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French Multicentre Observational Study on SARS-CoV-2 infections Intensive care initial management: the FRENCH CORONA Study

Claire ROGER[1,2]*, Olivier COLLANGE[3], Myriam MEZZAROBBA[4], Osama ABOU ARAB[5], Lauranne TEULE[6], Marc GARNIER[7], Clément HOFFMANN[8], Laurent MULLER[1,2], Jean-Yves LEFRANT[1,2], Pierre Grégoire GUINOT[9], Emmanuel NOVY[10], Paul ABRAHAM[11], Thomas CLAVIER[12], Jérémy BOURENNE[13], Guillaume BESCH[14], Laurent FAVIER[15], Michel FIANI[16], Alexandre OUATTARA[17], Olivier JOANNES-BOYAU[17], Marc-Olivier FISCHER[18], Marc LEONE[19], Younes AIT TAMLIHAT[20], Julien POTTECHER[21], Pierre-Yves CORDIER[22], Philippe AUSSANT[23], Mouhamed DJAHOUM MOUSSA[24], Etienne HAUTIN[25], Marine BOUEX[26], Jean-Michel JULIA[27], Julien CADY[28], Marc DANGUY DES DÉSERTS[29], Nicolas MAYEUR[30], Thibault MURA[4], Bernard ALLAOUCHICHE[31] for the AZUREA group

[1]Service des Réanimations, Pôle Anesthésie Réanimation Douleur Urgence, CHU Nîmes, Nîmes, France

[2]UR UM103 IMAGINE, Faculté de médecine, Univ Montpellier, Montpellier, France

[3]Service d'Anesthésie-Réanimation, Nouvel Hôpital Civil, Hôpitaux Universitaires de Strasbourg, 67000 Strasbourg, France

[4]Department of Biostatistics, Clinical Epidemiology, Public Health, and Innovation in Methodology, CHU Nîmes, University Montpellier, Nîmes, France

[5]Department of Anaesthesiology and Critical Care Medicine, Amiens Picardie University Hospital, 1 rue du Professeur Christian Cabrol, 80054 Amiens, France

[6]Medical and Surgical Intensive Care Unit, Centre Hospitalier de Perpignan, Perpignan, France

[7]Sorbonne University, GRC29, AP-HP, DMU DREAM, Department of Anaesthesiology and Critical Care Medicine, St Antoine Hospital, Paris, France

[8]Percy Military Teaching Hospital, Burn centre

[9]Anaesthesiology and Critical Care Department, Dijon Bourgogne University Hospital, 2 Bd Maréchal de Lattre de Tassigny, 21000, Dijon, France

[10]Department of Anaesthesiology and Critical Care Medicine, Institut Lorrain du Coeur et des Vaisseaux, University Hospital of Nancy-Brabois, Vandoeuvre-Lès-Nancy, France

[11]Department of Anaesthesiology and Intensive Care Medicine, Edouard Herriot Hospital, Hospices Civils de Lyon, Lyon, France

[12]Department of Anaesthesiology and Critical Care, Rouen University Hospital, Rouen, France; Normandie Univ, UNIROUEN, inserm U1096, 76000 Rouen, France

[13]Department of Emergency and Intensive Care Medicine, University Hospital of Marseille, Hôpital de la Timone, Marseille, France, Aix Marseille University

[14]Department of Anaesthesiology and Intensive Care Medicine, University Hospital of Besançon, Besançon, France; University of Franche-Comte, EA3920, Besançon, France

[15]Service de réanimation polyvalente, centre hospitalier de Béziers, France

[16]Service de réanimation, CH Château Thierry, France

[17]Service d'Anesthésie-Réanimation Sud, Centre Médico-Chirurgical Magellan, Centre Hospitalier Universitaire (CHU) de Bordeaux, 33000 Bordeaux, France

[18]Department of Anaesthesiology and Critical Care, Normandie Université, UNICAEN, CHU de Caen Normandie, 14000 Caen, France

[19]Department of Anaesthesiology and Intensive Care Medicine, Hôpital Nord, Assistance Publique Hôpitaux de Marseille, Aix Marseille University, 13015, Marseille, France

[20]Service de réanimation, CH Saintonge, France

[21]Service d'Anesthésie-Réanimation & Médecine Péri-opératoire, Hôpitaux Universitaires de Strasbourg (HUS), Strasbourg, France; UR 3072, Fédération de Médecine Translationnelle de Strasbourg (FMTS), Université de Strasbourg, Strasbourg, France

[22]Hôpital d'Instruction des Armées Laveran, Marseille, France

[23] Service de réanimation, CH Lisieux, France

[24]CHU Lille, Pôle d'Anesthésie-Réanimation, F-59000, Lille, France

[25]Department of Anaesthesiology and Intensive Care, Ramsay Sante, Clinique de la Sauvegarde, Lyon, France

[26]Service de réanimation, CH Alès, France

[27]Anesthésie et Réanimation, Clinique du Parc, Castelnau-Le-Lez, France

[28]Institut Arnault Tzanck, Saint Laurent du Var, France

[29]Service de Réanimation Polyvalente, Pôle Bloc Anesthésie Réanimation Urgences, Hôpital d'Instruction des Armées Clermont Tonnerre, Brest, France

[30]Department of Anaesthesiology and Intensive Care Unit, Clinique Pasteur, 45 avenue de Lombez BP27617, 31076 Toulouse Cedex 03, France

[31]Centre Hospitalier Lyon-Sud, Hospices Civils de Lyon, Service de Réanimation, 69310, Pierre-Bénite, France

***Corresponding author:** Claire Roger

Department of Anaesthesiology and Intensive Care, Pain and Emergency medicine, Nîmes-Caremeau University Hospital, Place du Professeur Robert Debré, 30029 Nîmes cedex 9, France

Email: claire.roger@chu-nimes.fr

Abbreviations

ICU: intensive care unit
LOS: length of stay
ARDS: acute respiratory distress syndrome
SAPS II: Simplified Acute Physiology Score
SOFA: Sequential Organ Failure Assessment
RRT: renal replacement therapy
ECMO: extra corporeal membrane oxygenation
IMV: invasive mechanical ventilation
NIV: non-invasive ventilation
HFNC: high-flow nasal cannula

Investigators list

Names of the individual members of the FRENCH CORONA study collaborators to be searchable through their individual PubMed records:

Nadiejda Antier, Bruno Langevin (CH Alès)
Nadège Ngapmen, Habibou Mahamenrabiou (CH Château Thierry)
Antoine Dewitte (CHU Bordeaux)
Eline Bonnardel (CHU Bordeaux)
Pauline Ponsin, Emma Forsans, Astrée Swiech, Mathieu Pissot, Elisabeth Falzone (Hia Percy, Clamart)
Elsa Josefowicz, Julie Bellet, Benoit Graffin (CHU Lille)
Fabrice Thiolliere (Hospices Civiles de Lyon, Hôpital Lyon Sud)
Thomas Rimmelé, Elodie Brie (Hospices Civiles de Lyon, Hôpital Edouard Herriot)
Marc Gainnier (CHU La Timone Marseille, Aix Marseille University)
Laurent Zieleskiewicz (CHU Hôpital Nord Marseille)
Olivier Barbot, Aziz Akouz (CH Perpignan)
Diane Léna, Arnaud Causeret (Institut Arnault Tzanck, Saint Laurent du Var)
Hélène Charbonneau, Benoît Richard (Clinique Pasteur Toulouse)
Olivier Desebbe (Clinique de la Sauvegarde, Lyon)
Nicolas Herzog, Christophe Giacardi (HIA Clermont Tonnerre, Brest)
Pauline Ponsin (Percy Military Teaching Hospital, Burn centre)
Emma Forsans (Percy Military Teaching Hospital, Department of Anaesthesiology)
Sebastien Pili-Floury (CHU Besançon)
Thien-Nga Chamaraux-Tran (Hôpitaux Universitaires de Strasbourg, Hôpital de Hautepierre)

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Authors' contributions

CR and BA contributed to study design, data collection, data analysis and drafting the manuscript. LM, JYL contributed to study design, data collection and data interpretation. OC, OAA, LT, MG, CH, PGG, EN, PA, TC, JB, GB, LF, MF, AO, OJB, MOF, ML, YAT,JP,PYC, PA,MDM, EH, MB, JMJ, JC, MDD, NM contributed to data collection and data analysis. SL contributed to study coordination and data monitoring, MM, TM contributed to study design, data analysis and statistical analysis. All authors read and approved the final manuscript.

Abstract

Aim

Describing acute respiratory distress syndrome patterns, therapeutics management, and outcomes of ICU COVID-19 patients and to determine risk factors of 28-day mortality.

Methods

Prospective multicentre, cohort study conducted in 29 French ICUs. Baseline characteristics, comorbidities, adjunctive therapies, ventilatory support at ICU admission and survival data were collected.

Results

From March to July 2020, 966 patients were enrolled with a median age of 66 (interquartile range 58-73) years and a median SAPS II of 37 (29-48). On the first 24 hours of ICU admission, COVID-19 patients received one of the following respiratory supports: mechanical ventilation for 559 (58%), standard oxygen therapy for 228 (24%) and high-flow nasal cannula (HFNC) for 179 (19%) patients. Overall, 721 (75%) patients were mechanically ventilated during their ICU stay. Prone positioning and neuromuscular blocking agents were used in 494 (51%) and 460 (48%) patients, respectively. Bacterial co-infections and ventilator-associated pneumonia were diagnosed in 79 (3%) and 411 (43%) patients, respectively. The overall 28-day mortality was 18%. Age, pre-existing comorbidities, severity of respiratory failure and the absence of antiviral therapy on admission were identified as independent predictors of 28-day outcome.

Conclusion

Severity of hypoxaemia on admission, older age (> 70 years), cardiovascular and renal comorbidities were associated with worse outcome in COVID-19 patients. Antiviral treatment on admission was identified as a protective factor for 28-day mortality. Characterising the determinants of outcomes of critically ill COVID-19 patients is crucial to optimise hospital and ICU resources and to provide the appropriate intensity level of care.

Keywords: viral pneumonia, outcome, COVID-19, management

Introduction

Since December 2019, a new agent, the SARS-CoV-2 coronavirus, has been spreading originally from the region of Wuhan in China and rapidly outside the country, causing an international outbreak of respiratory illnesses named by the World Health Organization (WHO), COVID-19. In France, the first cases of COVID-19 have been reported at the end of January 2020. The increasing numbers of patients requiring intensive care urged local health and government officials to significantly increase ICU beds capacity to face COVID-19 patients [1].

While outbreak has progressed, it appeared that SARS-Cov-2 was responsible for a very specific disease leading to a severe acute respiratory failure. Despite sharing a similar aetiology, COVID-19 patients may present quite different patterns from severely hypoxaemic patients to normally breathing hypoxaemic patients with or without associated hypercapnia and inconsistent response to prone position as an example [2, 3]. It is therefore difficult to identify which patients could benefit from one therapy to another. Currently, a variety of therapeutic strategies to manage COVID-19 patients in ICU have been suggested from supportive care alone to prescribing unproven medications. Apart from corticosteroids and tocilizumab, evidence from randomised clinical trials that potential therapies could significantly improve outcomes in patients suffering from severe COVID-19 is still needed [4-6]. Clinical features of hospitalised COVID-19 patients have been described in China, Europe and the United States [7-10]. Although male gender, older age, comorbidities such as diabetes, immunosuppression and severe obesity appear as the most common risk factors of COVID-19 outcome worldwide, a great heterogeneity in COVID-19 features is reported amongst countries limiting potential extrapolation from other countries [11].

Accordingly, the primary objective was to perform a prospective, multicentre, observational study to provide a detailed description of the initial management of COVID-19 patients admitted to French ICUs. The secondary objective was to identify risk factors associated with 28-day mortality in a large cohort of ICU patients. These could promote an individualised therapeutic approach for COVID-19 patients during the current and potential future coronavirus-related outbreaks.

Methods

Study design and population

This study is reported in accordance with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines.[12] The AZUREA group, a French research network, conducted a prospective, observational, multicentre cohort study in 16 French university and 13 general hospitals. The study was approved by the "Comité de Protection des Personnes – Sud Méditerranée IV" (2020-A00797-32) for prospective (from the 2nd of April to the 3rd of July 2020) data collection and the Institutional Review Board of the Nimes University Hospital for retrospective (from the 4th of March 4th to the 1st of April) data collection, respectively. This study was registered in ClinicalTrials.gov on the 9th of April 2020, NCT04340466. According to French law, written informed consent was waived due to the non-interventional design of the study [13]. Patient or his/her surrogate decision-maker received an information letter prior to patient enrolment where possible.

All patients admitted to the intensive care unit for a diagnosis of probable or confirmed SARS-Cov-2 infection were enrolled into the study according to the predefined following criteria:

- Age ≥ 18 years

- Patient presenting a confirmed SARS-CoV-2 infection (defined as positive result by reverse transcriptase polymerase chain reaction (RT-PCR) testing of a nasopharyngeal or lower respiratory tract swab) OR a probable SARS-Cov-2 infection (defined as a severe acute respiratory infection associated with inconclusive or unavailable RT-PCR testing) according to WHO guidance. This guidance was implemented locally with the adjunct of consistent COVID-19 CT scan imaging to classify SARS-Cov-2 infection as probable. (https://www.who.int/publications-detail/global-surveillance-for-human-infection-with-novel-coronavirus-(2019-ncov))

Were not included:

- Patient presenting a severe acute respiratory syndrome with negative SARS-CoV-2 PCR and CT scan results
- Patient already enrolled in the present study
- Patient refusal to participate to the present study

Data collection

For each included patient, the following data were recorded: demographic data (age, gender, weight, height), clinical data (admission diagnosis, comorbidities, Charlson score [14]), severity scores (SAPS II (Simplified Acute Physiology Score) [15], SOFA (Sequential Organ Failure Assessment) [16] scores) at ICU admission, and at day 7 and 14 for SOFA. Additionally, biological data (including serum creatinine concentration, lactate, ferritin, troponin, CRP, WBC count, haemoglobin, D-dimers, fibrinogen), infection data including clinical symptoms, antimicrobial therapy modalities (timing of initiation, dosing regimen, combination therapy), sedatives and mode of respiratory support (invasive mechanical ventilation (IMV), non-invasive mechanical ventilation (NIV), oxygen mask, high-flow nasal

cannula oxygen), adjunctive therapies, microbiological and imaging data (chest X-ray, thoracic CT scan, US exam) were collected. Moreover, complications (pulmonary embolism, acute kidney injury, cardiac arrhythmias, myocarditis, ventilator-associated pneumonia (VAP), liver failure) were recorded until hospital discharge or death. VAP was diagnosed based on French VAP/HAP guidelines and microbiological cultures [17]. Date of death was recorded and mortality at day 7, at ICU discharge and at day 28 as well as organ support requirement during 28-day follow-up were also reported.

ARDS was graded according to the Berlin Definition for patients receiving mechanical ventilation on ICU admission [18]. Mild ARDS was defined as a PaO_2/FIO_2 ratio of ≤ 300mmHg to 200 mmHg with PEEP or continuous positive airway pressure of ≥ 5 H_2O, moderate ARDS was defined as PaO_2/FIO_2 ratio of ≤ 200mmHg to 100 mmHg with PEEP ≥ 5 H_2O and severe ARDS defined as PaO_2/FIO_2 ≤ 100 mmHg with PEEP ≥ 5 cm H_2O.

Data management

Data collection was performed by trained staff at each participating centre. Data were entered into a structured electronic password-protected and secured web-based case report form (eCRF). The eCRF was developed using the REDCap Data Management Platform designed to support data capture for research studies [19]. Data monitoring was handled by the coordinating Centre (Nîmes University Hospital, France). Outstanding queries regarding the completion of the CRF were undertaken with each participating centre where necessary to ensure accuracy of data.

Study outcomes

The primary outcome was all-cause mortality determined from patient medical chart at day 28. The secondary outcomes were ICU and hospital mortality, ICU and hospital length of stay (LOS), all-cause mortality at day 7 and requirement of organ support.

Statistical analysis

Simple descriptive statistics were used to characterise the study population; continuous data were summarised by median and interquartile range or median and (min; max), categorical data as n (%). Comparisons between survivors and non-survivor patients at 28 days were performed using Student's t-test for quantitative variables, or the Mann–Whitney U test when the distribution of variables was non-Gaussian, and the Chi-square test for qualitative variables. We used a mixed logistic regression model with a centre-specific random intercept to assess relationships with mortality at day 28, taking into account the clustered structure of the data.

A primary analysis focused on patients' characteristics at inclusion: age, gender, BMI (> 40 *vs.* < = 40), SOFA score without respiratory SOFA score component (< 2 *vs.* > = 2), chronic obstructive pulmonary disease, chronic heart failure, chronic kidney failure, cancer, arterial hypertension (with or without angiotensin-receptor blockers or ACE inhibitors treatment), and partial oxygen arterial blood pressure (PaO_2) to fraction of inspired oxygen (FiO_2) ratio (PaO_2/FiO_2 ratio).

A secondary analysis focused on care at admission with adjustment on characteristics at admission. Care parameters included in the model were: type of respiratory support, anticoagulants, antiviral therapy, hydroxychloroquine and corticosteroids.

Sensitivity analyses were made using generalised estimating equation (GEE) model with an exchangeable correlation matrix and Cox proportional hazards model with gamma frailty distribution. Statistical analyses were performed at the conventional two-tailed α level of 0.05 using SAS statistical software, version 9.4 (SAS Institute Inc).

Results

Between the 4th of March and the 3rd of July 2020, data from 966 patients admitted to 29 ICUs were analysed (**Figure 1**, study flow diagram). The distribution of included patients among the different participating hospitals is shown in **Table S1** (Supplemental material). Baseline characteristics of the study cohort are presented in **Table 1**. Among patients under mechanical ventilation on admission, 44 (8%) presented mild ARDS, 249 (47%) moderate ARDS and 224 (42%) severe ARDS. The main symptoms at ICU admission were fever (71%, n = 691), shortness of breath (69%, n = 666) and cough (58%, n = 565). Lymphopaenia, elevated D-dimer, fibrinogen and ferritin levels were the most frequent biological abnormalities observed at ICU admission. Most patients underwent CT scan (76%, n = 740) and/or PCR testing (98%, n = 944) for SARS-Cov-2 infections diagnosis (**Table 2**).

Microbiology

Microbiological samples were obtained from 963 (97%) patients with 96% of lower respiratory tract samples. For 857 (92%) patients, SARS-CoV-2 infections were proven by RT-PCR (**Table 3**). In 79 (3%) of patients, bacterial co-infection was diagnosed. During ICU stay, 342 (43%) patients developed ventilator-associated pneumonia (VAP).

COVID-19 management

Respiratory, haemodynamic and therapeutic COVID-19 initial management are presented in **Table 4**. More than half of the included patients received mechanical ventilation on ICU admission. For non-intubated patients on admission, median time to intubation and mechanical ventilation was 2 [1-3] days. Overall, 721 (75%) patients were mechanically ventilated during their ICU stay. Four hundred and ninety four (51%) received prone positioning at a median time of 2 [1-5] days post admission in the ICU. Two-thirds of patients required vasopressor support. Antiviral treatment was prescribed in 242 (25%) patients with

lopinavir/ritonavir being the most common used antiviral therapy (**Table 4**). Among adjunctive therapies, corticosteroids were administered to 212 (22%) patients and hydroxychloroquine to 289 (30%) patients.

Patient Outcomes

Overall 28-day mortality, ICU mortality and 7-day mortality were 18% (173/966), 17% (166/966) and 8% (77/966), respectively. Twenty-eight-day mortality increased with the severity of hypoxaemia on admission (**Figure 2**). Among deaths occurring in ICU, 78/166 (53%) were preceded by end-of-life decisions. The median (IQR) time from admission to death was 8 [4-16] days. Among the 793 patients alive at day 28, 250 (32%) patients were still hospitalised. Complications and organ support therapy are described in **Table 5**. Median time to renal replacement therapy (RRT) and extra corporeal membrane oxygenation (ECMO) support were 5.5 [3-9] days and 5 [0-8] days post ICU admission. Multivariate analysis identified age, chronic kidney failure, chronic heart failure, SOFA score and PaO_2/FiO_2 at admission as independent risk factors of death at day 28 (**Table 6**). After adjustment on admission characteristics, antiviral therapy use was significantly associated with a lower risk of death at day 28. Sensitivity analyses confirmed these findings.

Discussion

Key findings

This large multicentre observational French cohort reports the initial management of 966 severe COVID-19 patients admitted to ICU over 4 months with complete data on 28-day outcome. The overall 28-day mortality was 18% with age, pre-existing comorbidities, severity of respiratory failure and the use of antiviral therapy as independent predictors of 28-day outcome. Initial management of COVID-19 patients consisted in IMV in 58%, in

standard oxygen therapy in 53% and HFNC in 23% of patients on ICU admission. Prone positioning and neuromuscular blocking agents were used in half of patients. Bacterial co-infection rates were low (3%) whereas secondary pulmonary infections occurred in 43% patients.

Relationship with previous literature

The pandemic of COVID-19 has dramatically and rapidly challenged the global health care system in terms of hospital resources and patient care management. Reported rates of IMV may vary according to resources available among centres and experience. In this cohort, half of COVID-19 patients were intubated on admission ending to two-thirds of patients under IMV during their ICU stay in line with previous data from 4244 critically ill COVID-19 patients, showing a rate of 63% and 80% of patients mechanically ventilated on admission and during their ICU stay, respectively [20]. The rate of IMV was much higher (82 to 87%) in Italian and Spanish cohorts compared to reports from China (43%) [8-10]. The lack of experience in the treatment of patients with acute respiratory failure from a previously unknown viral agent and heterogeneity in recommendations might have had an effect on respiratory management of COVID-19 patients [21]. This may partially explain differences observed in rates of mechanical ventilation in COVID-19 patients with similar median severity scores and similar severity of acute respiratory failure on admission. Although most of patients presented severe hypoxaemia on admission in the present cohort, intubation was not performed in half of cases. Some authors found a beneficial effect of early initial intubation after HFNC, whereas a recent meta-analysis suggested that timing of intubation might have no effect on critically ill COVID-19 patients' outcome [22, 23]. Thus, the optimal timing for intubation in critically ill COVID-19 patients remains uncertain [24]. Performing unnecessary

intubation in patients who may have improved without invasive MV can be detrimental, especially in medical resource-limited settings. A recently published cohort of 13 301 Brazilian critically ill patients found that non-invasive respiratory support was associated with improved outcome at day 60 but causal inference remains uncertain due to the observational nature of this study [25]. Additionally, early intubation itself may contribute to ventilator associated pneumonia (VAP) risk in COVID-19 patients, and consequently had some negative impact on clinical outcomes. The high rate (43%) of VAP in our cohort is similar to the rate reported in the coVAPid study showing that ventilator-associated lower respiratory tract infections incidence was significantly higher in SARS-CoV-2 patients (36.1%), as compared to influenza patients (22.2%) or patients with no viral infection (16.5%) [26]. Several hypotheses have been formulated to explain the higher rate of secondary infections observed in critically ill COVID-19 patients, such as the use of immunosuppressive agents, the longer duration of mechanical ventilation and the severity of endothelial injury that may promote lung infection [26].

As previously reported, the most common comorbidities found in COVID-19 patients admitted to ICU were arterial hypertension, chronic cardiovascular disease, diabetes and obesity [8, 10, 27]. Among these comorbidities, chronic heart and kidney failures were associated with 28-day mortality in the present study. The 28-day mortality rate in the present cohort is lower than first published cohorts of critically ill COVID-19 patients with similar median severity score and median age on admission but in line with most recently published cohorts on the same study period [10, 25]. The mortality rates reported in the literature widely vary and could be potentially related to rationing of resources in overwhelmed ICUs, differences in respiratory and therapeutic interventions or cohorts reporting incomplete follow-up [28]. The lower mortality rate reported in our cohort could

be partially explained by an increased use of corticosteroids compared to the COVID-ICU cohort [20]. Even though this factor was not associated with 28-day mortality in our cohort, the beneficial impact of corticosteroids in severe COVID-19 pneumonia has been demonstrated in a large randomised controlled trial and further confirmed in a meta-analysis [6, 29]. At the time of the present study data collection, benefits of corticosteroids were not clearly demonstrated.

Interestingly, after adjusting on patient characteristics on admission, receiving an antiviral treatment was an independent protective factor for 28-day mortality. At the time of enrolment in the study, lopinavir/ritonavir was the most common antiviral therapy used. However, lopinavir/ritonavir alone was not significantly associated with 28-day mortality when this variable was tested in the model. To date, no antiviral therapy has confirmed its efficacy in COVID-19 patients. Due to the observational nature of this study, some residual confounders may play a role in the association between antiviral treatment and outcome so that this association may be interpreted with caution. Finally, severe hypoxaemia (PaO_2/FiO_2 < 100) on admission and age > 70 years have been identified as prognostic factors in the present cohort. Elderly COVID-19 patients have much more severe disease and show poorer response to treatments than younger patients with reported 6-month mortality rate up to 72% [10, 20, 30, 31]. Consequently, the level of care intensity should be discussed in older patients with severe respiratory failure.

Clinical implications

This study provides large outcome data and detailed treatment strategies to establish risk stratification for COVID-19 patients on admission. Identifying prognostic factors on admission such as severity of hypoxaemia, older age, cardiovascular and renal comorbidities may allow the early identification of patients infected with SARS-CoV-2 who are at the

highest risk of death to guide initial management and optimise resource allocation. Compared to the reported wave, current critically ill COVID-19 management has evolved with corticosteroids becoming a key component of therapeutic strategy as well as HFNC that was first considered cautiously. In future pandemics, taking into account patient medical conditions and severity of hypoxaemia will help to determine the best therapeutic approach and guide patient admission to appropriate care settings.

Study limitations

This study has several limitations. First, due to the design of the study, the reasons determining therapeutic approaches (antiviral agents, corticosteroids) or adjunctive therapies (prone position) used were not analysable and the ventilatory strategy may not be representative of clinical practice in non-pandemic circumstances. Second, due to the critical moment of the pandemic and the limited resources to conduct research at that time, some variables have missing data and 400 critically ill COVID-19 patients admitted to participating ICUs could not be included and may differ from the study cohort in terms of outcome. However, our multivariable model included 908 (94%) patients of the cohort, which is higher than previously reported [20]. Third, as the participating ICUs were exclusively located in different French regions, these results may not be extrapolated to other countries. Still, this cohort provides an interesting national overview of the initial management of COVID-19 patients.

Conclusion

Severity of hypoxaemia, older age (> 70 years), cardiovascular and renal comorbidities are prognostic factors for COVID-19 patients. Identifying the determinants of outcomes of

critically ill COVID-19 patients is crucial to optimise hospital and ICU resources and to provide the appropriate intensity level of care.

Table 1: Patients' characteristics of COVID-19 patients admitted to ICU

	Day 28 status			
	Survivors (n = 793)	Non survivors (n = 173)	All (n = 966)	*p-value*
Age, years (n = 966)	65 [57;72]	70 [62;77]	66 [58; 73]	< 0.0001 (a)
< 50 years	95 (12%)	7 (4%)	102 (11%)	< 0.0001 (b)
50 – 59 years	157 (20%)	25 (15%)	182 (19%)	
60 – 69 years	278 (35%)	47 (27%)	325 (34%)	
70 – 79 years	218 (28%)	61 (35%)	279 (29%)	
> 80 years	45 (6%)	33 (19%)	78 (8%)	
Sex, male (n = 966)	593 (75%)	127 (73%)	720 (75%)	0.7081 (b)
Weight, kg (n = 955)	85 [74; 97]	86 [73; 99]	85 [74; 97]	0.5119 (a)
Height, cm (n = 931)	171 [165; 178]	170 [165; 175]	171 [165; 178]	0.0110 (c)
Body Mass Index, $kg.m^{-2}$ (n = 930)	28.4 [25.2; 32.1]	29.4 [26.0; 34.2]	28.7 [25.2; 32.6]	0.0523 (a)
BMI > 30, $kg.m^{-2}$	305 (40%)	74 (46%)	379 (41%)	0.1390 (b)
BMI > 40, $kg.m^{-2}$	42 (6%)	14 (9%)	56 (6%)	0.1167 (b)
Settings (n = 962)				0.3533 (b)
Home or emergency department	370 47%)	83 (48%)	453 (47%)	
Long term care facility	6 (1%)	2 (1%)	8 (1%)	
Ward	217 (28%)	47 (27%)	264 (27%)	
Transfer from another hospital	114 (14%)	30 (17%)	144 (15%)	
Transfer from another ICU	83 (11%)	10 (6%)	93 (10%)	
SAPS II score [15] (n = 957)	36 [27; 46]	45 [38; 60]	37 [29; 48]	< 0.0001 (a)
SOFA score [16] (n = 960)	4 [2; 7]	7 [4; 9]	4 [2; 8]	< 0.0001 (a)
Underlying conditions				
Arterial hypertension (n = 965)	394 (50%)	104 (61%)	498 (52%)	0.0103 (b)
Chronic cardiovascular disease (n = 965)	439 (55%)	118 (69%)	557 (58%)	0.0014 (b)
Diabetes (n = 966)	240 (30%)	57 (33%)	297 (31%)	0.4883 (b)
Ischemic heart disease (n = 964)	65 (8%)	18 (11%)	83 (9%)	0.3246 (b)
Chronic heart failure (n = 960)	25 (3%)	18 (11%)	43 (5%)	< 0.0001 (b)
Immunosuppression (n = 965)	34 (4%)	9 (5%)	43 (4%)	0.5861 (b)
COPD (n = 966)	138 (17%)	43 (25%)	181 (19%)	0.0228 (b)
Chronic kidney failure (n = 966)	48 (6%)	30 (17%)	78 (8%)	< 0.0001 (b)
Cancer (n = 966)	70 (9%)	31 (18%)	101 (10%)	0.0004 (b)
Charlson score [14] (n = 966)	1 [0; 2]	2 [1; 4]	1 [0; 2]	< 0.0001 (a)
Recent travel (n = 957)	33 (4%)	8 (5%)	41 (4%)	0.8072 (b)

Previous medications (n = 966)				
Use of angiotensin-receptor blockers	137 (17%)	41 (24%)	178 (18%)	0.0483 (b)
Use of ACE inhibitors	159 (20%)	41 (24%)	200 (21%)	0.2667 (b)
Anticoagulants	53 (7%)	25 (14%)	78 (8%)	0.0007 (b)
Antiplatelets	162 (20%)	47 (27%)	209 (22%)	0.0511 (b)

For continuous variables mean ± standard deviation or median [interquartile-range] are given. For categorical variables, numbers (%) are given. BMI: body mass index. SOFA: Sequential Organ failure Assessment. SAPS: Simplified Acute Physiology Score. COPD: Chronic Obstructive Pulmonary Disease. ACE: Angiotensin Converting Enzyme. ICU: Intensive Care Unit.

(a) Wilcoxon test, (b) Chi² test, (c) Student test

Table 2: Clinical, biological and radiological characteristics at ICU admission

	Day 28 status			
	Survivors (n = 793)	Non survivors (n = 173)	All (n = 966)	*p*-value
Number of days since symptoms onset (n = 961), days	8 [6; 12]	7 [3; 10]	8 [6; 11]	< 0.0001 (a)
Symptoms at ICU admission (n = 966)				
Cough	472 (60%)	91 (53%)	563 (58%)	0.0945 (b)
Shortness of breath	538 (68%)	127 (73%)	665 (69%)	0.1520 (b)
Fever	573 (72%)	117 (68%)	690 (71%)	0.2222 (b)
Diarrhoea	186 (23%)	33 (19%)	219 (23%)	0.2125 (b)
Nausea	20 (3%)	3 (2%)	23 (2%)	0.7831 (d)
Asthenia	51 (6%)	8 (5%)	59 (6%)	0.3685 (b)
Anorexia	14 (2%)	4 (2%)	18 (2%)	0.5460 (d)
Weakness	235 (30%)	60 (35%)	295 (31%)	0.1915 (b)
Confusion	31 (4%)	13 (8%)	44 (5%)	0.0393 (b)
Headache	94 (12%)	13 (8%)	107 (11%)	0.0994 (b)
Myalgia	171 (22%)	23 (13%)	194 (20%)	0.0139 (b)
Anosmia	71 (9%)	13 (8%)	84 (9%)	0.5428 (b)
Ageusia	40 (5%)	6 (3%)	46 (5%)	0.3778 (b)
Vital signs				
Temperature, °C (n = 951)	37.8 (± 1.1)	37.7 (± 1.5)	37.8 (± 1.2)	0.5668 (a)
SAP, mmHg (n = 955)	128 (± 27)	125 (± 32)	128 (± 28)	0.0479 (a)
MAP, mmHg (n = 956)	89 (± 18)	84 (± 22)	88 (± 18)	0.0019 (a)
Heart rate, beat/min (n=957)	89 (± 20)	93 (± 24)	89 (±21)	0.0415 (a)
Laboratory tests				
Haemoglobin, g/dL (n = 950)	12.7 [11.5; 14.0]	11.9 [10.6; 13.4]	12.6 [11.3; 13.9]	< 0.0001 (a)
WBC count, $10^3/mm^3$ (n = 948)	8.2 [5.9; 10.9]	8.3 [5.7; 11.7]	8.2 [5.8; 11.1]	0.4432 (a)
Neutrophil count, $10^3/mm^3$ (n = 830)	6.5 [4.6; 9.0]	6.3 [4.4; 9.6]	6.5 [4.6; 9.2]	0.8653 (a)
Lymphocyte count, $10^3/mm^3$ (n = 814)	0.8 [0.6; 1.1]	0.7 [0.5; 1.0]	0.8 [0.5; 1.1]	0.0083 (a)
Platelet count, $10^3/mm^3$ (n = 945)	229 [172; 304]	212 [145; 264]	225 [169; 296]	0.0002 (a)
Platelet/lymphocyte ratio (n = 811)	283 [190; 425]	272 [174; 453]	283 [186; 428]	0.8170 (a)
D-dimer, $ng.mL^{-1}$ (n = 440)	1570 [827; 3690]	1480 [788; 3495]	1560 [821; 3690]	0.6687 (a)
Ferritin, (µg/L) (n = 211)	1407 [843; 2407]	1149 [409; 1976]	1383 [738; 2389]	0.0924 (a)
Fibrinogen, $g.L^{-1}$ (n = 619)	6.9 [5.9; 7.8]	6.4 [5.2; 7.4]	6.8 [5.8; 7.8]	0.0008 (a)

Prothrombin, % (n = 844)	85.0 [74.0; 96.0]	80.5 [69.5; 91.5]	84.5 [73.0; 95.0]	0.0022 (a)
Procalcitonin, µg. L^{-1} (n = 568)	0.5 [0.2; 1.3]	0.7 [0.2; 4.0]	0.5 [0.2; 1.6]	0.0109 (a)
CRP, mg. L-1 (n=753)	157.7 [100.0; 233.0]	143.4 [95.8; 235.4]	154.9 [99.8; 234.0]	0.6810 (a)
Arterial lactate, mmol. L^{-1} (n = 873)	1.3 [1.0; 1.7]	1.4 [1.0; 2.0]	1.3 [1.0; 1.7]	0.0070 (a)
Serum creatinine, µmol. L^{-1} (n = 947)	74 [60; 96]	93 [66; 142]	77 [61; 103]	< 0.0001 (a)
Troponin Ic, ng.mL^{-1} (n = 353)	3.4 [0.0; 15.0]	13.0 [0.1; 81.5]	4.0 [0.0; 18.1]	0.0008 (a)
Troponin T, pg.mL^{-1} (n = 254)	14 [8; 27]	39 [24; 86]	17 [10; 37]	< 0.0001 (a)
PaO_2/FiO_2, mmHg (n = 701)	114 [83; 160]	103 [77; 148]	112 [81; 159]	0.0456 (a)
PaO_2, mmHg (n = 922)	76 [65; 94]	74 [63; 94]	76 [64; 94]	0.3592 (a)
$PaCO_2$, mmHg (n = 922)	37 [32; 42]	38 [31; 46]	37 [32; 43]	0.3099 (a)
Radiological exams				
X-ray (n = 966)	715 (90%)	149 (86%)	864 (89%)	0.1175 (b)
CT-scan (n = 966)	622 (78%)	116 (67%)	738 (76%)	0.0014 (b)
US exam (n = 959)	369 (47%)	91 (53%)	460 (48%)	0.1522 (b)

For continuous variables, mean ± standard deviation or median [interquartile-range] are given. For categorical variables, numbers (%) are given. SAP: systolic arterial pressure, WBC: white blood cells, CRP: C-reactive protein. PaO_2: oxygen arterial pressure, PCO_2: carbon dioxide arterial pressure, CT: computerised tomography, US: ultrasound.
(a) Wilcoxon test, (b) Chi^2 test, (d) Fisher's exact test

Table 3: Infection-related data from COVID-19 patients admitted to ICU (n = 966)

Respiratory samples for SARS Cov-2 Test (n = 931)	
BAL	43 (5%)
Aspirates	66 (7%)
Nasopharyngeal swab	822 (88%)
SARS-CoV-2 Test (n = 944)	
RT-PCR	926 (98%)
Rapid Diagnostic Testing	3 (0.3%)
Unknown	15 (2%)
SARS-CoV-2 Test result (n = 937)	
Positive	857 (91%)
Negative	80 (9%)
Microbiological tests on admission (n = 966)	963 (99.5%)
Respiratory samples	318 (33%)
Positive	79 (3%)
Blood cultures	465 (48%)
Positive	32 (7%)
PCR Influenza A	308 (32%)
Positive	2 (0.6%)
PCR Influenza B	303 (31%)
Positive	3 (1%)
Pneumococcal urinary antigen	425 (44%)
Positive	8 (2%)
Legionella urinary antigen	579 (60%)
Positive	6 (1%)
Microbiological tests during ICU stay (n = 966)	550 (57%)
Respiratory samples	394 (41%)
PCR *Pneumocystis jirovecii*	50 (5%)
Positive	2 (4%)
Viral PCR	267 (28%)
Positive HSV	16 (6%)
Positive CMV	3 (1%)
Positive HBV	3 (1%)
Positive VZV	2 (2%)
Galactomannan in BAL	126 (13%)
Positive	8 (6%)
Blood cultures	156 (16%)
Positive	69 (44%)

BAL: bronchoalveolar lavage, RT-PCR: Reverse Transcriptase Polymerase Chain Reaction, HSV: Herpes Simplex Virus, CMV: cytomegalovirus, HBV: Hepatitis B virus, VZV: Varicella Zoster virus. Results are given as numbers and percentages.

Table 4: COVID-19 management (n = 966)

	Day 28 status			
	Alive at day 28 (n = 793)	Dead at day 28 (n = 173)	All (n = 966)	*p*-value
Maximal respiratory support during the first 24 hours in ICU (n = 966)				0.0001 (b)
Standard oxygen therapy	203 (26%)	25 (15%)	228 (24%)	
High-Flow Nasal Cannula	156 (20%)	23 (13%)	179 (19%)	
Non-Invasive Ventilation	25 (3%)	8 (5%)	33 (3%)	
Mechanical Ventilation	434 (55%)	125 (72%)	559 (58%)	
Mechanical Ventilation mode (n = 545)				0.3209 (d)
VAC	403 (96%)	123 (99%)	526 (97%)	
BIPAP	2 (0%)	1 (1%)	3 (1%)	
PSV	5 (1%)	0 (0%)	5 (1%)	
APRV	9 (2%)	0 (0%)	9 (2%)	
Tidal volume (mL) (n = 507)	423 [241-658]	418 [300-540]	420 [241-658]	0.1611 (a)
Respiratory rate (/min) (n = 528)	22 [10-42]	22 [12-35]	22 [10-42]	0.3712 (a)
PEEP (cmH_20) (n = 535)	12 [3-22]	10 [2-20]	12 [2-22]	0.0683 (a)
FiO_2 (%) (n = 543)	80 [30-100]	80 [40-100]	80 [30-100]	0.0427 (a)
Plateau pressure (cmH_20) (n = 360)	24 [10-40]	25 [12-53]	24 [10-53]	0.0700 (a)
Intubation management (n = 489)				0.9511 (b)
Video laryngoscopy	156 (42%)	52 (44%)	208 (43%)	
Fiberoptic bronchoscopy	37(10%)	12 (10%)	49 (10%)	
Direct Laryngoscopy	177 (48%)	55 (46%)	232 (47%)	
Haemodynamic support				
Vasopressor support (n = 964)	484 (61%)	137 (79%)	621 (64%)	< 0.0001 (b)
Inotropes (n = 963)	41 (5%)	29 (17%)	70 (7%)	< 0.0001 (b)
Adjunctive therapies				
Antiviral therapy (n = 966)	268 (34%)	35 (20%)	303 (31%)	0.0005 (b)
Lopinavir/ritonavir	213 (27%)	29 (17%)	242 (25%)	0.0055 (b)
Remdesivir	13 (2%)	0 (0%)	13 (1%)	0.1410 (d)
Oseltamivir	37 (5%)	7 (4%)	44 (5%)	0.7232 (b)
Lamivudine	1 (0%)	0 (0%)	1 (0%)	1.0000 (d)
Nevirapine	1 (0%)	0 (0%)	1 (0%)	1.0000 (d)
Darunavir	1 (0%)	0 (0%)	1 (0%)	1.0000 (d)
Immunomodulatory agents (n = 966)				
Hydroxychloroquine	236 (30%)	53 (31%)	289 (30%)	0.8198 (b)
Corticosteroids	175 (22%)	37 (21%)	212 (22%)	0.8446 (b)
Tocilizumab	12 (2%)	1 (1%)	13 (1%)	0.4831 (d)
Interferon γ	9 (1%)	1 (1%)	10 (1%)	1.0000 (d)
Anti-interleukin 1	5 (1%)	0 (0%)	5 (1%)	0.5922 (d)
Intravenous immunoglobulin	2 (0%)	1 (1%)	3 (0%)	0.4472 (d)
Antibiotics (n = 965)	730 (92%)	163 (94%)	893 (92%)	0.3530 (b)
Type of antibiotic therapy (n = 893)				0.9372 (b)
Monotherapy	141 (19%)	33 (20%)	174 (19%)	
Dual combination therapy	481 (66%)	105 (64%)	586 (66%)	
Multiple combination therapy	108 (15%)	25 (15%)	133 (15%)	
Anticoagulants (n = 963)	703 (89%)	152 (88%)	855 (89%)	0.8498 (b)

Anticoagulant dosing (n = 855)				0.0189 (b)
Therapeutic dosing	192 (27%)	56 (37%)	248 (29%)	
Prophylactic dosing	511 (73%)	96 (63%)	607 (71%)	
Sedatives (n = 964)	434 (55%)	129 (75%)	563 (58%)	< 0.0001 (b)
Neuromuscular blocking agents (n = 966)	357 (45%)	103 (60%)	460 (48%)	0.0004 (b)

ICU: Intensive Care Unit. VAC: Volume Assist Control mode, BIPAP: Bi-level Positive Airway Pressures, APRV: Airway Pressure Release Ventilation, PSV: Pressure Support Ventilation. PEEP: Positive End Expiratory Pressure, VA: veno-arterial, VV: veno-venous. FIO_2: inspired oxygen fraction.
For continuous variables mean ± standard deviation or median [min-max] are given. For categorical variables, numbers (%) are given.
(a) Wilcoxon test, (b) Chi^2 test, (d) Fisher's exact test.

Table 5: Clinical outcomes

	Day-28 status			
	Alive (n = 793)	Dead (n = 173)	All (n = 966)	*p-value*
SOFA score at day 7 (n = 828)	4 [2-7]	8 [5-12]	4 [2-8]	< 0.0001 (a)
SOFA score at day 14 (n = 686)	3 [0-6]	7 [5-10]	3 [1-7]	< 0.0001 (a)
Overall complications (n = 966)				
Mechanical ventilation	576 (73%)	143 (83%)	719 (74%)	0.0062 (b)
Vasopressor support	484 (61%)	137 (79%)	621 (64%)	< 0.0001 (b)
VAP/HAP	342 (43%)	69 (40%)	411 (43%)	0.4344 (b)
Myocarditis	15 (2%)	8 (5%)	23 (2%)	0.0488 (d)
Cardiac arrest	18 (2%)	28 (16%)	46 (5%)	< 0.0001 (b)
Pulmonary embolism	106 (13%)	32 (19%)	138 (14%)	0.0806 (b)
AKI	201 (25%)	86 (50%)	287 (30%)	< 0.0001 (b)
AKIN 1 score [32] (n = 287)	63 (31%)	7 (8%)	70 (24%)	
AKIN 2 score [32](n = 287)	41 (20%)	20 (24%)	61 (21%)	
AKIN 3 score [32] (n = 287)	97 (48%)	58 (68%)	155 (54%)	
RRT	99 (13%)	43 (25%)	142 (15%)	0.0001 (b)
RRT mode (n = 136)				0.2344 (b)
CVVH	19 (20%)	14 (34%)	33 (24%)	
CVVHD	12 (13%)	2 (5%)	14 (10%)	
CVVHD Ci-Ca	35 (37%)	13 (32%)	48 (35%)	
CVVHDF	29 (31%)	12 (29%)	41 (30%)	
Duration to RRT (days)	5 [3-10]	6 [3-9]	5 [3-9]	
ECMO (n = 966)	43 (5%)	20 (12%)	63 (7%)	< 0.0031 (b)
Mode (n = 62)				
VA	2 (5%)	6 (30%)	8 (13%)	
VV	40 (95%)	14 (70%)	54 (87%)	
Duration to ECMO (days) (n = 63)	5 [0-18]	4 [0-15]	5 [0-18]	0.1088 (a)
Liver dysfunction	46 (6%)	15 (9%)	61 (6%)	0.1597 (b)
No complication	263 (33%)	19 (11%)	282 (29%)	< 0.0001 (b)

ICU: intensive care unit, LOS: length of stay, SOFA: Sequential Organ Failure Assessment, VAP/HAP: ventilator/healthcare-associated pneumonia, AKI: acute kidney injury, AKIN: acute kidney injury network, RRT: renal replacement therapy. CVVH: continuous veno-venous haemofiltration, CVVHD: continuous veno-venous haemodialysis, CVVHDF: continuous veno-venous haemodiafiltration. ECMO: Extra Corporeal Membrane Oxygenation. VA: venous-arterial. VV: Veno-venous.
For continuous variables median [interquartile-range] are given. For categorical variables, numbers (%) are given.
(a) Wilcoxon test, (b) Chi² test, (d) Fisher's exact test

Table 6: Independent risk factors associated with 28-day mortality

	OR	95% CI	*p*-value
Model 1: Multivariate analyses of admission characteristics			
Age			
< 50 years	1.0	ref	_
50 – 59 years	2.2	[0.8 - 5.7]	0.1126
60 – 69 years	2.0	[0.8 - 5]	0.1423
70 – 79 years	**3.3**	**[1.3 - 8.3]**	**0.0113**
≥ 80 years	**9.0**	**[3.3 - 24.6]**	**< .0001**
Gender, female	1.0	[0.6 - 1.5]	0.8533
Body Mass Index > 40, kg.m-2	1.7	[0.8 - 3.7]	0.1793
COPD	1.3	[0.8 - 2]	0.2497
Chronic heart failure	**2.4**	**[1.1 - 5]**	**0.0241**
Chronic renal failure	**2.1**	**[1.2 - 3.8]**	**0.0113**
Cancer	1.6	[0.9 - 2.7]	0.0956
Arterial hypertension			
No	1.0	ref	-
Yes, with treatment by ACEI or ARB	1.1	[0.7 - 1.7]	0.6448
Yes, without treatment by ACEI or ARB	0.9	[0.5 - 1.5]	0.6103
SOFA score (without respiratory component) at inclusion			
< 2	1.0	ref	-
≥ 2	**2.4**	**[1.6 - 3.7]**	**< .0001**
PaO2/FiO2			
> 200 mmHg	1.0	ref	-
150-200 mmHg	1.1	[0.6 - 2.1]	0.8012
100-150 mmHg	1.1	[0.7 - 1.9]	0.6798
< 100 mmHg	**1.8**	**[1.1 - 2.9]**	**0.0161**
Model 2: Multivariate analysis of care at admission*			
Respiratory support			
Oxygen therapy or no ventilation	1.0	ref	-
High-Flow Nasal Cannula or Non-Invasive Ventilation	0.6	[0.2 - 1.5]	0.2868
Mechanical Ventilation	1.6	[0.7 - 3.4]	0.2756
Anticoagulants			
No anticoagulants	1.0	ref	-
Prophylactic dosing	0.7	[0.4 - 1.4]	0.3762
Therapeutic dosing	0.9	[0.5 - 1.8]	0.7503
Antiviral therapy on admission			
No antiviral therapy on admission	1.0	ref	
Antiviral therapy on admission	**0.5**	**[0.3 - 0.9]**	**0.0194**
Hydroxychloroquine on admission	1.0	[0.6 - 1.6]	0.9414
Corticosteroids on admission	1.0	[0.5 - 1.9]	0.9000

OR were calculated using random effects logistic regression. The regression was based on 908 patients for 28-day mortality.
OR: odds ratio, CI: Confidence Interval, SOFA: Sequential Organ Failure Assessment. COPD: Chronic Obstructive Pulmonary Disease

*Model 2 was adjusted for characteristics at admission

ICU: Intensive Care Unit; SOFA: Sequential Organ failure Assessment; PaO_2: Oxygen Arterial Pressure; PCO_2: carbon dioxide arterial pressure; COPD: chronic obstructive pulmonary disease; ACEI: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker.

Supplemental material

Table S1: Study enrolment according to participating sites

Strasbourg - Nouvel Hôpital Civil	110 (11.4%)
Amiens - CHU	104 (10.7%)
Lyon - CHU Lyon Sud	89 (9.2%)
Perpignan - CH	65 (6.7%)
Paris - APHP - Hôpital Saint-Antoine	54 (5.6%)
Clamart - Hôpital d'Instruction des Armées Percy	52 (5.4%)
Nîmes - CHU Carémeau	47 (4.9%)
Nancy - CHU	41 (4.2%)
Lyon - HCL E Herriot	41 (4.2%)
Dijon - CHU	41 (4.2%)
Rouen - CHU	37 (3.8%)
Marseille - La Timone	32 (3.3%)
Besançon - CHU	27 (2.8%)
Béziers - CH	27 (2.8%)
Château-Thierry - CH	26 (2.7%)
Bordeaux - CHU	23 (2.4%)
Caen - CHU	17 (1.8%)
Marseille - APHM Hôpital Nord	16 (1.7%)
Saintes - CH Saintonge	16 (1.7%)
Strasbourg - CHU Hautepierre	15 (1.5%)
Marseille - Hôpital d'Instruction des Armées Laveran	15 (1.5%)
Lisieux - CH	13 (1.3%)
Lille - CHRU	12 (1.2%)
Alès - CH	11 (1.1%)
Lyon - Clinique de la Sauvegarde	11 (1.1%)
Saint Laurent du Var - Institut Arnault Tzanck	7 (0.7%)
Castelnau-le-Lez	7 (0.7%)
Brest - HIA Clermont-Tonnerre	7 (0.7%)
Toulouse - Clinique Pasteur	5 (0.5%)

Figure 1: Flow Diagram

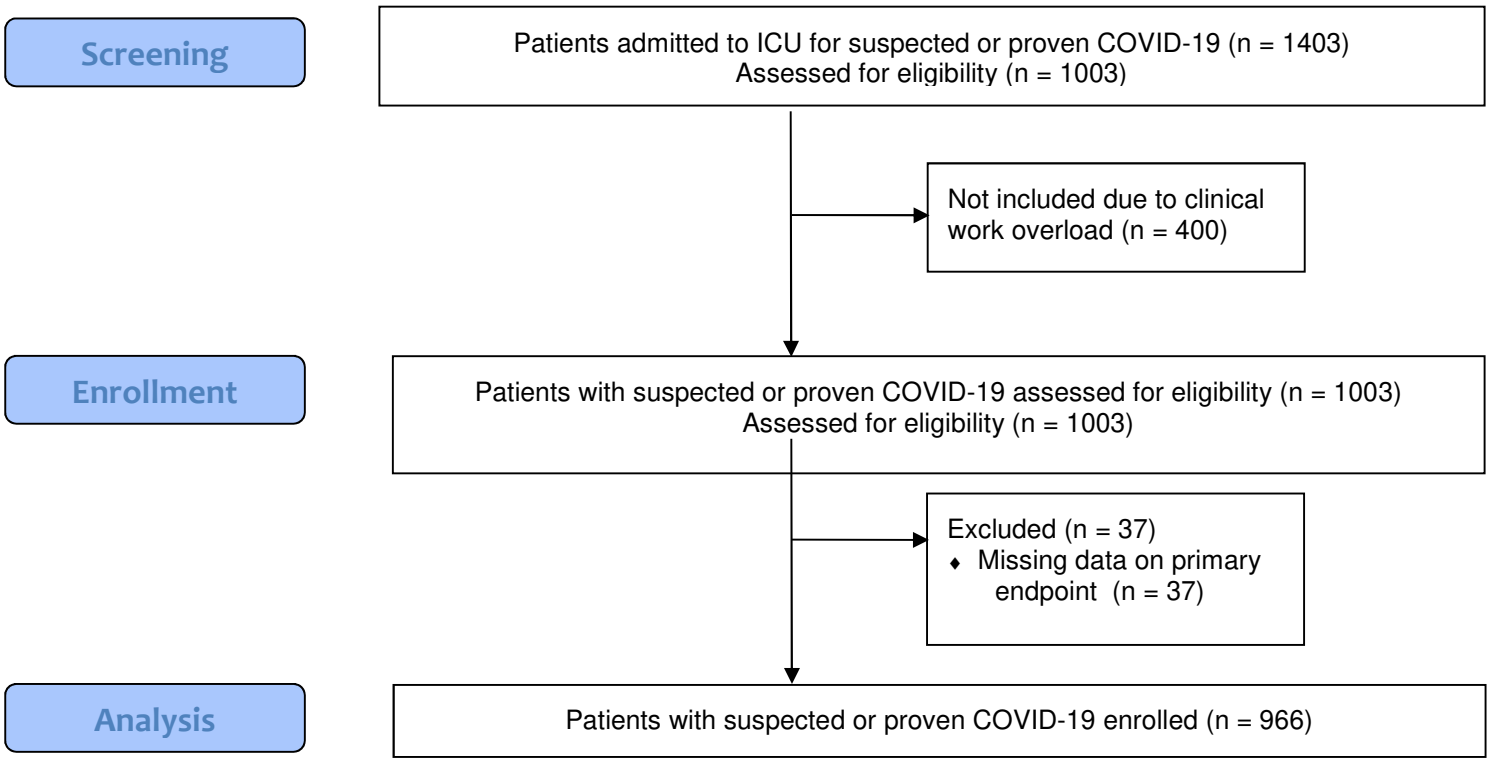
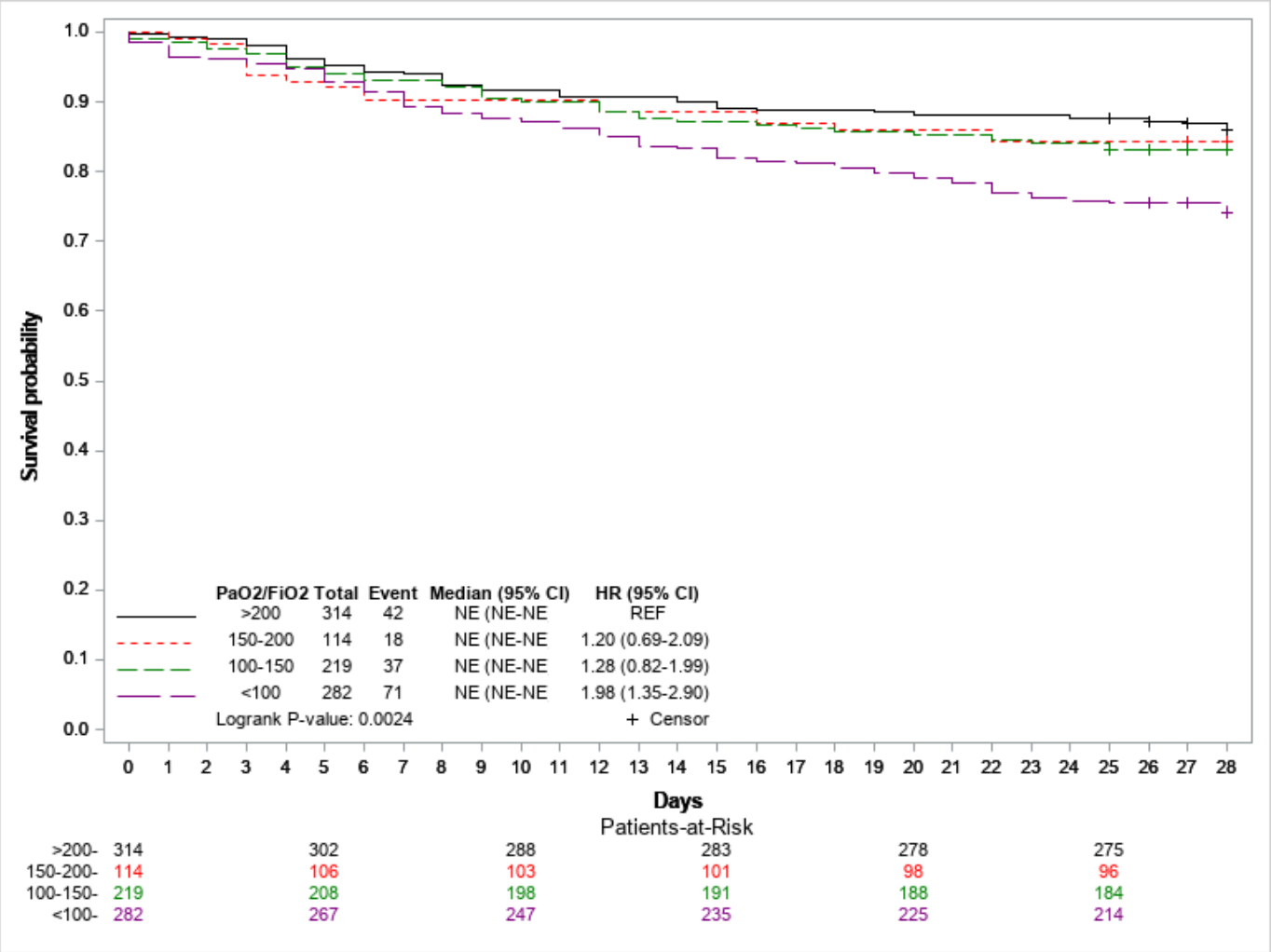


Figure 2: Kaplan-Meyer survival estimates during the 28 days following intensive care unit admission according to PaO_2/FIO_2 ratio at admission



PaO2: partial oxygen arterial blood pressure. FIO2: fraction of inspired oxygen

References

1. Aziz S, Arabi YM, Alhazzani W, Evans L, Citerio G, Fischkoff K, Salluh J, Meyfroidt G, Alshamsi F, Oczkowski S *et al*: Managing ICU surge during the COVID-19 crisis: rapid guidelines. *Intensive Care Med* 2020, 46(7):1303-1325.
2. Gattinoni L, Chiumello D, Caironi P, Busana M, Romitti F, Brazzi L, Camporota L: COVID-19 pneumonia: different respiratory treatments for different phenotypes? *Intensive Care Med* 2020, 46(6):1099-1102.
3. Guerin C, Albert RK, Beitler J, Gattinoni L, Jaber S, Marini JJ, Munshi L, Papazian L, Pesenti A, Vieillard-Baron A *et al*: Prone position in ARDS patients: why, when, how and for whom. *Intensive Care Med* 2020.
4. Group RC, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, Staplin N, Brightling C, Ustianowski A *et al*: Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. *N Engl J Med* 2020.
5. Group RC: Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2021, 397(10285):1637-1645.
6. Group WHOREAfC-TW, Sterne JAC, Murthy S, Diaz JV, Slutsky AS, Villar J, Angus DC, Annane D, Azevedo LCP, Berwanger O *et al*: Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. *JAMA* 2020, 324(13):1330-1341.
7. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X *et al*: Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020, 395(10223):497-506.
8. Ferrando C, Suarez-Sipmann F, Mellado-Artigas R, Hernandez M, Gea A, Arruti E, Aldecoa C, Martinez-Palli G, Martinez-Gonzalez MA, Slutsky AS *et al*: Clinical features, ventilatory management, and outcome of ARDS caused by COVID-19 are similar to other causes of ARDS. *Intensive Care Med* 2020.
9. Xie J, Wu W, Li S, Hu Y, Hu M, Li J, Yang Y, Huang T, Zheng K, Wang Y *et al*: Clinical characteristics and outcomes of critically ill patients with novel coronavirus infectious disease (COVID-19) in China: a retrospective multicenter study. *Intensive Care Med* 2020, 46(10):1863-1872.
10. Grasselli G, Greco M, Zanella A, Albano G, Antonelli M, Bellani G, Bonanomi E, Cabrini L, Carlesso E, Castelli G *et al*: Risk Factors Associated With Mortality Among Patients With COVID-19 in Intensive Care Units in Lombardy, Italy. *JAMA Intern Med* 2020, 180(10):1345-1355.
11. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC: Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. *JAMA* 2020, 324(8):782-793.
12. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, Initiative S: The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007, 370(9596):1453-1457.
13. Toulouse E, Lafont B, Granier S, McGurk G, Bazin JE: French legal approach to patient consent in clinical research. *Anaesth Crit Care Pain Med* 2020.

14. Charlson ME, Pompei P, Ales KL, MacKenzie CR: A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987, 40(5):373-383.
15. Le Gall JR, Lemeshow S, Saulnier F: A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. *JAMA* 1993, 270(24):2957-2963.
16. Vincent JL, Rello J, Marshall J, Silva E, Anzueto A, Martin CD, Moreno R, Lipman J, Gomersall C, Sakr Y *et al*: International study of the prevalence and outcomes of infection in intensive care units. *JAMA* 2009, 302(21):2323-2329.
17. Leone M, Bouadma L, Bouhemad B, Brissaud O, Dauger S, Gibot S, Hraiech S, Jung B, Kipnis E, Launey Y *et al*: Hospital-acquired pneumonia in ICU. *Anaesth Crit Care Pain Med* 2018, 37(1):83-98.
18. Force ADT, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L, Slutsky AS: Acute respiratory distress syndrome: the Berlin Definition. *JAMA* 2012, 307(23):2526-2533.
19. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, McLeod L, Delacqua G, Delacqua F, Kirby J *et al*: The REDCap consortium: Building an international community of software platform partners. *J Biomed Inform* 2019, 95:103208.
20. Network C-IGobotR, the C-ICUI: Clinical characteristics and day-90 outcomes of 4244 critically ill adults with COVID-19: a prospective cohort study. *Intensive Care Med* 2021, 47(1):60-73.
21. Alhazzani W, Moller MH, Arabi YM, Loeb M, Gong MN, Fan E, Oczkowski S, Levy MM, Derde L, Dzierba A *et al*: Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). *Intensive Care Med* 2020, 46(5):854-887.
22. Zhang Q, Shen J, Chen L, Li S, Zhang W, Jiang C, Ma H, Lin L, Zheng X, Zhao Y: Timing of invasive mechanic ventilation in critically ill patients with coronavirus disease 2019. *J Trauma Acute Care Surg* 2020, 89(6):1092-1098.
23. Papoutsi E, Giannakoulis VG, Xourgia E, Routsi C, Kotanidou A, Siempos, II: Effect of timing of intubation on clinical outcomes of critically ill patients with COVID-19: a systematic review and meta-analysis of non-randomized cohort studies. *Crit Care* 2021, 25(1):121.
24. Lee YH, Choi KJ, Choi SH, Lee SY, Kim KC, Kim EJ, Lee J: Clinical Significance of Timing of Intubation in Critically Ill Patients with COVID-19: A Multi-Center Retrospective Study. *J Clin Med* 2020, 9(9).
25. Kurtz P, Bastos LSL, Dantas LF, Zampieri FG, Soares M, Hamacher S, Salluh JIF, Bozza FA: Evolving changes in mortality of 13,301 critically ill adult patients with COVID-19 over 8 months. *Intensive Care Med* 2021.
26. Rouze A, Martin-Loeches I, Povoa P, Makris D, Artigas A, Bouchereau M, Lambiotte F, Metzelard M, Cuchet P, Boulle Geronimi C *et al*: Relationship between SARS-CoV-2 infection and the incidence of ventilator-associated lower respiratory tract infections: a European multicenter cohort study. *Intensive Care Med* 2021, 47(2):188-198.
27. Network C-IGobotR, the C-ICUI: Clinical characteristics and day-90 outcomes of 4244 critically ill adults with COVID-19: a prospective cohort study. *Intensive Care Med* 2020.
28. Quah P, Li A, Phua J: Mortality rates of patients with COVID-19 in the intensive care unit: a systematic review of the emerging literature. *Crit Care* 2020, 24(1):285.

29. Group RC, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, Staplin N, Brightling C, Ustianowski A *et al*: Dexamethasone in Hospitalized Patients with Covid-19. *N Engl J Med* 2021, 384(8):693-704.
30. Liu Y, Mao B, Liang S, Yang JW, Lu HW, Chai YH, Wang L, Zhang L, Li QH, Zhao L *et al*: Association between age and clinical characteristics and outcomes of COVID-19. *Eur Respir J* 2020, 55(5).
31. Guillon A, Laurent E, Godillon L, Kimmoun A, Grammatico-Guillon L: Long-term mortality of elderly patients after intensive care unit admission for COVID-19. *Intensive Care Med* 2021.
32. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, Levin A, Acute Kidney Injury N: Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 2007, 11(2):R31.