICU group, for the REVA network

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Take-Home Message

In this cohort study that included 4,244 adult patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection admitted to the ICU, 80% received invasive mechanical ventilation. Mortality 90 days after ICU admission was 31% in the whole cohort and 37% in the subgroup of patients who received invasive mechanical ventilation on the day of ICU admission. Among these patients with early intubation, mortality increased with the severity of ARDS at ICU admission (30%, 34%, and 50% for mild, moderate, and severe ARDS, respectively).

Abstract:

PURPOSE: To describe acute respiratory distress syndrome (ARDS) severity, ventilation management, and the outcomes of ICU patients with laboratory-confirmed COVID-19 and to determine risk factors of 90-day mortality post-ICU admission.

METHODS: COVID-ICU is a multi-center, prospective cohort study conducted in 138 hospitals in France, Belgium, and Switzerland. Demographic, clinical, respiratory support, adjunctive interventions, ICU length-of-stay, and survival data were collected.

RESULTS: From February 25 to May 4, 2020, 4,643 patients (median [IQR] age 63 [54-71] years and SAPS II 37 [28-50]) were admitted in ICU, with day-90 post-ICU admission status available for 4,244. On ICU admission, standard oxygen therapy, high-flow oxygen, and non-invasive ventilation were applied to 29%, 19%, and 6% patients, respectively. 2,635 (63%) patients were intubated during the first 24-hours whereas overall 3,376 (80%) received invasive mechanical ventilation at one point during their ICU stay. Median (IQR) positive end-expiratory and plateau pressures were 12 (10-14) cmH_2O, and 24 (21-27) cmH_2O, respectively. The mechanical power transmitted by the MV to the lung was 26.5 (18.6-34.9) J/min. Paralyzing agents and prone position were applied to 88% and 70% of patients intubated at Day-1, respectively. Pulmonary embolism and ventilator-associated pneumonia were diagnosed in 207 (9%) and 1,209 (58%) of these patients. On day 90, 1,298/4,244 (31%) patients had died. Among patients who received invasive or non-invasive ventilation on the day of ICU admission, day-90 mortality increased with the severity of ARDS at ICU admission (30%, 34%, and 50% for mild, moderate, and severe ARDS, respectively) and decreased from 42 to 25% over the study period. Early independent predictors of 90-day mortality were older age, immunosuppression, severe obesity, diabetes, higher renal and cardiovascular SOFA score components, lower PaO_2/FiO_2 ratio and a shorter time between first symptoms and ICU admission.

CONCLUSION: Among more than four thousand critically ill patients with COVID-19 admitted to our ICUs, 90-day mortality was 31% and decreased from 42 to 25% over the study period. Mortality was higher in older, diabetic, obese and severe ARDS patients.

Introduction

From March to May 2020, Europe was massively affected by the COVID-19 outbreak. In that context, the REVA network [1] designed a specific registry (COVID-ICU), to prospectively collect characteristics, management, and outcomes of patients admitted to ICUs for severe COVID-19 in France, Belgium, and Switzerland. In France, as of October 1st, 2020, 395,104 patients had been tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and 32,365 deaths have been associated with the disease. On April 8, 2020, the number of COVID-19 patients hospitalized in French ICUs peaked at 7,148.

A few case-series [2–5] have described baseline characteristics and short-term mortality (up to 28-days after ICU admission) ranging from 26 to more than 50% in critically ill patients with COVID-19. However, recovery from severe COVID-19 often takes several weeks and a substantial number of these patients were still in the ICU or the hospital at the time their outcome was evaluated [4, 5]. Notably, 28-day mortality was 41% in the control care group of the RECOVERY trial, which showed that dexamethasone improved the survival of patients receiving invasive mechanical ventilation or oxygen at randomization [6].

The present study reports data of 4,244 patients with laboratory-confirmed SARS-CoV-2 infection admitted to the ICU and for whom day-90 status was available. We also evaluated risk factors associated with 90-day mortality in these critically ill patients.

Methods

Study Design, Patients

COVID-ICU is a multi-center, prospective cohort study conducted in 149 ICUs from 138 centers, across three countries (France, Switzerland, and Belgium). Centers were invited to participate by public announcements and by the Reseau European de recherche en Ventilation Artificielle (REVA) network (70 centers were active members of this network). We included in the present report data from participating ICUs that had enrolled at least one patient with complete data on age and 90-day vital status. COVID-ICU received approval from the ethical committee of the French Intensive Care Society (CE-SRLF 20-23) in

accordance with our local regulations. All patients or close relatives were informed that their data were included in the COVID-ICU cohort.

All consecutive patients over 16 years of age admitted to the participating ICU between February 25, 2020, and May 4, 2020, with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection were included. Laboratory confirmation for SARS-Cov-2 was defined as a positive result of real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay from either nasal or pharyngeal swabs, or lower respiratory tract aspirates [7]. Patients without laboratory-confirmed COVID-19 were not included, even if they presented with a typical radiological pattern.

Inclusions were stopped on May 4, 2020, after enrollment of 4,643 patients admitted to the ICU. Survival status up to 90 days after ICU admission was obtained for 4,244 of them.

Data collection

Day 1 was defined as the first day when the patient was in ICU at 10 am. Each day, the study investigators completed a standardized electronic case report form. Baseline information collected at ICU admission were: age, sex, body mass index (BMI), active smoking, Simplified Acute Physiology Score (SAPS) II score [8], Sequential Organ Failure Assessment (SOFA) [9], comorbidities, immunodeficiency (if present), clinical frailty scale [10], date of the first symptom, dates of the hospital and ICU admissions. The case report form prompted investigators to provide a daily-expanded data set including respiratory support devices (oxygen mask, high flow nasal cannula, or non-invasive ventilation), mechanical ventilation settings (positive end-expiratory pressure (PEEP), the fraction of inspired oxygen (FiO_2), respiratory rate, tidal volume, plateau pressure, arterial blood gas, standard laboratory parameters, and adjuvant therapies for acute respiratory distress syndrome (ARDS) such as the use of continuous neuromuscular blockers, nitric oxide, prone position, corticosteroids, or extracorporeal membrane oxygenation until day-90. Driving pressure was defined as plateau pressure minus PEEP and mechanical power (J/min) was calculated as follows: Mechanical power (J/min) = 0,098 × tidal volume × respiratory rate × (peak pressure – 1/2 × driving pressure) [11]. If not specified, peak pressure was considered equal to plateau pressure. Ventilatory ratio was defined as (minute ventilation × $PaCO_2$) – (predicted bodyweight × 100 × 37,5) [12].

ARDS severity, complications, and outcomes

ARDS was graded based on the Berlin Definition for patients undergoing mechanical ventilation (invasive or non-invasive) on ICU day 1 [13]. Patients on nasal, mask or high-flow oxygen therapy were not included in this group. However, their day-1 PaO_2/FiO_2 was calculated by converting O_2 flow to estimated FiO_2 (see conversion tables in the supplement) [14]. ICU-complications and organ dysfunction included acute kidney failure requiring renal replacement therapy, thromboembolic complications (distal venous thrombosis or proven pulmonary embolism by either pulmonary CT angiography or cardiac echography), ventilator-associated pneumonia, and cardiac arrest. Clinical suspicion of ventilator-associated pneumonia was confirmed before antibiotics either by quantitative distal bronchoalveolar lavage cultures growing $\geq 10^4$cfu/mL, blind protected specimen brush distal growing $\geq 10^3$cfu/mL, or endotracheal aspirates growing $\geq 10^6$cfu/mL.

Patient outcomes included the date of liberation from mechanical ventilation, dates of ICU and hospital discharge, vital status at ICU and hospital discharge, and 28, 60, and 90 days after ICU admission.

Statistical Analyses

Characteristics of patients were described as frequencies and percentages for categorical variables and as means and standard deviations or medians and interquartile ranges for continuous variables. Categorical variables were compared by chi-square or Fisher's exact test, and continuous variables were compared by Student's *t*-test or Wilcoxon's rank-sum test. Kaplan-Meier overall survival curves until Day 90 were computed, and were compared using log-rank tests. The median length of stay in ICU and in hospital were also estimated using a Kaplan-Meier estimator to take into account patients that may be still in ICU at the time of the analysis.

Baseline risk factors of death at Day 90 were assessed within the whole cohort using univariate and multivariate cox regression. Baseline variables (i.e obtained during the first 24 hours in the ICU) included in the multivariate model were defined *a priori*, and no variable selection was performed (see the description of the statistical analysis plan in the Supplement). ICU admission dates were split into four calendar periods (i.e

before March, 15; from March 16 to 31; from April 1 to 15; and after April 16). Proportional hazard assumption was assessed by inspecting the scaled Shoenfeld residuals and Harrel's test [15] (Table S4). Multiple imputations were used to replace missing values when appropriate (Figure S1-S2). Ten copies of the dataset were created with the missing values replaced by imputed values, based on observed data including outcomes and baseline characteristics of participants. Each dataset was then analyzed and the results from each dataset were pooled into a final result using Rubin's rule [16]. Lastly, a sensitivity analysis using a Cox model stratified on the center variable was also performed. Hazard ratios and their 95% confidence interval were estimated. A p value < 0.05 was considered statistically significant. Statistical analyzes were conducted with R v3.5.1.

Results

Participating ICUs and Patients Enrolled

Patients were included in 149 ICUs (71 [48%] university, 66 [44%] public regional, and 12 [8%] private, semi-private, or military hospitals, respectively) from 138 centers in three countries. The median (interquartile) number of ICU beds in these centers and these ICUs were 26 (18-55) and 20 (14-28), respectively. Fifty-six percent of the patients were recruited in Paris and the surrounding area (see Table S1-S3 in the Supplement for an extensive description of ICUs and center characteristics). Ninety-four percent of the centers reported having extended the number of ICU beds during the COVID-19 outbreak.

Of the 4,643 patients enrolled on May 4, 2020, 399 were lost to follow-up at Day-90. Thereafter we describe the characteristics of the remaining 4,244 patients with available day-90 vital status (Figure 1).

There were 1,085/4,244 (26%) female patients (Table 1). At ICU admission, their median (interquartile) age, SAPS II, and SOFA scores were 63 (54-71) years, 37 (28-50), and 5 (3-8), respectively. The rate of obese (BMI ≥ 30kg/m^2) patients was 1,607/3,935 (41%). The most frequent comorbidities were hypertension 2,018/4,197 (48%), known diabetes 1,167/4,196 (28%), and immunocompromised status 314/4,192 (7%). Median (IQR) time between first symptoms and ICU admission was 9 (6-12) days. Of note,

only 176/4,124 (4%) patients were active smokers and only 208/4,116 (5%) had concomitant bacterial pneumonia at ICU admission.

Ventilatory support, adjunctive therapies, and ARDS severity

On day-1, standard oxygen therapy, high flow oxygen, and non-invasive ventilation were applied to 1,219/4,157 (29%), 786/4,096 (19%), and 230/4,109 (6%) patients, respectively. The use of these modalities tended to increase over time (Table S5 and Figure S3). 2,635/4,175 (63%) were placed on invasive mechanical ventilation during the first 24 hours, whereas in total 3,376/4,209 (80%) were intubated during their ICU stay. On the first day in ICU, median tidal volume, PEEP, plateau, driving pressures, and mechanical power were 6.1 (5.8-6.7) mL/kg, 12 (10-14) cmH_2O, 24 (21-27) cmH_2O, 13 (10-17) cmH_2O, and 26.5 (18.6-34.9) J/min, respectively (Table 1). 1,841/2,560 (72%) patients required a $FiO_2 \geq$ 50%, while 1,371 (54%) received a PEEP ≥12 cmH_2O.

Mild, moderate, and severe ARDS was reported in 539/2,233 (24%), 1,154/2,233 (52%), and 540/2,233 (24%) patients on mechanical ventilation (invasive or non-invasive) on ICU day 1, respectively (Table 2). Continuous neuromuscular blockade and prone position were used in 1,966/2,224 (88%), and 1,556/2,223 (70%) in these patients. Moderate and severe ARDS patients were more likely to receive these adjunct therapies, with a median number of 3 (IQR, 2-6) prone positioning sessions per patient. Of note, 888/2,224 (41%) of them received corticosteroids for a median of 5 (IQR, 2-8) days. Lastly, 321/4,187 (8%) patients were placed on extracorporeal membrane oxygenation (ECMO). Table S6 provides the use of adjunct therapies in the whole cohort of 4,224 patients.

ICU complications and organ support in patients intubated on ICU-day 1

Ventilator-associated pneumonia was diagnosed in 1,209/2,101 (58%) patients who were intubated on ICU day 1, whereas 623/2,227 (28%) patients had an acute kidney failure requiring renal replacement therapy (Table 2). A venous thromboembolic complication was diagnosed in 373/2,226 (17%) patients, of whom 207/2,226 (9%) had proven pulmonary embolism.

Patient outcomes and predictors of 90-day mortality

Overall 90-day mortality was 31%. Within the first 7 days after ICU admission, 64 (12%, 95 confidence interval [CI], 9-15%) patients with mild and 183 (16%, 95 CI, 14-18%) with moderate ARDS progressed to severe ARDS. In patients on mechanical ventilation (invasive or non-invasive) at ICU day one, 90-day mortality was 820/2,233 (37%), and increased with the severity of ARDS at ICU admission (30%, 34% and 50% in mild, moderate, and severe ARDS patients, respectively) (Table 3 and Figure 2). 90-day mortality was 292/1,219 (24%), 202/786 (26%), and 96/230 (42%) in patients who received standard oxygen therapy, high flow oxygen, or non-invasive ventilation at day-1. Noticeably, 90-day mortality declined over time from 42% to 25% (P<0.001) in the first and the last period, respectively (Table S5 and Figure S3). Of note, 90-day mortality was 36% in patients intubated during their ICU stay and 11% for those not intubated (see Table S7). The overall median durations of mechanical ventilation, ICU, and hospital stay for 90-day survivors were 13 (8-18), 21 (13-36), and 30 (20-48) days, respectively. Of note, these durations increased with the severity of the ARDS (Table 3).

Results of the multivariable analysis are reported in Table 4. After inspection of the proportional hazard assumption, a time-varying effect was introduced in the multivariate Cox model for four variables: body mass index, active smoking, renal component of the SOFA score, and lymphopenia. Thus, for these variables, two types of hazard ratio are reported, indicating the early effect (before 14 days of follow-up) or the late effect (after 15 days of follow-up) of the corresponding baseline characteristic on the risk of death, respectively.

Non-survivors were older, and more frequently diabetic or immunocompromised than survivors. At ICU admission, they had a higher renal and hemodynamic SOFA component scores and lower PaO_2/FiO_2 ratio. Interestingly, they also had a shorter time since the onset of the first symptoms. Day-1 patients' characteristics significantly associated with higher 90-day mortality identified by the Cox regression model were older age, known diabetes, class 2 and extreme obesity, immunodeficiency, higher renal and cardiovascular components of the SOFA score, lower PaO_2/FiO_2, lower pH, and a shorter time between first symptoms and ICU admission (Table 4). The same analysis re-run after multiple imputations of missing data (Table S8), and a sensitivity analysis introducing the center variable as a stratification variable in the multivariable model yielded similar results (Table S9). Kaplan–Meier survival estimates according to age,

ICU admission period, the renal component of the SOFA score, the delay between the first symptoms and ICU admission, immunocompromised status, diabetes, severe lymphopenia, and static pulmonary compliance categories at day-1 are provided in Figures 2B, S4-S10. Lastly, outcomes of patients who progressed from mild to moderate or severe ARDS and those who progressed from moderate to severe ARDS within the first week of mechanical ventilation are reported in Figures 2C and 2D.

Discussion

We report herein one of the largest prospective case-series of COVID-19 patients who required intensive care admission, with detailed information on their baseline characteristics, ARDS severity, and 90-day outcomes. Overall 90-day mortality was 31% and was higher in older and obese patients, diabetics, immunocompromised patients, and those who had multiple organ dysfunction at ICU admission. 90-day mortality rates were 30%, 34%, and 50%, in patients with mild, moderate, and severe ARDS who were on mechanical ventilation (invasive or non-invasive) on ICU day-1, respectively. Noticeably, mortality rates decreased over time during the study period, while ICU and hospital length of stay were substantially longer than in other cohorts of ARDS patients [17].

Acute respiratory failure was the main indication for ICU admission, with 80% of our COVID-19 patients requiring invasive mechanical ventilation which is consistent with the experience in Lombardy, Italy [2], where 88% of ICU patients were intubated. However, lower rates of intubation in ICU patients were reported in Wuhan, China by Wang *et al* (47%), and Yang *et al* (42%) [18, 19], and in Washington state, USA (71%) [20]. While early single-center reports in small groups of COVID patients reported well-preserved lung mechanics despite the severity of hypoxemia [21], more recent data [22] and our observations suggested that lung compliance and driving pressure were close to those of reported in classical ARDS. Mechanical power which is the energy delivered to the respiratory system over time during mechanical ventilation was very high in our patients with ARDS, reaching 26.5 (18.6 – 34.9) J/min, while a higher mortality risk has been suggested for patients with ARDS whose value exceeded 17.0 J/min [23]. In that context, the application of evidence-based ARDS care, such as lung-protective mechanical ventilation and

proning are both warranted [24]. ECMO, which was used in 15% of severe ARDS in our cohort should be considered when these measures have failed [25].

28-day mortality was 39% in 257 critically-ill COVID-19 patients in New-York city, of whom 203 (79%) received invasive mechanical ventilation [4], 41% in patients on invasive mechanical ventilation included in the usual care group of the RECOVERY randomized trial [6] and >50% in 733 Chinese patients admitted in the ICU [3]. Despite similar severity at baseline, day-28 mortality were 26% in the whole cohort and 30% in our patients intubated at day-1, a rate close to that reported in the large LUNG-SAFE study [17]. Different characteristics of patients admitted to ICUs and different degrees of stress on healthcare systems could explain these discrepancies [26]. Besides, we report a progressive decrease in 90-day mortality over the study period with a higher proportion of patients on high flow oxygen and non-invasive ventilation and a lower rate of intubation on ICU day-1 in the last period of the study (Table S5 and Figure S3). Similar findings have been reported by other groups [27] and might reflect better knowledge of the pathophysiology of the disease over time and less reluctance to use non-invasive oxygenation strategies. It should however be noticed that duration of invasive mechanical ventilation and length of ICU and hospital stays were substantially longer than those of in ARDS unrelated to COVID-19. For instance, ICU length of stay in patients surviving severe ARDS was 26 (13-43) days, compared to 14 (7-23) days in the LUNG-SAFE study [17]. These patients rapidly overwhelmed ICU's capacity, forcing a major reorganization of ICU beds during the crisis [28].

Identifying the determinants of outcomes of critically ill patients with severe COVID-19 is crucial to optimize the use of ICU care and other hospital resources. Older age, obesity, diabetes, being immunocompromised, lower PaO2/FiO2 and higher hemodynamic and renal SOFA score at ICU admission were independently associated with 90-day mortality, highlighting the dismal impact of premorbid conditions and multiorgan damage on the outcomes of patients with the most severe forms of COVID-19 [3, 29]. The rate of class 2 or extreme obesity (BMI ≥35kg/m^2) was 41% in our cohort and unusually high compared to the prevalence of obesity in the French population [33]. More severe COVID-19 in obese patients may be explained by impairments in the adaptive immune response [34], cardiometabolic and thrombotic derangements [35], and alterations in lung function [36]. Obesity may also be a marker of poorer

baseline health conditions since it is frequently associated with a lower socio-economic status [37]. As previously reported [30], a shorter time between first symptoms and ICU admission was also independently associated with increased mortality. Lastly, we and others [38, 39] observed an unusually high rate of thromboembolic complications, with 9% of proven pulmonary embolism. This rate may likely be higher since pulmonary CT angiography was not systematically performed in all patients. Diffuse vascular endothelium injury and intense activation of the coagulation cascade may explain this increased risk of venous thrombosis [40].

The major strength of this study is the detailed report of physiological, clinical features, ventilatory management, and 90-day outcomes of a large, multicenter series of 4,244 critically ill COVID-19 patients. We acknowledge several limitations to our study. First, we conducted this cohort at a time where the national health system was extremely pressured with a need for a large number of ICU beds in some regions. Then, we cannot rule out that ICU admission policies and patients' management were similar in all centers, although a sensitivity analysis introducing the center variable in the multivariable model found similar results. Second, testing was not standardized across sites, which might have led to misclassification. Third, some variables have missing data (as reported in the tables) due to a large number of patients included in a short period and intense clinical activity during the crisis. Indeed, our multivariable model included only 51% of the whole cohort of patients because of these missing data, which may explain, together with other residual confounders, the unanticipated lower mortality before 14 days of follow-up associated with baseline lymphopenia. However, this association was no longer statistically significant in the model with multiple imputations. Fourth, Grasselli *et al* recently reported that high D-dimer concentration was significantly associated with mortality in COVID-19-related ARDS patients when associated with low values of static respiratory system compliance [22]. Unfortunately, we were unable to confirm that result in our multivariable model due to inconsistent collection of this data at ICU admission.

Conclusions

In this case series of 4,244 critically ill patients with laboratory-confirmed COVID-19 admitted to our ICUs, overall 90-day mortality was 31% and decreased over time during the study period. Mortality was

higher in older patients, immunocompromised, extreme obese, diabetics, those with a shorter delay between first symptoms and ICU admission, and those with extra-pulmonary organ dysfunction at ICU admission. Ninety-day mortality increased with the severity of ARDS from 30% in mild to 50 % in severe ARDS. These information, together with the very long durations of mechanical ventilation and of ICU stay, which have contributed to the swamping of our ICU's capacity, will be critical for the management of the second wave of the epidemic. Lastly, long term follow-up is warranted to provide a complete description of the outcomes and potential sequelae associated with the most severe forms of COVID-19 requiring ICU treatment.

References:

1. REVA network http://www.reseau-reva.org/

2. Grasselli G, Zangrillo A, Zanella A, et al (2020) Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. JAMA. https://doi.org/10.1001/jama.2020.5394

3. Xie J, Wu W, Li S, et al (2020) Clinical characteristics and outcomes of critically ill patients with novel coronavirus infectious disease (COVID-19) in China: a retrospective multicenter study. Intensive Care Med. https://doi.org/10.1007/s00134-020-06211-2

4. Cummings MJ, Baldwin MR, Abrams D, et al (2020) Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. Lancet. https://doi.org/10.1016/S0140-6736(20)31189-2

5. Grasselli G, Greco M, Zanella A, et al (2020) Risk Factors Associated With Mortality Among Patients With COVID-19 in Intensive Care Units in Lombardy, Italy. JAMA Intern Med. https://doi.org/10.1001/jamainternmed.2020.3539

6. RECOVERY Collaborative Group, Horby P, Lim WS, et al (2020) Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. N Engl J Med. https://doi.org/10.1056/NEJMoa2021436

7. Clinical management of severe acute respiratory infection when COVID-19 is suspected - Accessed April 27, 2020. https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected. Accessed 27 Apr 2020

8. Le Gall JR, Lemeshow S, Saulnier F (1993) A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA 270:2957–2963

9. Vincent JL, Moreno R, Takala J, et al (1996) The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med 22:707–710

10. Juma S, Taabazuing M-M, Montero-Odasso M (2016) Clinical Frailty Scale in an Acute Medicine Unit: a Simple Tool That Predicts Length of Stay. Can Geriatr J 19:34–39. https://doi.org/10.5770/cgj.19.196

11. Gattinoni L, Tonetti T, Cressoni M, et al (2016) Ventilator-related causes of lung injury: the mechanical power. Intensive Care Med 42:1567–1575. https://doi.org/10.1007/s00134-016-4505-2

12. Sinha P, Calfee CS, Beitler JR, et al (2018) Physiological Analysis and Clinical Performance of the Ventilatory Ratio in Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med. https://doi.org/10.1164/rccm.201804-0692OC

13. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, et al (2012) Acute respiratory distress syndrome: the Berlin Definition. JAMA 307:2526–2533. https://doi.org/10.1001/jama.2012.5669

14. Vincent J-L, Rello J, Marshall J, et al (2009) International study of the prevalence and outcomes of infection in intensive care units. JAMA 302:2323–2329. https://doi.org/10.1001/jama.2009.1754

15. Grambsch PM, Therneau TM (1994) Proportional hazards tests and diagnostics based on weighted residuals. Biometrika 81:515–526. https://doi.org/10.1093/biomet/81.3.515

16. Sterne JAC, White IR, Carlin JB, et al (2009) Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ 338:b2393. https://doi.org/10.1136/bmj.b2393

17. Bellani G, Laffey JG, Pham T, et al (2016) Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. JAMA 315:788–800. https://doi.org/10.1001/jama.2016.0291

18. Wang D, Hu B, Hu C, et al (2020) Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. https://doi.org/10.1001/jama.2020.1585

19. Yang X, Yu Y, Xu J, et al (2020) Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. https://doi.org/10.1016/S2213-2600(20)30079-5

20. Arentz M, Yim E, Klaff L, et al (2020) Characteristics and Outcomes of 21 Critically Ill Patients With COVID-19 in Washington State. JAMA. https://doi.org/10.1001/jama.2020.4326

21. Gattinoni L, Chiumello D, Caironi P, et al (2020) COVID-19 pneumonia: different respiratory treatments for different phenotypes? Intensive Care Med 46:1099–1102. https://doi.org/10.1007/s00134-020-06033-2

22. Grasselli G, Tonetti T, Protti A, et al (2020) Pathophysiology of COVID-19-associated acute respiratory distress syndrome: a multicentre prospective observational study. Lancet Respir Med. https://doi.org/10.1016/S2213-2600(20)30370-2

23. Serpa Neto A, Deliberato RO, Johnson AEW, et al (2018) Mechanical power of ventilation is associated with mortality in critically ill patients: an analysis of patients in two observational cohorts. Intensive Care Med 44:1914–1922. https://doi.org/10.1007/s00134-018-5375-6

24. Gattinoni L, Meissner K, Marini JJ (2020) The baby lung and the COVID-19 era. Intensive Care Med 46:1438–1440. https://doi.org/10.1007/s00134-020-06103-5

25. Schmidt M, Hajage D, Lebreton G, et al (2020) Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome associated with COVID-19: a retrospective cohort study. Lancet Respir Med. https://doi.org/10.1016/S2213-2600(20)30328-3

26. Millar JE, Busse R, Fraser JF, et al (2020) Apples and oranges: international comparisons of COVID-19 observational studies in ICUs. Lancet Respir Med. https://doi.org/10.1016/S2213-2600(20)30368-4

27. Auld SC, Caridi-Scheible M, Robichaux C, et al (2020) Declines in Mortality Over Time for Critically Ill Adults With Coronavirus Disease 2019. Critical Care Medicine. https://doi.org/10.1097/CCM.0000000000004687

28. Alban A, Chick SE, Dongelmans DA, et al (2020) ICU capacity management during the COVID-19 pandemic using a process simulation. Intensive Care Med 46:1624–1626. https://doi.org/10.1007/s00134-020-06066-7

29. Gabarre P, Dumas G, Dupont T, et al (2020) Acute kidney injury in critically ill patients with COVID-19. Intensive Care Med 46:1339–1348. https://doi.org/10.1007/s00134-020-06153-9

30. Azoulay E, Fartoukh M, Darmon M, et al (2020) Increased mortality in patients with severe SARS-CoV-2 infection admitted within seven days of disease onset. Intensive Care Med. https://doi.org/10.1007/s00134-020-06202-3

31. Liu Z, Long W, Tu M, et al (2020) Lymphocyte subset (CD4+, CD8+) counts reflect the severity of infection and predict the clinical outcomes in patients with COVID-19. The Journal of Infection 81:318–356. https://doi.org/10.1016/j.jinf.2020.03.054

32. Zhou F, Yu T, Du R, et al (2020) Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 395:1054–1062. https://doi.org/10.1016/S0140-6736(20)30566-3

33. https://www.santepubliquefrance.fr/les-actualites/2017/etude-esteban-2014-2016-chapitre-corpulence-stabilisation-du-surpoids-et-de-l-obesite-chez-l-enfant-et-l-adulte

34. Green WD, Beck MA (2017) Obesity Impairs the Adaptive Immune Response to Influenza Virus. Ann Am Thorac Soc 14:S406–S409. https://doi.org/10.1513/AnnalsATS.201706-447AW

35. Chait A, den Hartigh LJ (2020) Adipose Tissue Distribution, Inflammation and Its Metabolic Consequences, Including Diabetes and Cardiovascular Disease. Front Cardiovasc Med 7:22. https://doi.org/10.3389/fcvm.2020.00022

36. Gong MN, Bajwa EK, Thompson BT, Christiani DC (2010) Body mass index is associated with the development of acute respiratory distress syndrome. Thorax 65:44–50. https://doi.org/10.1136/thx.2009.117572

37. McLaren L (2007) Socioeconomic status and obesity. Epidemiol Rev 29:29–48. https://doi.org/10.1093/epirev/mxm001

38. Poissy J, Goutay J, Caplan M, et al (2020) Pulmonary Embolism in COVID-19 Patients: Awareness of an Increased Prevalence. Circulation. https://doi.org/10.1161/CIRCULATIONAHA.120.047430

39. Helms J, Tacquard C, Severac F, et al (2020) High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med. https://doi.org/10.1007/s00134-020-06062-x

40. Tang N, Li D, Wang X, Sun Z (2020) Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 18:844–847. https://doi.org/10.1111/jth.14768

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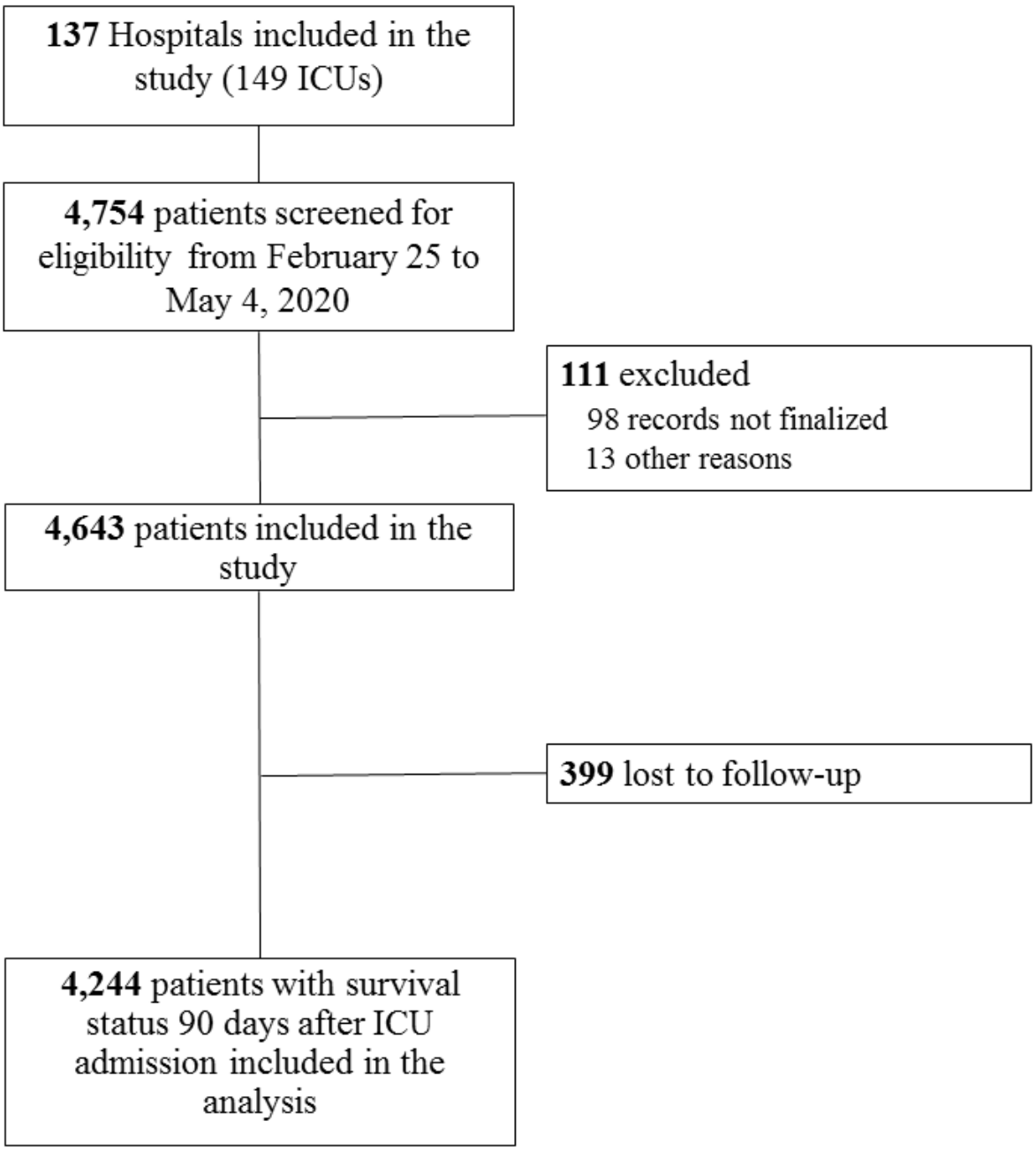
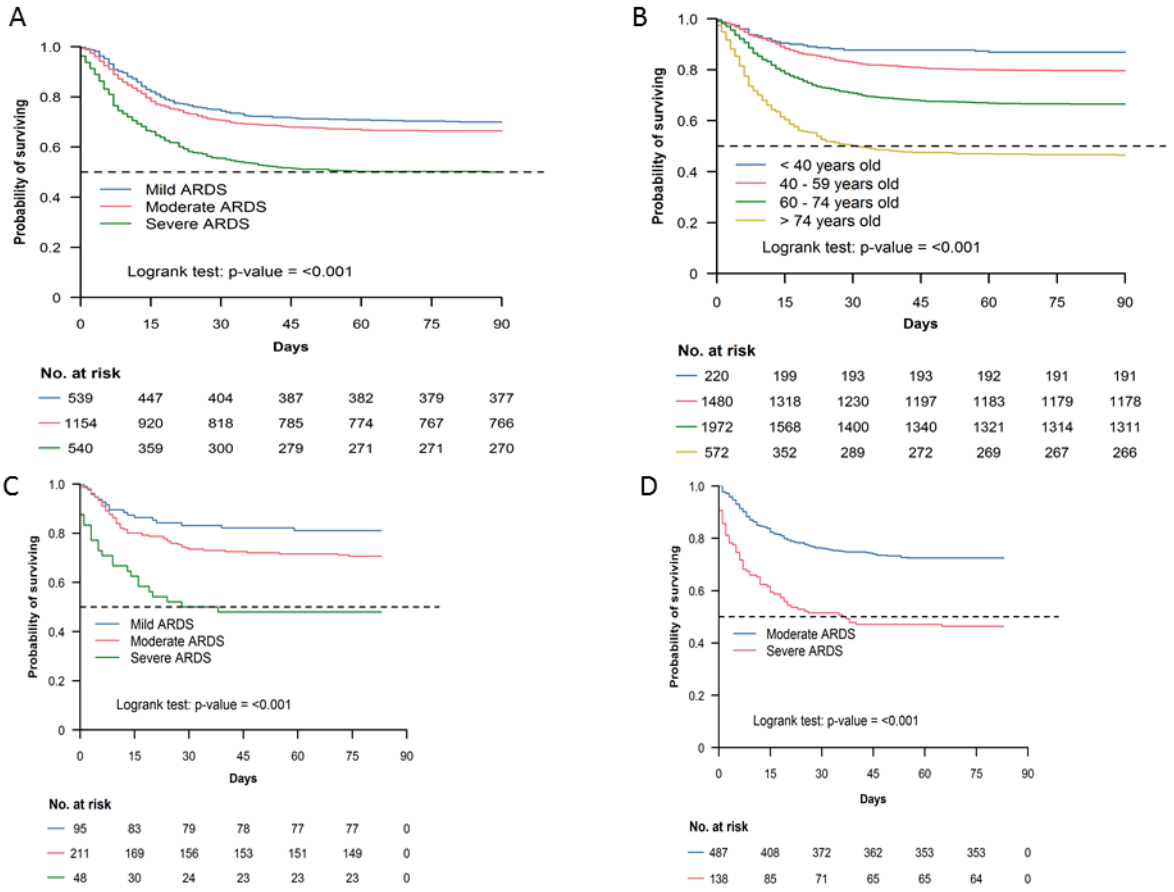
Figure 1: Flow of Patient Screening and Inclusion



ICU, intensive care unit

Figure 2: Kaplan–Meier survival estimates during the 90 days following ICU admission, according to A) Acute Respiratory Distress Syndrome Severity in patients on invasive mechanical ventilation or non-invasive ventilation at Day-1; B) age categories; C) ARDS severity progression within 7 days in patients with mild ARDS at Day-1*; D) their ARDS severity progression within 7 days in patients with moderate ARDS at Day-1

**** only patients alive at day-7 were included in this analysis***



ICU, intensive care unit

Table 1: Demographic, Clinical, and Ventilatory Support Characteristics of 4,244 patients according to their 90-Day Survival Status.

	No.	All patients (n=4,244)	90-Day status		*P* value
			Alive (n=2,946)	Death (n=1,298)	
Age, years,	4,244	63 (54-71)	61 (52-69)	68 (59-74)	<0.001
Women, No (%)	4,226	1,085 (26)	771 (26)	314 (24)	0.170
Body mass index, kg/m^2	3,935	28 (25-32)	29 (26-32)	28 (25-32)	0.006
≥ 30 kg/m^2		1,607 (41)	1,167 (42)	440 (37)	0.004
Active smokers,	4,124	176 (4)	116 (4)	60 (5)	0.234
SAPS II score,	3,935	37 (28-50)	34 (27-46)	44 (33-58)	<0.001
SOFA score at ICU admission,	3,676	5 (3-8)	4 (3-8)	7 (4-10)	<0.001
Treated hypertension	4,197	2,018 (48)	1,310 (45)	708 (55)	<0.001
Known diabetes	4,196	1,167 (28)	704 (24)	463 (36)	<0.001
Immunodeficiency [a]	4,192	314 (7)	178 (6)	136 (11)	<0.001
Long term corticosteroids [b]	4,178	178 (4)	94 (3)	84 (7)	<0.001
Clinical frailty scale,	3,152	2 (2-3)	2 (2-3)	3 (2-4)	<0.001
Time between :					
First symptoms to ICU admission, days	4,007	9 (6-12)	9 (7-12)	8 (5-11)	<0.001
ICU admission to invasive MV, hours	2,010[c]	8 (1-27)	9 (1-27)	7 (1-29)	0.482
During the first 24 hours in ICU [b]					
Standard oxygen therapy	4,157	1,219 (29)	927 (32)	292 (23)	<0.001
High-flow oxygen	4,096	786 (19)	584 (21)	202 (16)	<0.001
Noninvasive ventilation	4,109	230 (6)	134 (5)	96 (8)	<0.001
Invasive mechanical ventilation	4,175	2,635 (63)	1,678 (58)	957 (75)	<0.001
PaO_2/FiO_2	2,500	154 (106-223)	163 (116-229)	136 (91-206)	<0.001
VT, mL/kg PBW	2,306	6.1 (5.8-6.7)	6.1 (5.8-6.6)	6.1 (5.7-6.7)	0.652
Set PEEP, cm H_2O	2,542	12 (10-14)	12 (10-14)	12 (10-14)	0.429
Plateau pressure, cmH_2O	1,847	24 (21-27)	24 (21-26)	25 (21-28)	<0.001
Driving pressure, cmH_2O [d]	2,256	13 (10-17)	12 (10-16)	14 (11-18)	<0.001
Static compliance, mL/ cmH_2O [e]	1,746	33 (26-42)	34 (27-43)	32 (24-41)	<0.001
< 30		635 (36)	367 (33)	268 (43)	<0.001
30-39		562 (32)	380 (34)	182 (29)	
≥ 40		549 (31)	376 (33)	173 (28)	
Dynamic compliance, mL/ cmH_2O [f]	409	17 (14-25)	18 (14-26)	17 (13-22)	0.010
Mechanical power, J/min [g]	1,987	26.5 (18.6 -34.9)	26.1 (18.4-34.2)	27.1 (18.9-36.1)	0.120
Ventilatory ratio [h]	2,251	1.7 (1.4-2.2)	1.7 (1.4-2.1)	1.8 (1.4-2.3)	0.017
Concomitant bacterial pneumonia	4,116	208 (5)	138 (5)	70 (6)	0.298

Hemodynamic component of the SOFA,	4,065	1 (0-4)	0 (0-3)	3 (0-4)	<0.001
Renal component of the SOFA,	4,014	0 (0-1)	0 (0-0)	0 (0-1)	<0.001
Corticosteroids [i]	4,134	459 (11)	278 (10)	181 (14)	<0.001
Blood gases					
pH	4,003	7.41 (7.34-7.46)	7.43 (7.36-7.47)	7.38 (7.30-7.44)	<0.001
$PaCO_2$, mmHg	4,004	40 (35-46)	39 (35-45)	41 (35-49)	<0.001
PaO_2/FiO_2 [j]	3,080	154 (103-222)	162 (112-227)	134 (90-205)	<0.001
HCO_3, mmol/L	3,942	25 (22-27)	25 (23-27)	24 (21-27)	<0.001
Lactate, mmol/L	3,795	1.2 (0.9-1.6)	1.2 (0.9-1.5)	1.3 (1.0-1.8)	<0.001
Biology					
Lymphocyte count, $\times 10^9$/L	3,481	0.8 (0.6-1.2)	0.8 (0.6-1.2)	0.8 (0.5-1.1)	<0.001
Platelet count, $\times 10^9$/L	3,867	224 (167-291)	230 (176-299)	205 (151-271)	<0.001
Total bilirubin, µmol/L	3,029	10 (7-14)	10 (7-14)	10 (7-16)	0.210
Serum creatinine, µmol/L	3,915	78 (61-112)	73 (59-98)	94 (69-152)	<0.001
D-dimers, µg/L	1,697	1,600 (897-3,690)	1,450 (843-3,212)	2,200 (1,127-5,516)	<0.001

Abbreviations: FiO_2, fraction of inspired oxygen; HCO3, bicarbonate; PEEP, positive end-expiratory pressure; $PaCO_2$, partial pressure of carbon dioxide; PBW, predicted body weight;PaO_2, partial pressure of oxygen; SAPS, simplified acute physiology score; SOFA, Sequential Organ Failure Assessment; VT, tidal volume.
Results are expressed as n (%) or median (25^{th} - 75^{th} percentiles).

[a] *defined as hematological malignancies, active solid tumor, or having received specific anti-tumor treatment within a year, solid-organ transplant, human immunodeficiency virus, or immunosuppressants.*
[b] *several ventilation modalities could have been used during the first 24 hours*
[c] *Time of intubation was available for 1,939/3,280 patients with invasive mechanical ventilation during their ICU stay*
[d] *defined as plateau pressure - PEEP; If plateau pressure was missing, peak pressure was considered instead*
[e] *defined as tidal volume /(Plateau pressure – PEEP)*
[f] *defined as tidal volume /(Peak pressure – PEEP)*
[g] *Mechanical power (J/min)=0,098 × tidal volume × respiratory rate × (peak pressure – 1/2 × driving pressure). If not specified, peak pressure was considered equal to plateau pressure.*
[h] *defined as (minute ventilation × PaCO2) – (predicted bodyweight × 100 × 37,5)*
[i] *irrespective of the dose and the indication*
[j] *calculated for all patients, including those on oxygen therapy by using conversion tables provided in the online supplement*

Table 2: Use of Adjunct Measures, organ dysfunction and Major Complications according to Acute Respiratory Distress Syndrome Severity for patients on mechanical ventilation (invasive or non-invasive) on ICU day 1.

Parameter	No.	All [a] (n=2,233)	Mild ARDS[b] (n=539)	Moderate ARDS[c] (n=1,154)	Severe ARDS[d] (n=540)	*P* Value
Ventilatory features on Day-1						
Plateau pressure, cmH_2O	1,617	24 (21-27)	24 (21-26)	24 (21-27)	25 (22-28)	<0.001
Driving pressure, cmH_2O [e]	1,965	13 (10-17)	12 (10-15)	13 (10-18)	14 (11-18)	<0.001
Static compliance, mL/cmH_2O [f]	1,531	33 (26-42)	36 (29-44)	33 (26-42)	30 (24-37)	<0.001
Mechanical power, J/min [g]	1,735	26.6 (18.7-34.9)	24.9 (18.3-33.3)	26.4 (18.5-34.4)	29.1 (20.3-37.6)	0.001
Tracheotomy	2,229	198 (9)	53 (10)	107 (9)	38 (7)	0.207
Prone position	2,223	1,556 (70)	308 (57)	822 (71)	426 (79)	<0.001
Number of session	1,553	3 (2-6)	3 (2-6)	3 (2-6)	3 (2-6)	0.585
Continuous neuromuscular blockers	2,224	1,966 (88)	441 (82)	1,025 (89)	500 (93)	<0.001
Nitric oxide	2,224	425 (19)	74 (14)	206 (18)	145 (27)	<0.001
Corticosteroids [h]	2,224	888 (41)	192 (37)	458 (41)	238 (46)	0.012
ECMO	2,153	235 (11)	41 (8)	111 (10)	83 (15)	<0.001
Cardiac arrest	2,227	133 (6)	31 (6)	58 (5)	44 (8)	0.038
Thromboembolic complications	2,226	373 (17)	107 (20)	174 (15)	92 (17)	0.043
Pulmonary embolism		207 (9)	59 (11)	95 (8)	53 (10)	0.872
Proven distal venous thrombosis		184 (8)	54 (10)	89 (8)	41 (8)	0.567
Renal replacement therapy	2,227	623 (28)	135 (25)	320 (28)	168 (31)	0.080
Bacterial coinfection	1,951	144 (7)	24 (5)	84 (8)	36 (8)	0.062
Ventilator associated pneumonia	2,101	1,209 (58)	276 (54)	628 (58)	307 (61)	0.084

Definition of abbreviations: ECMO, extracorporeal membrane oxygenation *Results are expressed as n (%) or median (25^{th} - 75^{th} percentiles).*

[a] *Only patients on invasive mechanical ventilation or non-invasive ventilation within the first 24 hours in ICU*
[b] *defined as 200 mmHg < $PaO_2/FIO_2 \leq 300$ mmHg with PEEP ≥5 cm H_2O or continuous positive airway pressure ≥5 cm H_2O*
[c] *defined as 100 mmHg < $PaO_2/FIO_2 \leq 200$ mmHg with PEEP ≥ 5 cm H_2O*
[d] *defined as $PaO_2/FIO_2 \leq 100$ mmHg with PEEP ≥ 5 cm H_2O*
[e] *defined as plateau pressure - PEEP; If plateau pressure was missing, peak pressure was considered instead*
[f] *defined as tidal volume / (plateau pressure – PEEP)*

[g] *Mechanical power (J/min)=0,098 × tidal volume × respiratory rate × (peak pressure – 1/2 × driving pressure). If not specified, peak pressure was considered equal to plateau pressure.*

[h] *Irrespective of the indication, the dose, and the timing*

Table 3: Outcome of patients on mechanical ventilation (invasive or non-invasive) according to Acute Respiratory Distress Syndrome Severity assessed the first day in the ICU

Parameter	No.	All [a] (n=2,233)	Mild ARDS [b] (n=539)	Moderate ARDS [c] (n=1,154)	Severe ARDS [d] (n=540)	*P* Value[e]
Progression of ARDS severity, No (%) [95 CI]	2,233	2,233	539 (24) [22 - 26]	1,154 (52) [50 - 54]	540 (24) [22 - 26]	
Progression to moderate [c]			237 (44) [40 - 48]	-	-	
Progression to severe [d]			64 (12) [9 - 15]	183 (16) [14 - 18]	-	
Duration of invasive ventilation, days	1,448					
All patients		12 (7-17)	11 (6-17)	12 (7-17)	11 (6-17)	0.021
Surviving patients at day-90		13 (8-18)	12 (6 - 18)	14 (8-18)	14 (10-19)	0.007
ICU length of stay, days	2,187					
All patients		16 (9-28)	15 (8 - 27)	17 (9 - 28)	16 (8 - 30)	0.149
Surviving patients at day-90		21 (13-36)	18 (10 - 31)	21 (13 - 35)	26 (16 - 43)	<0.001
ICU mortality	2,214	773 (35)	146 (27)	366 (32)	261 (49)	<0.001
Hospital length of stay, days	2,041					
All patients		23 (12-39)	22 (13 - 39)	24 (13 - 40)	22 (9 - 36)	0.002
Surviving patients at day-90		30 (20-48)	28 (17 - 47)	31 (20 - 47)	32 (23 - 49)	0.012
Hospital mortality	2,086	797 (38)	154 (30)	375 (35)	268 (53)	<0.001
Still in the hospital at day-28		1,152 (53)	286 (54)	628 (56)	238 (45)	<0.001
Day-28 mortality	2,233	703 (31)	134 (25)	331 (29)	238 (44)	<0.001
Day-60 mortality	2,233	808 (36)	157 (29)	382 (33)	269 (50)	<0.001
Day-90 mortality	2,233	820 (37)	162 (30)	388 (34)	270 (50)	<0.001

Definition of abbreviations: ARDS, acute respiratory distress syndrome; ICU, intensive care unit. Results are expressed as n (%) or median (25^{th} - 75^{th} percentiles).

[a] *Only patients on invasive mechanical ventilation or non-invasive ventilation within the first 24 hours in the ICU*
[b] *defined as 200 mmHg < $PaO_2/FIO_2 \leq 300$ mmHg with PEEP ≥5 cm H_2O or continuous positive airway pressure ≥5 cm H_2O*
[c] *defined as 100 mmHg < $PaO_2/FIO_2 \leq 200$ mmHg with PEEP ≥ 5 cm H_2O*
[d] *defined as $PaO_2/FIO_2 \leq 100$ mmHg with PEEP ≥ 5 cm H_2O*
[e] *p global value*

Table 4: Predictive Patient Factors Associated with 90-day mortality in critically ill adults with COVID-19.

	No.	Univariate HR (95% CI)	*P* value	Multivariate HR (95% CI) [a]	*P* value
Age, years	4,244	1.05 (1.04 - 1.05)	<0.001	1.05 (1.04 - 1.06)	<0.001
Date of ICU admission	4,244		<0.001		0.311
Before March, 15		–		–	
From March, 16 to 31		0.69 (0.56 - 0.84)		0.86 (0.64 - 1.16)	
From April, 1 to 15		0.61 (0.50 - 0.76)		0.75 (0.54 - 1.04)	
After April, 16		0.54 (0.40 - 0.72)		0.82 (0.52 - 1.29)	
Immunodeficiency	4,192	1.64 (1.38 - 1.96)	<0.001	1.38 (1.06 - 1.80)	0.020
Body mass index, kg/m^2 [b]	3,935		0.013		0.007
<25		–		–	
25≤BMI< 30		0.92 (0.68 - 1.25)		1.06 (0.78 - 1.43)	
		0.77 (0.57 - 1.03)		0.81 (0.60 - 1.10)	
30 ≤BMI< 35		0.94 (0.68 - 1.29)		1.11 (0.80 - 1.55)	
		0.59 (0.42 - 0.83)		0.63 (0.44 - 0.89)	
35 ≤BMI< 40		1.16 (0.79 - 1.69)		1.50 (1.02 - 2.21)	
		0.49 (0.30 - 0.79)		0.60 (0.37 - 0.97)	
≥40		1.47 (0.93 - 2.33)		2.05 (1.28 - 3.27)	
		0.60 (0.32 - 1.14)		0.87 (0.45 - 1.66)	
Active smoking [b]	3,935	1.51 (0.96 - 2.36)	0.225	1.30 (0.82 - 2.05)	0.314
		0.87 (0.45 - 1.70)		0.71 (0.36 - 1.39)	
Treated hypertension	4,197	1.44 (1.29 - 1.60)	<0.001	1.01 (0.85 - 1.19)	0.940
Known diabetes	4,196	1.62 (1.44 - 1.81)	<0.001	1.51 (1.28 - 1.78)	<0.001
Time between first symptoms to ICU admission, days	3,862		<0.001		0.010
< 4 days		–		–	
4 to 7 days		0.87 (0.65 - 1.16)		1.07 (0.80 - 1.43)	
≥ 8 days		0.52 (0.39 - 0.70)		0.73 (0.54 - 0.98)	
During the first 24-hours in the ICU					
CV component of the SOFA score ≥ 3	4,065	1.77 (1.58 - 1.98)	<0.001	1.79 (1.52 - 2.11)	<0.001
Renal component of the SOFA score ≥ 3 [b]	4,014	3.01 (2.30 - 3.92)	<0.001	2.38 (1.81 - 3.13)	<0.001
		1.66 (1.11 - 2.48)		1.32 (0.87 - 2.01)	
Coagulation component of the SOFA score ≥ 3	4,002	2.01 (1.21 - 3.34)	0.016	1.73 (0.81 - 3.69)	0.190
PaO_2/FiO_2 [c]	3,080		<0.001		<0.001
200 < PaO_2/FiO_2 ≤ 300		0.94 (0.72 - 1.21)		0.93 (0.67 - 1.29)	
100 < PaO_2/FiO_2 ≤ 200		1.09 (0.87 - 1.38)		1.12 (0.83 - 1.51)	
PaO_2/FiO_2 ≤ 100		1.73 (1.36 - 2.19)		2.05 (1.51 - 2.78)	
Lymphocyte count ≤ 1 × 10^9/L [b]	3,481	0.92 (0.75 - 1.14)	0.008	0.80 (0.65 - 0.99)	0.030
		1.46 (1.14 - 1.88)		1.24 (0.96 - 1.60)	

pH	4,003	0.67 (0.60 - 0.75)	<0.001	0.80 (0.65 - 0.97)	0.065

BMI, body mass index; CV, cardiovascular; SOFA, Sequential Organ Failure Assessment; ICU, intensive care unit; HR, hazard ratio; CI, confidence interval
[a] *complete analysis cases on 2,152 patients*
[b] *early effect before 14 days of follow-up (first line); late effects (i.e after day-15) in the second line*
[c] *calculated for all patients, including those on oxygen therapy by using conversion tables provided in the online supplement*

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Online Supplement

Clinical Characteristics and Day-90 Outcomes of 4,244 critically ill adults with COVID-19: a prospective cohort study

COVID-ICU group, for the REVA network
and the COVID-ICU investigators*

Description of the statistical methods plan

COVID-ICU is a multi-center, prospective cohort study. The main objective was to describe characteristics, ventilation management and the outcomes of ICU patients with laboratory-confirmed COVID-19 and to determine risk factors of 90-day post-ICU admission mortality.

1. FLOW CHART

A flow chart will be performed to describe the recruitment and the follow-up of the whole study population.

2. DESCRIPTIVE ANALYSIS

Categorical variables will be described as frequencies and percentages, and quantitative variables as mean and standard deviation or median and interquartile range.
Kaplan-Meier overall survival curves until Day 90 will be computed. The median length of stay in ICU and in hospital will also be estimated using a Kaplan-Meier estimator to take into account patients still in ICU at the time of the analysis.

3. PRIMARY ANALYSIS

Risk factors of death at Day 90 will be assessed within the whole cohort using univariate and multivariate Cox regression models. Variables included in the multivariate model will comprise age [1], SOFA Cardiovascular system, SOFA Coagulation, SOFA Renal [2], the delay between first signs and ICU admission [3], immunodepression, active smoking, body mass index, treated hypertension, diabetes, lymphopenia, pH, and PaO_2/FiO_2 [4]. No variable selection will be performed.

- Based on the body mass index (BMI), five categories will be created: normal range (BMI<25), overweight range (BMI 25-30), obesity class 1 (BMI 30-35), obesity class 2 (BMI 35-40), obesity class 3 or extreme obesity (BMI ≥ 40),
- Based on the Berlin ARDS definition, three categories will be created with the PaO_2/FiO_2 ratio.
- A SOFA cardiovascular system ≥ 3 will identify a severe cardiovascular failure
- A SOFA renal ≥ 3 will identify a severe renal failure
- A SOFA coagulation ≥ 3 will identify a severe coagulation dysfunction
- Severe lymphopenia will be defined as lymphocyte ≤ 1 x10^9/L
- The time between first symptoms to ICU admission will be split into 3 periods: ≤ 4 days; 4 to 7 days, and ≥ 8 days.

Hazard ratios and their 95% confidence interval will be estimated. Proportional hazard assumption will be assessed by inspecting the scaled Shoenfeld residuals and Harrel's test [5].
Multiple imputations by chained equations (MICE) technique will be used to replace missing values when appropriate, assuming that missing data are missing at random:

Variables used in the imputation phase

Age, SOFA Cardiovascular system ≥ 3, SOFA Coagulation≥ 3, SOFA Renal≥ 3, delay between first signs and ICU admission, immunodepression, body mass index, treated hypertension, diabetes, lymphopenia, pH, PaO_2/FiO_2, ICU admission period.

Procedure chosen and software used

Multiple-imputation analyses using chained equations procedure, with linear imputation for continuous variables and logistic or multinomial regression for categorical variables. Analyses will performed using the R software and the mice package.

Number of imputations: 10

Pooling procedures for analysis

Results from each imputed datasets will be pooled using Rubin's rules to obtain overall estimates and their standard errors.

4. SECONDARY ANALYSES

For the secondary outcomes, categorical variables will be compared by Chi-square test or Fisher's exact test, as appropriate. Continuous variables will be compared by Student's t-test or Wilcoxon's rank-sum test, as appropriate, if two groups will be compared, and one way ANOVA analysis or Kruskall-Wallis test, as appropriate, if more than two groups will be compared. The 95% confidence

intervals for the proportions will be estimated based on binomial distribution. Kaplan-Meier overall survival curves until Day 90 will be compared by log-rank tests.

5. STATISTICAL SIGNIFICANCE LEVEL

All statistical tests will be performed with 5% significance level.

6. STATISTICAL SOFTWARE

All analyses will be performed with R software version 3.5.1 including mice package.

7. POST-HOC ANALYSES (16/06/2020)

A sensitivity analysis will be performed using a Cox model stratified on the follow-up center variable.

8. POST-HOC ANALYSES (02/10/2020)

Risk factors of death at Day 90 will be assessed within the whole cohort using univariate and multivariate Cox models, with the "ICU admission periods" entered in the model.

ICU admission will be split into four calendar periods of approximately equal duration (Before March 15, From March 16 to 31, From April 1 to 15, after April 16).

References:

1. Grasselli G, Zangrillo A, Zanella A, et al (2020) Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. JAMA. https://doi.org/10.1001/jama.2020.5394

2. Gabarre P, Dumas G, Dupont T, et al (2020) Acute kidney injury in critically ill patients with COVID-19. Intensive Care Med 46:1339–1348. https://doi.org/10.1007/s00134-020-06153-9

3. Azoulay E, Fartoukh M, Darmon M, et al (2020) Increased mortality in patients with severe SARS-CoV-2 infection admitted within seven days of disease onset. Intensive Care Med. https://doi.org/10.1007/s00134-020-06202-3

4. Bellani G, Laffey JG, Pham T, et al (2016) Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. JAMA 315:788–800. https://doi.org/10.1001/jama.2016.0291

5. Grambsch PM, Therneau TM (1994) Proportional hazards tests and diagnostics based on weighted residuals. Biometrika 81:515–526. https://doi.org/10.1093/biomet/81.3.515

Estimating FiO_2 from a given O_2 flow

Method	O_2 flow (l/min)	Estimated FiO2 (%)
Nasel cannula	1	24
	2	28
	3	32
	4	36
	5	40
	6	44
Nasopharyngeal catheter	4	40
	5	50
	6	60
Face mask	5	40
	6-7	50
	7-8	60
Face mask with reservoir	6	60
	7	70
	8	80
	9	90
	10	95

Table S1 : Main characteristics of the 149 participating intensive care units

Hospital type	
University	71 (48)
Public regional	66 (44)
Semi-private	7 (5)
Private / Military	5 (3)
ICU type	
Medical	41 (28)
Surgical	14 (10)
Medical-surgical	82 (57)
Neuro-surgical	3 (2)
Cardiac and thoracic	3 (1)
Other	1 (1)
Number of ICU beds in the hospital	26 (18-55)
Number of ICU beds in the center	20 (14-28)
Number of attending physicians per ICU	7 (6-9)
Number of residents per ICU	6 (4-8)
Number of nurses per ICU	39 (28-54)

Table S2 : Number of patients per center included in this cohort of 4,244 patients

Number of patients included	Number of centers (N=138)
1 to 10 patients	37 (27%)
11 to 20 patients	30 (22%)
21 to 30 patients	22 (16%)
31 to 40 patients	10 (7%)
> 40 patients	39 (28%)

Table S3: Number of patients per region included in this cohort of 4,244 patients

Region	Number of patients (%) (N=4,244)
Ile-de-France, France	2,370 (56%)
Hauts-de-France, France	260 (6%)
Auvergne-Rhône-Alpes, France	255 (6%)
Grand Est, France	219 (5%)
Provence-Alpes-Côte d'Azur, France	146 (3%)
Pays de la Loire, France	145 (3%)
Nouvelle-Aquitaine, France	145 (3%)
Normandie, France	137 (3%)
Switzerland	128 (3%)
Centre-Val de Loire, France	106 (2%)
Bretagne, France	99 (2%)
Belgium	92 (2%)
Occitanie, France	47 (1%)
Bourgogne-Franche-Comté, France	37 (1%)
Guadeloupe, France	27 (1%)
Martinique, France	18 (0%)
La Réunion, France	12 (0%)
Nouvelle-Calédonie, France	1 (0%)

Table S4: Results of the statistical tests investigating proportional hazard assumption of the multivariate model

A P value < 0.05 was considered as a significant deviation from the proportional hazard assumption (Harrel's test)

Before introduction of a time-varying effect

	P value
Age, years	0.696
ICU admission before March, 15	0.601
ICU admission from March, 16 to 31	0.950
ICU admission from April, 1 to 15	0.744
ICU admission after April, 16	0.283
Immunodeficiency	0.649
Body mass index	0.007
Active smoking	0.042
Treated hypertension	0.090
Known diabetes	0.874
Time between first symptoms to ICU admission, days	0.171
Cardiovascular component of the SOFA score ≥ 3	0.283
Renal component of the SOFA score ≥ 3	0.030
Coagulation component of the SOFA score ≥ 3	0.790
PaO_2/FiO_2	0.152
Lymphocyte count ≤ 1×10^9/L	0.009
pH	0.222
Overall	0.002

After introduction of a time-varying effect for body mass index, active smoking, renal component of the SOFA score and lymphopenia

	P value
Age, years	0.160
ICU admission before March, 15	0.530
ICU admission from March, 16 to 31	0.430
ICU admission from April, 1 to 15	0.810
ICU admission after April, 16	0.750
Immunodeficiency	0.690
Body mass index (< 14 days of follow-up)	0.531
Body mass index (≥ 14 days of follow-up)	0.529
Active smoking (< 14 days of follow-up)	0.216
Active smoking (≥ 14 days of follow-up)	0.327
Treated hypertension	0.290
Known diabetes	0.220
Time between first symptoms to ICU admission, days	0.113
Cardiovascular component of the SOFA score ≥ 3	0.726
Renal component of the SOFA score ≥ 3 (< 14 days of follow-up)	0.540
Renal component of the SOFA score ≥ 3 (≥ 14 days of follow-up)	0.260
Coagulation component of the SOFA score ≥ 3	0.550
PaO_2/FiO_2	0.146
Lymphocyte count ≤ 1×10^9/L (< 14 days of follow-up)	0.670
Lymphocyte count ≤ 1×10^9/L (≥ 14 days of follow-up)	0.340
pH	0.440
Overall	0.640

Table S5: Oxygenation modalities and 90-Day mortality according to four periods of admission in ICU.

	Before March, 15 (n=273)	From March, 16 to 31 (n=2,471)	From April, 1 to 15 (n=1,213)	After April, 16 (n=287)
Oxygen therapy	98 (37)	758 (31)	296 (25)	67 (24)
High-flow oxygen	39 (15)	331 (14)	319 (27)	97 (35)
Non-invasive ventilation	10 (4)	83 (3)	111 (9)	26 (10)
Intubation at Day-1	158 (59)	1654 (68)	692 (58)	146 (52)
Invasive mechanical ventilation during their ICU-stay	222 (82)	2061 (84)	900 (75)	193 (68)
90-Day mortality	114 (42)	766 (31)	345 (28)	73 (25)

Results are expressed as n (%)

Table S6: Acute Respiratory Distress Syndrome Adjunct Measures, organ dysfunction, Major Complications, and length of stay in 4,224 critically-ill patients according to their 90-Day Survival Status.

	No.	All patients (n=4,224)	90-Day status		*P* value
			Alive (n=2,946)	Death (n=1,298)	
Invasive mechanical ventilation	4,209	3,376 (80)	2,175 (74)	1,201 (93)	<0.001
Tracheotomy	4,044	283 (7)	226 (8)	57 (5)	<0.001
Prone position	3,315	2269 (68)	1373 (64)	896 (76)	<0.001
Number of sessions		3 (2-6)	3 (2-6)	4 (2-6)	<0.001
Continuous neuromuscular blockades	3,311	2,892 (87)	1,829 (85)	1,063 (91)	<0.001
Nitric oxide	3,308	593 (18)	272 (13)	321 (27)	<0.001
Corticosteroids [a]	4,176	1,554 (37)	959 (33)	595 (47)	<0.001
Corticosteroids duration, days	1,552	5 (2-8)	5 (2-8)	4 (2-8)	0.488
ECMO	4,187	321 (8)	175 (6)	146 (11)	<0.001
Cardiac arrest	4,183	215 (5)	78 (3)	137 (11)	<0.001
Thromboembolic complications	4,183	600 (14)	390 (13)	210 (17)	0.008
Pulmonary embolism		350 (8)	215 (7)	135 (10)	<0.001
Proven distal venous thrombosis		270 (6)	195 (7)	75 (6)	<0.001
Renal replacement therapy	4,180	929 (22)	458 (16)	471 (37)	<0.001
Ventilator associated pneumonia	3,832	1,893 (49)	1,298 (49)	595 (51)	0.246
Duration of invasive ventilation, days	2,239	11 (7-17)	13 (8-18)	9 (5-15)	<0.001
ICU length of stay, days	4,179	13 (6-25)	14 (7-27)	11 (5-20)	<0.001
Hospital length of stay, days	3,914	20 (12-35)	24 (15-41)	13 (7-22)	<0.001

Definition of abbreviations: ECMO, extracorporeal membrane oxygenation;

[a] *Irrespective of the indication, the dose, and the timing*

Table S7: Outcome of the whole cohort according to invasive mechanical ventilation in the ICU

Parameter	All (n=4,224)	Intubated during their ICU stay (n=3,376)	No intubation (n=810)	*P* Value[e]
Duration of invasive ventilation, days				
All patients	11 (7-17)	11 (7-17)	-	-
Surviving patients at day-90	13 (8-18)	13 (8-18)	-	-
ICU length of stay, days				
All patients	13 (6-25)	17 (9-29)	4 (2-7)	<0.001
Surviving patients at day-90	15 (7-27)	20 (12-33)	4 (2-8)	<0.001
ICU mortality	1,188 (29)	1,133 (34)	55 (7)	<0.001
Hospital length of stay, days				
All patients	20 (12-35)	23 (13-39)	14 (9-19)	<0.001
Surviving patients	24 (15-41)	30 (19-48)	14 (9-20)	<0.001
Hospital mortality	1,260 (32)	1,173 (37)	87 (11)	<0.001
Day-28 mortality	1,106 (26)	1,019 (30)	87 (10)	<0.001
Day-60 mortality	1,272 (30)	1,184 (35)	88 (11)	<0.001
Day-90 mortality	1,289 (31)	1,201 (36)	88 (11)	<0.001

Definition of abbreviations: ARDS, acute respiratory distress syndrome; ICU, intensive care unit.
Results are expressed as n (%) or median (25^{th} - 75^{th} percentiles).

Table S8: Predictive Patient Factors Associated with 90-day mortality in 4,244 critically ill adults with COVID-19 with multiple imputations.

	Multivariate with multiple imputation HR (95% CI) [a]	*P* value
Age, years	1.05 (1.04 - 1.05)	<0.001
Date of ICU admission		0.088
Before March, 15	–	
From March, 16 to 31	0.82 (0.67 - 1.01)	
From April, 1 to 15	0.78 (0.63 – 0.98)	
After April, 16	0.70 (0.52 - 0.94)	
Immunodeficiency	1.50 (1.24 - 1.80)	<0.001
Body mass index, kg/m^2 [b]		0.023
<25	–	
25≤BMI< 30	1.00 (0.82 - 1.24)	
	0.87 (0.70 - 1.09)	
30 ≤BMI< 35	0.96 (0.76 - 1.21)	
	0.66 (0.50 - 0.87)	
35 ≤BMI< 40	1.20 (0.91 - 1.59)	
	0.67 (0.47 - 0.96)	
≥40	1.53 (1.06 - 2.21)	
	0.94 (0.59 - 1.52)	
Active smoking [c]	1.33 (0.98 - 1.83)	0.167
	0.85 (0.53 - 1.36)	
Treated hypertension	0.96 (0.85 - 1.09)	0.564
Known diabetes	1.36 (1.20 - 1.54)	<0.001
Time between first symptoms to ICU admission, days		<0.001
< 4 days	–	
4 to 7 days	0.95 (0.77 - 1.17)	
≥ 8 days	0.62 (0.49 - 0.77)	
During the first 24-hours in the ICU		
CV component of the SOFA score ≥ 3	1.68 (1.50 - 1.88)	<0.001
Renal component of the SOFA score ≥ 3 [b]	2.11 (1.72 - 2.60)	<0.001
	1.22 (0.88 - 1.70)	
Coagulation component of the SOFA score ≥ 3	1.59 (0.95 - 2.66)	0.078
PaO_2/FiO_2 [c]		<0.001
200 < PaO_2/FiO_2 ≤ 300	0.86 (0.66 - 1.12)	
100 < PaO_2/FiO_2 ≤ 200	1.05 (0.85 - 1.31)	
PaO_2/FiO_2 ≤ 100	1.73 (1.38 - 2.17)	
Lymphocyte count ≤ 1 × 10^9/L [b]	0.90 (0.77 - 1.06)	0.088
	1.21 (0.98 - 1.50)	
pH	0.73 (0.65 - 0.83)	<0.001

BMI, body mass index; CV, cardiovascular; SOFA, Sequential Organ Failure Assessment; ICU, intensive care unit; HR, hazard ratio; CI, confidence interval

[a] *multiple imputations on 4,244 patients*
[b] *early effect before 14 days of follow-up (first line); late effects (i.e after day-15) in the second line*
[c] *calculated for all patients, including those on oxygen therapy by using conversion tables provided in the online supplement*

Table S9: Sensitivity analysis: multivariate Cox model stratified on the center variable

	No.	Multivariate HR (95% CI) [a]	*P* value
Age, years	4,244	1.05 (1.04 - 1.06)	<0.001
Date of ICU admission	4,244		0.434
Before March, 15		–	
From March, 16 to 31		0.93 (0.67 - 1.31)	
From April, 1 to 15		0.82 (0.56 - 1.18)	
After April, 16		0.91 (0.55 - 1.50)	
Immunodeficiency	4,192	1.30 (0.98 - 1.73)	0.104
Body mass index, kg/m^2 [a]	3,935		0.007
<25		–	
25≤BMI< 30		1.09 (0.79 - 1.50)	
		0.84 (0.60 - 1.16)	
30 ≤BMI< 35		1.19 (0.84 - 1.68)	
		0.65 (0.45 - 0.95)	
35 ≤BMI< 40		1.50 (0.99 - 2.28)	
		0.74 (0.44 - 1.24)	
≥40		2.02 (1.22 - 3.34)	
		0.90 (0.45 - 1.78)	
Active smoking [a]	3,935	1.03 (0.64 -1.66)	0.794
		0.79 (0.39 - 1.61)	
Treated hypertension	4,197	0.95 (0.79 - 1.14)	0.700
Known diabetes	4,196	1.44 (1.21 - 1.72)	<0.001
Time between first symptoms to ICU admission, d	3,862		0.017
< 4 days		–	
4 to 7 days		0.82 (0.60 - 1.14)	
≥ 8 days		0.61 (0.44 - 0.85)	
During the first 24-hours in the ICU			
CV component of the SOFA score ≥ 3	4,065	1.84 (1.54 - 2.20)	<0.001
Renal component of the SOFA score ≥ 3 [a]	4,014	1.96 (1.45 - 2.66)	<0.001
		0.95 (0.76 - 1.90)	
Coagulation component of the SOFA score ≥ 3	4,002	1.59 (0.71 - 3.54)	0.190
PaO_2/FiO_2 [b]	3,080		<0.001
200 < PaO_2/FiO_2 ≤ 300		1.11 (0.79 - 1.56)	
100 < PaO_2/FiO_2 ≤ 200		1.28 (0.94 - 1.75)	
PaO_2/FiO_2 ≤ 100		2.03 (1.47 - 2.82)	
Lymphocyte count ≤ 1 × 10^9/L [a]	3,481	0.86 (0.69 - 1.08)	0.033
		1.36 (1.04 - 1.78)	
pH	4,003	0.49 (0.35 - 0.67)	0.001

BMI, body mass index; SOFA, Sequential Organ Failure Assessment; ICU, intensive care unit; HR, Hazards ratio; CI, confidence interval

[a] early effect before 14 days of follow-up (first line); late effects (i.e after day-15) in the second line
[b] calculated for all patients, including those on oxygen therapy by using conversion tables provided in the online supplement

Figure S1. Missing data map. Missing values (light blue) by observations on the x-axis and variable on the y-axis

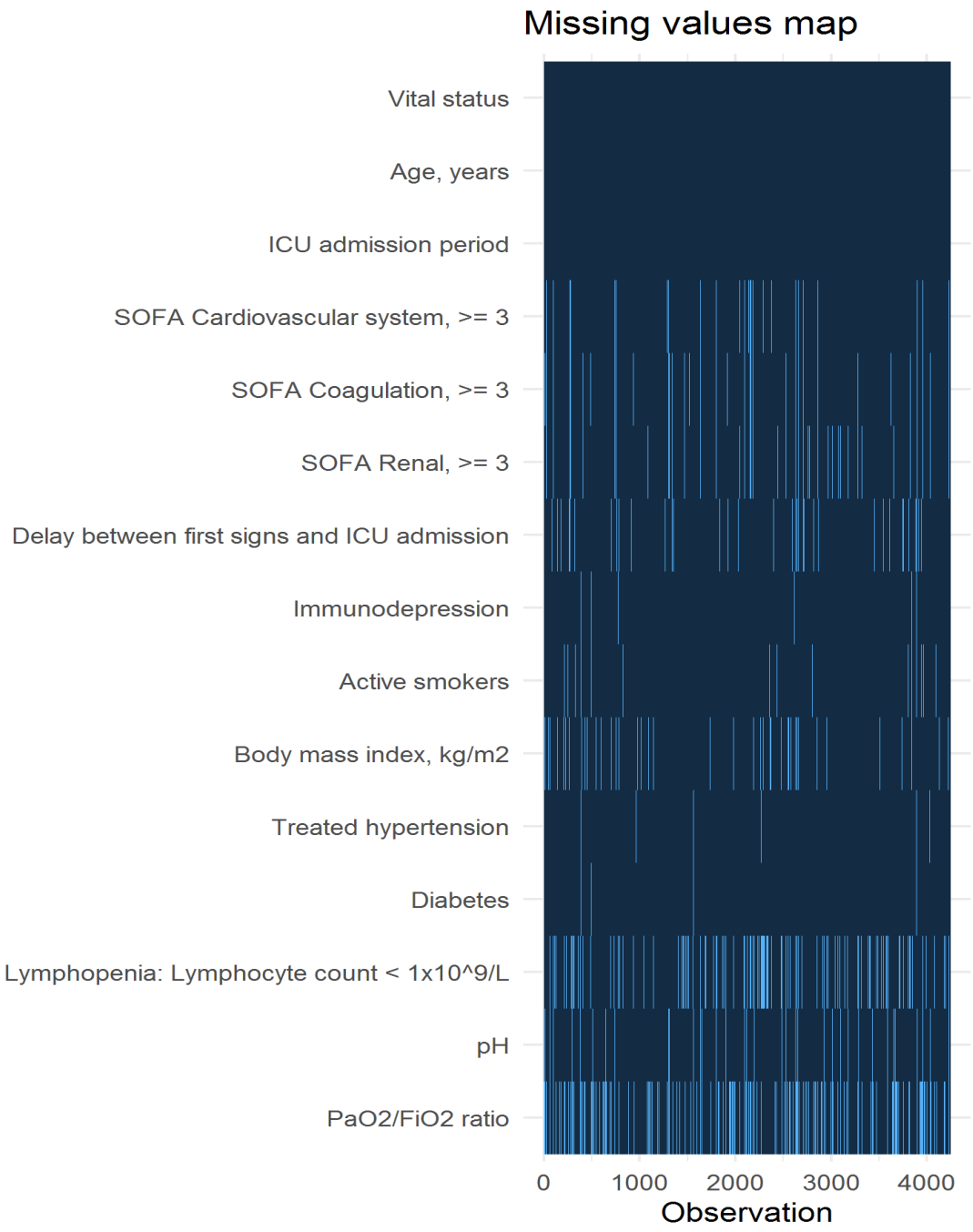
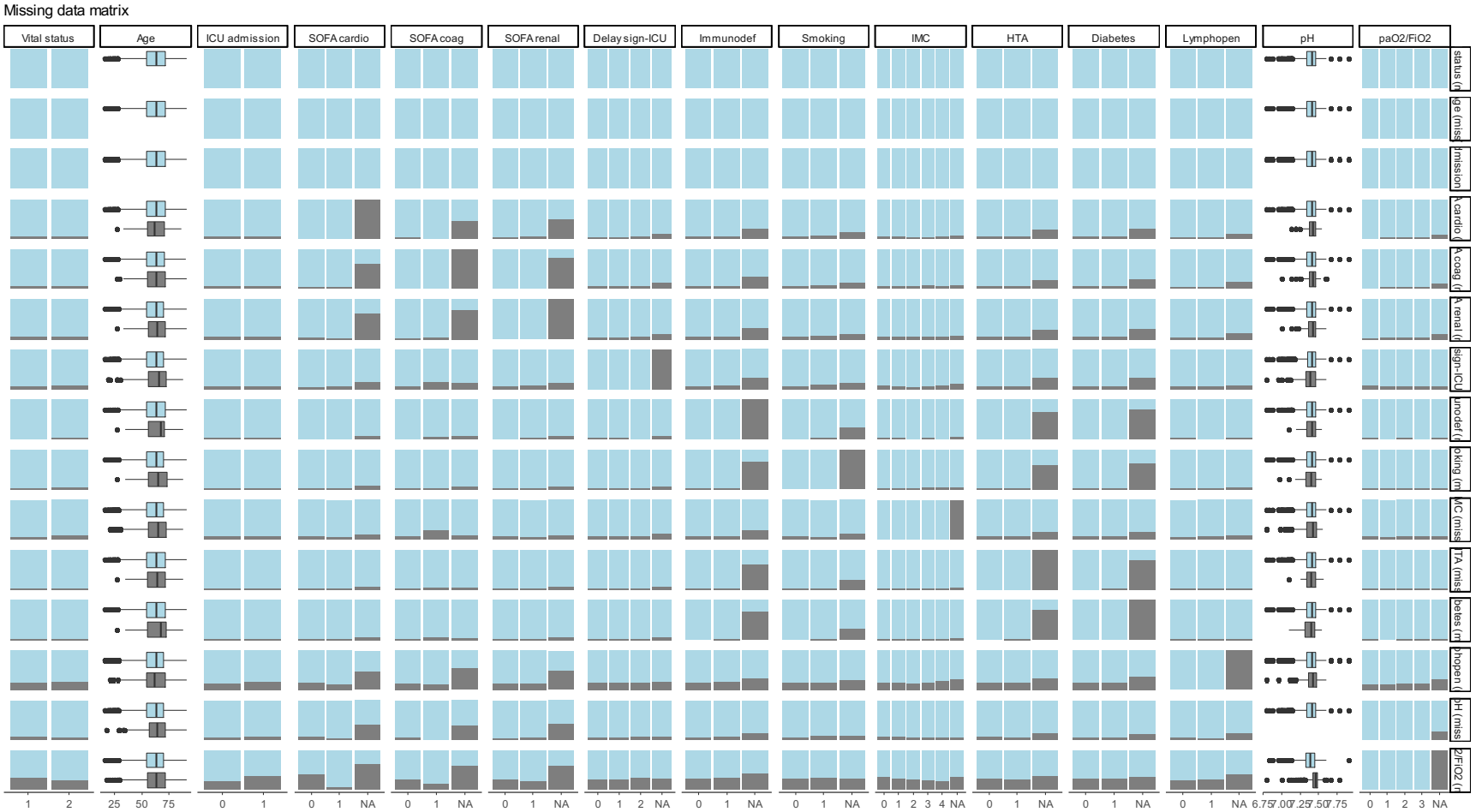


Figure S2. Missing values pairs plot. Compare the occurence of missing values in all variables by each other



For continuous variables (column “age” and “pH”), boxplot according the presence (light blue) or the absence (grey) of the corresponding variable.
For categorical variables, barplot of the proportion of missing values (grey) according to the level of the corresponding variable.

Figure S3: Pourcentage of use of oxygenation modalities and 90-Day mortality according to four time periods of ICU-admission.

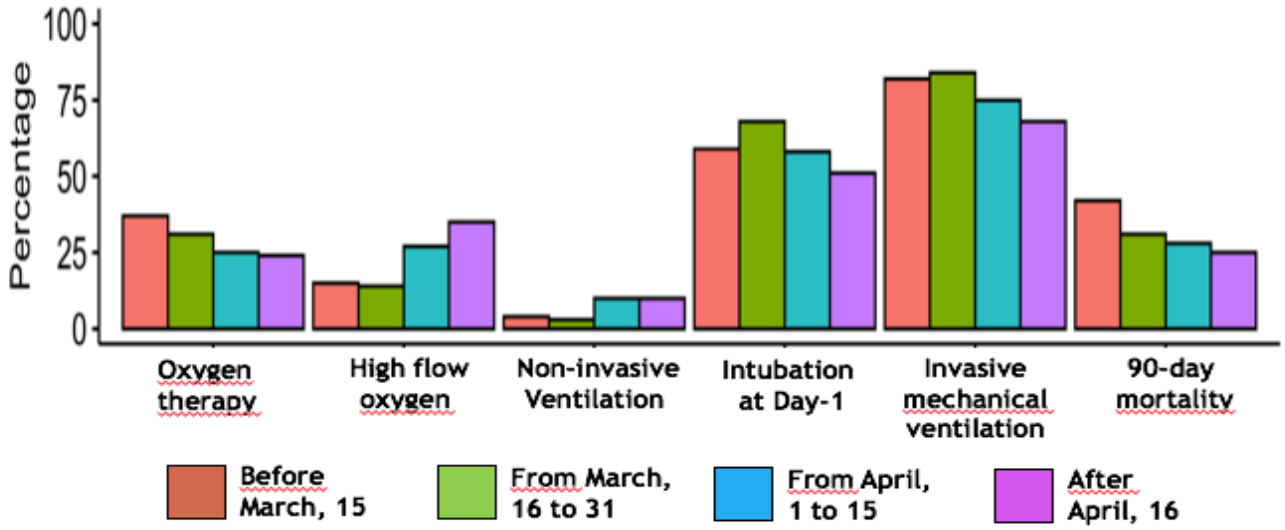


Figure S4. Kaplan–Meier survival estimates during the 90 days following ICU admission, according to the four ICU admission periods.

ICU, intensive care unit

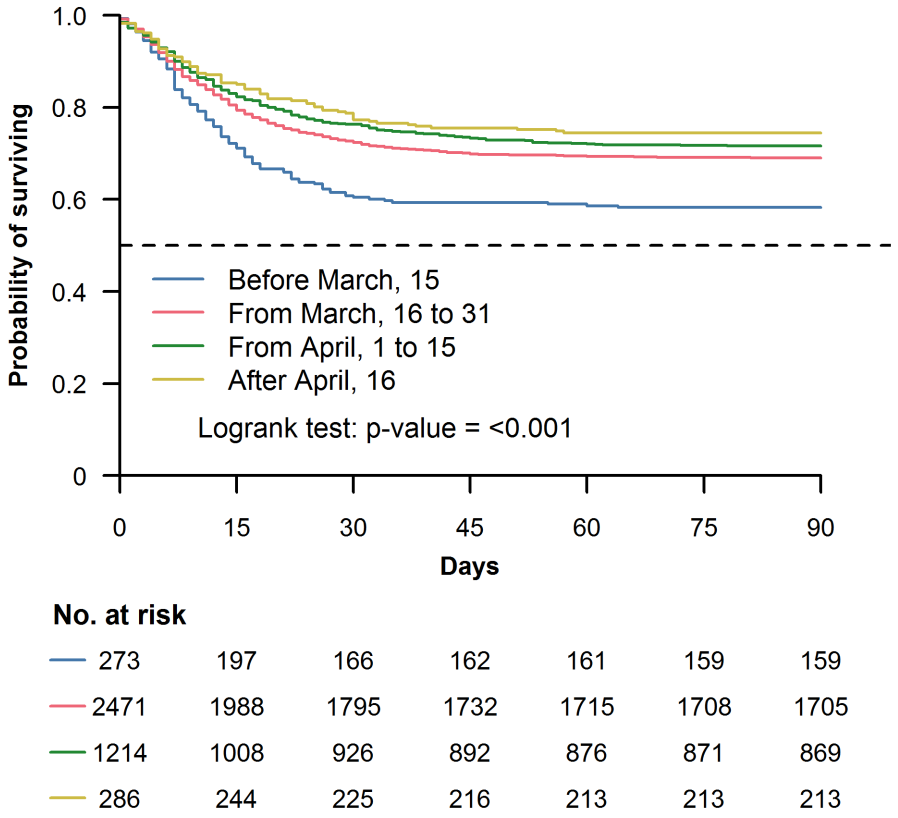


Figure S5. Kaplan–Meier survival estimates during the 90 days following ICU admission, according to the renal component of the SOFA score at ICU admission.

ICU, intensive care unit

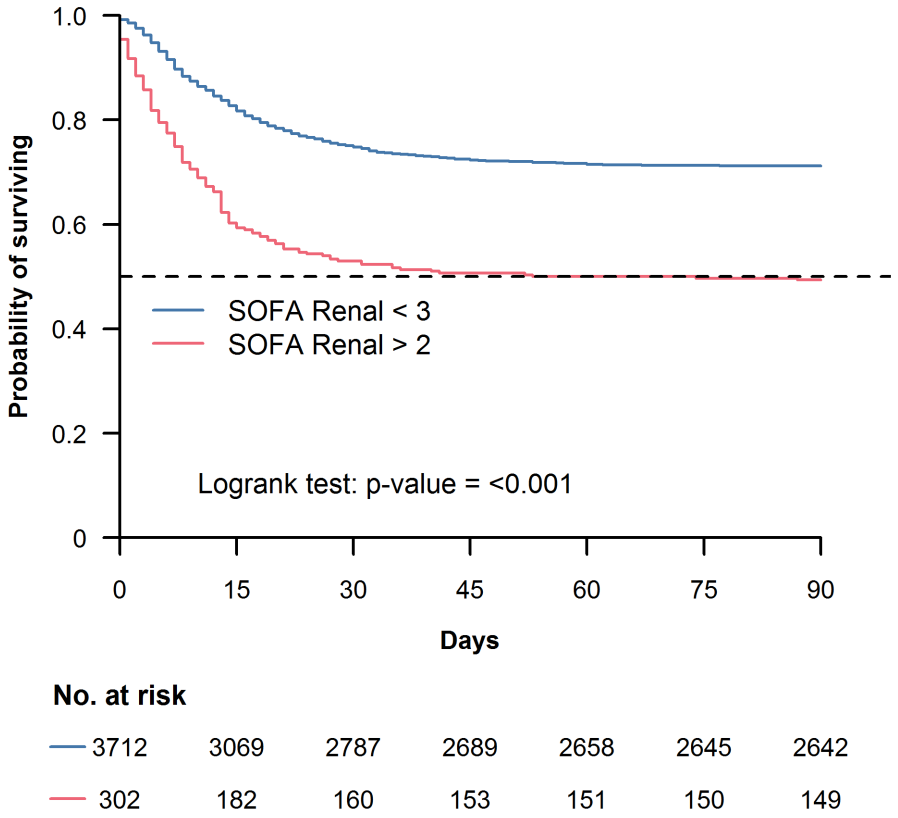


Figure S6. Kaplan–Meier survival estimates during the 90 days following ICU admission, according to the delay between the first symptoms and ICU admission.

ICU, intensive care unit

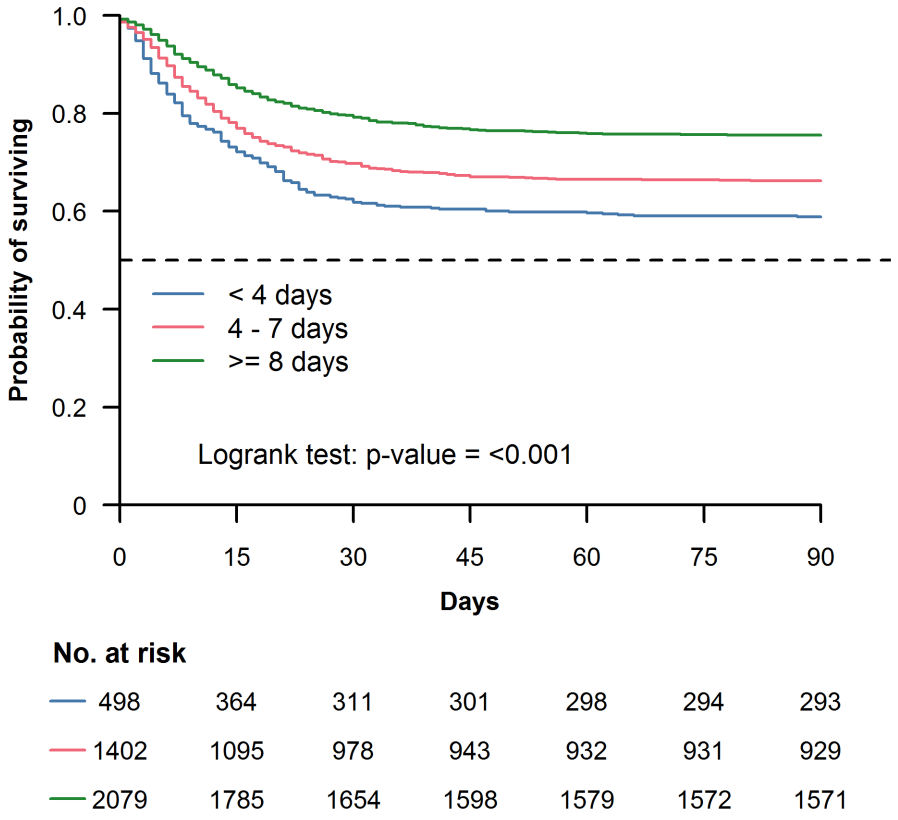


Figure S7. Kaplan–Meier survival estimates during the 90 days following ICU admission, according to immunocompromised status.

ICU, intensive care unit

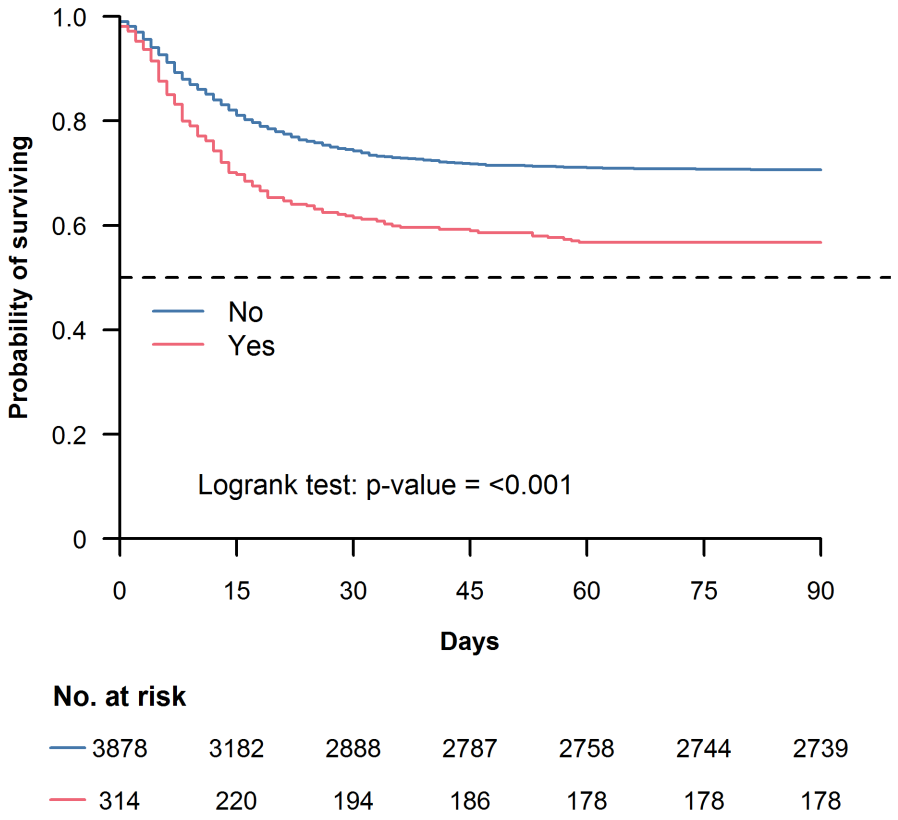


Figure S8. Kaplan–Meier survival estimates during the 90 days following ICU admission, according to diabetes.

ICU, intensive care unit

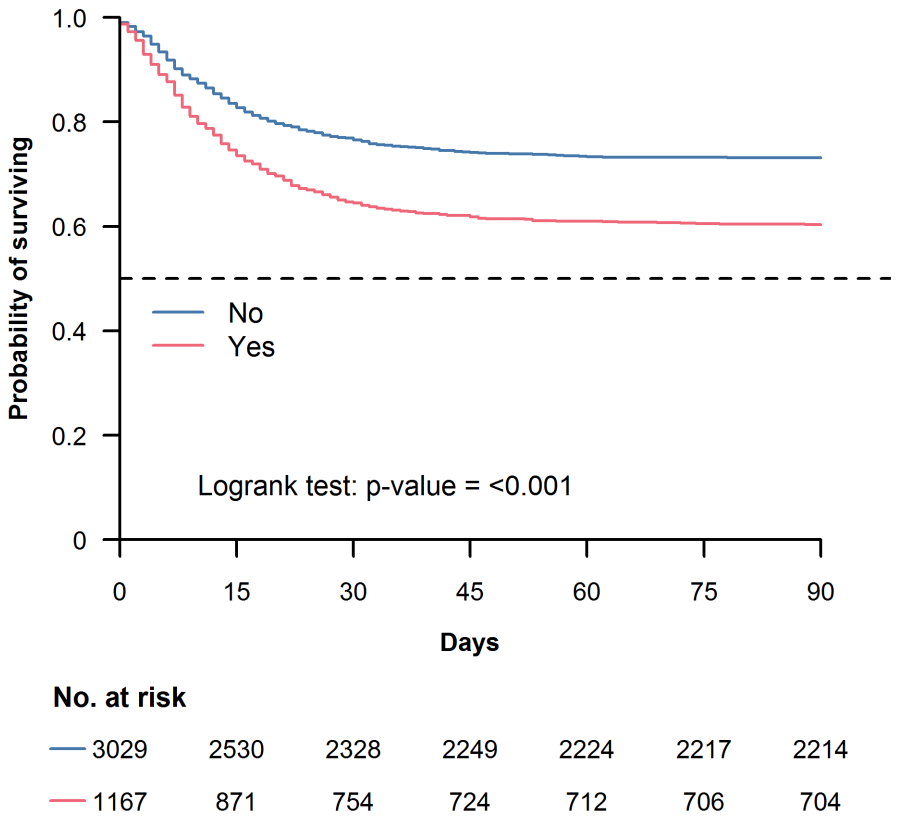


Figure S9. Kaplan–Meier survival estimates during the 90 days following ICU admission, according to severe lymphopenia (≤ 1G/L).

ICU, intensive care unit

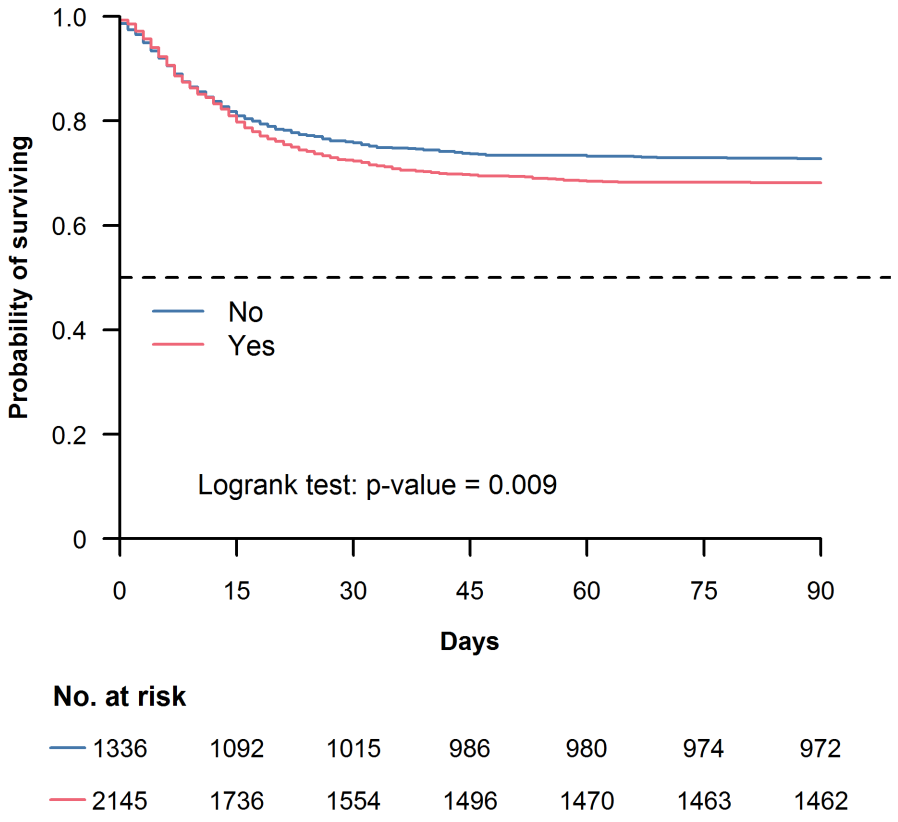


Figure S10. Kaplan–Meier survival estimates during the 90 days following ICU admission, according to static compliance categories at Day-1.

ICU, intensive care unit