Pneumonia

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Epidemiology, clinical and biological characteristics, and prognosis of critically ill COVID 19 patients: a single-center experience through 4 successive waves

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Abstract

Objective The aim of this study was to describe the characteristics of patients admitted to the intensive care unit with severe pneumonia due to SARS-CoV-2, comparing them according to successive waves, and to identify prognostic factors for morbidity and mortality.

Materials and methods This single-center retrospective observational descriptive study was conducted from March 10, 2020, to October 17, 2021. All adult patients admitted with SARS-CoV-2 pneumonia presenting acute respiratory failure were included. COVID 19 diagnosis was confirmed by RT-PCR testing of respiratory specimens. The primary endpoint was ICU mortality. Secondary endpoints were the occurrence of ventilator-associated pneumonia (VAP) or bronchopulmonary aspergillosis.

Results Over the study period, 437 patients were included of whom 282 (65%) patients were ventilated for 9 [5;20] days. Among the studied population, 38% were treated for one or more episodes of VAP, and 22 (5%) for bronchopulmonary aspergillosis. ICU mortality was 26% in the first wave, then fell and stabilized at around 10% in subsequent waves ($p=0.02$). Increased age, Charlson index, SOFA score and lactatemia on admission were predictive of mortality. Survival at 90 days was 85% (95% CI 82–88) and was unaffected by the presence of VAP. However, the occurrence of bronchopulmonary aspergillosis increased mortality to 36%.

Conclusion In this study, we observed mortality in the lower range of those previously reported. Risk factors for mortality mainly included age and previous comorbidities. The prognosis of these critically ill Covid 19 patients improved over the four waves, underlining the likely beneficial effect of vaccination and dexamethasone.

Keywords SARS-CoV-2, ARDS, ICU, Mortality, Prognosis, VAP, Aspergillosis, CAPA

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Introduction

SARS-CoV-2 appeared in China in December 2019 [1, 2], with acute respiratory distress syndrome (ARDS) being the most common severe form of the disease. On January 30, 2020, the World Health Organization (WHO) declared "that the outbreak (of cases) constitutes an international public health emergency (IPHE)". Since then, this virus has had a considerable impact on our modern societies and healthcare systems. There have been at least 774 million cases worldwide, and over 7, 031, 200 deaths [3]. This period was therefore conducive to research, the identification of risk factors, the sharing of experiences between centers, and the frantic race for anti-Covid treatments and vaccines. From the very first months of the pandemic, analysis of numerous data revealed risk factors for developing a severe form of the disease. We were able to identify subjects at risk, who were then targeted as a priority by vaccination campaigns. Among the risk factors for mortality, age and male gender are the most frequently found [4]. The role of certain comorbidities has also been highlighted: overweight, immunosuppression, diabetes, organ disease and the presence of a history of cardiovascular disease [5–9]. A gradual change was then observed in the affected populations treated in intensive care units, as well as a drop in mortality. This evolution is probably linked to government measures, improved medical care and the development of vaccination.

In France, transmission of the virus was initially rapid in "Ile de France" and eastern France, then spread throughout the country. Occitanie region was able to anticipate the influx of patients into its hospitals [10]. In Intensive Care Medicine at Montpellier University Hospital, the first patient to test positive for SARS-CoV-2 was admitted on 10/03/2020. Between March 2020 and October 2021, the department admitted 464 patients for ARDS with SARS-CoV-2, distributed unevenly over time according to 4 periods commonly known as "waves". We had observed a change in the epidemiological profile over time, with the advent of new therapies such as corticoids and vaccination. We had also observed a more frequent occurrence of nosocomial pneumonia, which had previously been attributed with a higher mortality rate [11]. These observations prompted us to investigate further.

The aim of our study was firstly to describe the population of patients with this severe form of SARS-CoV-2 infection admitted to our center during 4 successive waves, to determine the mortality rate of these patients and finally to identify risk factors for mortality. We were also interested in the occurrence of 2 complications: ventilator-associated pneumonia (VAP) and bronchopulmonary aspergillosis. We sought to identify patients with severe SARS-CoV-2 at risk of developing these 2 complications.

Patients and methods

This prospective observational study was carried out in the Intensive Care Department of the Lapeyronie University Hospital. On admission, an information note concerning the use of patient data in clinical research is distributed to each patient or trusted support person that stipulates that participation is implicitly granted unless the patient, or his or her family, expresses opposition. According to French law, signed consent of participants is not required due to the non-interventional design of the study.

During the pandemic, our department was the first line of care for severe patients. However, patients requiring respiratory assistance by Extracorporeal Membrane Oxygenation were referred as a matter of priority to another department with expertise in this technique. The pandemic evolved in successive waves, interspersed with periods of calm when admissions fell sharply until they were cancelled.

All patients aged over 18 admitted to our ICU between 10/03/2020 and 17/10/2021 with SARS-CoV-2 pneumonia were included consecutively in the study. Covid-19 was diagnosed if a clinical SARS-CoV-2 either nasopharyngeal or endotracheal polymerase-chain-reaction (RT-PCR) test was positive, at a cycle threshold value < 25, within 24 h of the patient's admission to the hospital. Exclusion criteria were pregnancy, a medical decision to limit therapy. The decision to admit patients to ICU was based on patients' prior condition (age, frailty, comorbidity, neurocognitive status), hypoxemia requiring oxygen therapy greater than 6 L/min or respiratory failure (polypnea > 30/min, signs of draught, signs of hypercapnia, paradoxical respiration), systolic blood pressure below 90mmHg, Glasgow score less than 12, and worsening organ failure. For patients aged over 80, the decision to admit them to the ICU was strongly discouraged, and in all cases discussed collegially, respecting the wishes of the patient and family.

Patient demographics and histories were collected: age, BMI, time (in days) from onset of symptoms to ICU, comorbidities -hypertension, diabetes mellitus, chronic kidney disease, inflammatory disease and Charlson score [12]. The patient was considered immunocompromised if he was receiving corticosteroid therapy greater than 0.5mg/kg/day for at least 3 months, a history of solid organ transplantation, solid tumor with chemotherapy in the last 5 years, hematologic malignancy, a primary immune deficiency. The severity of the disease was assessed 24 h after admission using the SAPS II and Sequential Organ Failure Assessment (SOFA) score. Glasgow coma score evaluated the level of consciousness. During the first 48 h, the worst value for PaO_2/FiO_2 ratio,

creatininemia, CRP, lactatemia, D-dimer, and renal function was collected.

Treatments implemented during ICU stay were also recorded including the need for and the duration of non-invasive and invasive ventilation or / and renal replacement therapy (RRT), as well as the use of vasoactive drugs. The use of the prone position was recorded, as was the number of sessions. The requiring for a veno-venous extracorporeal membrane oxygenation (ECMO) was also recorded.

The occurrence of nosocomial infections was recorded: ventilator-associated pneumonia (VAP), bacteremia, invasive fungal infections, and pulmonary aspergillosis. VAP was defined by clinical (fever, worsening hematosis and purulent secretions), radiological and microbiological signs, and by the initiation of antibiotic therapy in a patient ventilated for at least 48 h [13]. Covid-19-associated pulmonary aspergillosis (CAPA) was defined by mycological criteria (mycelial filaments on direct examination, plasma aspergillary Ag, bronchial aspergillary Ag, culture of respiratory specimens) and the introduction of specific treatment.

Specific management of COVID 19 included curative anticoagulation (in the absence of contraindication) with IVSE unfractionated heparin, and corticosteroid therapy with Dexamethasone at a dosage of 6mg/d intravenously for 10 days [14–16]. From May 2021, Tocilizumab 400-800mg was administered as a single intravenous infusion in severe patients with a CRP above 70mg/L, ensuring the absence of bacterial superinfection [17]. No systematic antibiotic therapy was prescribed except in cases of early "respiratory co-infection" [18], defined as the presence within the first 2 days of a bacterial pneumonia with bacteriological documentation.

ICU lengths of stay and ICU and hospital deaths were collected. Deaths due to limitation of care were recorded. We also collected mortality at 3 months. Factors predictive of in-hospital mortality were then identified.

Statistical analysis

Categorical variables are presented as numbers and percentages, and continuous variables as medians with their interquartile ranges (IQR, 25th and 75th percentiles). The total population was divided into two groups according to vital status at discharge from ICU and hospital. The total population was also divided into two groups according to the occurrence or non-occurrence of nosocomial pneumonia or aspergillosis. Variables were then compared between each group by the appropriate test for each case: categorical variables by chi2 test or Fisher test, and continuous variables by Student test or Wilcoxon test. Factors associated with ICU and in-hospital mortality, nosocomial pneumonia and aspergillosis were determined by multivariate logistic regression. For the multivariate analysis, variables were selected on the basis of their statistical significance in the univariate analysis (with a P value ≤ 0.2) of their association with ICU and in-hospital mortality, the occurrence of nosocomial pneumonia, aspergillosis or bacteremia. Before inclusion in the model, variables were tested for collinearity. The results of the multivariate logistic regression models are reported as odds ratios (OR) with their 95% confidence intervals (CI95%). Survival at 60 days in the total population was estimated using the Kaplan–Meier method. This method was used to estimate survival in the population according to whether or not they developed nosocomial pneumonia or aspergillosis. The curves were then compared using the Log-Rank test. All tests were two-tailed, and p values ≤ 0.05 were considered statistically significant. Analyses were performed using R software version 4.0.3 (Free Software Foundation, Boston, USA).

Results

During the study period, we observed 4 waves with chronological limits as follows: (1) March 10 to April 27, 2020, (2) August 12 to December 28, 2020, (3) January 1 to June 6, 2021, marked by the appearance of the alpha variant (known as "British") and the start of the anti-covid vaccination campaign for the most vulnerable subjects. (4) from July 17 to October 17, 2021, marked by the emergence of the delta variant (known as "Indian") in a context of widespread vaccination (Figs. 1 and 2).

As shown in the flowchart (Fig. 1) and in Fig. 2, 437 patients were included in the study including 51, 133, 191 and 62 patients in each wave chronologically. The population was predominantly male (71%), with a median age of 65 (56;72) years and a median BMI of 28 (28;32). Main features of the patients are displayed in Table 1. Median time to ICU admission from onset of disease symptoms was 9 (6;11) days. On admission, median SAPSII and SOFA scores were 32 (22;44) and 4 (2;7) respectively, and median PaO_2/FiO_2 ratio 147 (106;182) mmHg. A respiratory co-infection was present in 62 (14%) patients. Biological data are showed in Table 1.

Curative anticoagulant therapy was given to all patients, and intravenous dexamethasone to 82%.

During the ICU stay, 282 (65%) patients required mechanical ventilation, almost half of them within the first 24 h, for a median duration of 9 (5;20) days. Forty-eight (11%) patients required vasoconstrictive drugs. AKI occurred in 135 (31%) patients in which 54 (12%) were treated by RRT, while ECMO was performed in only 8 (2%) patients. Several nosocomial infections occurred including VAP in 170 patients (39%), CAPA in 22 (5%), bacteremia in 62 patients (14%) and fungemia in 16 patients (4%) (Table 1).

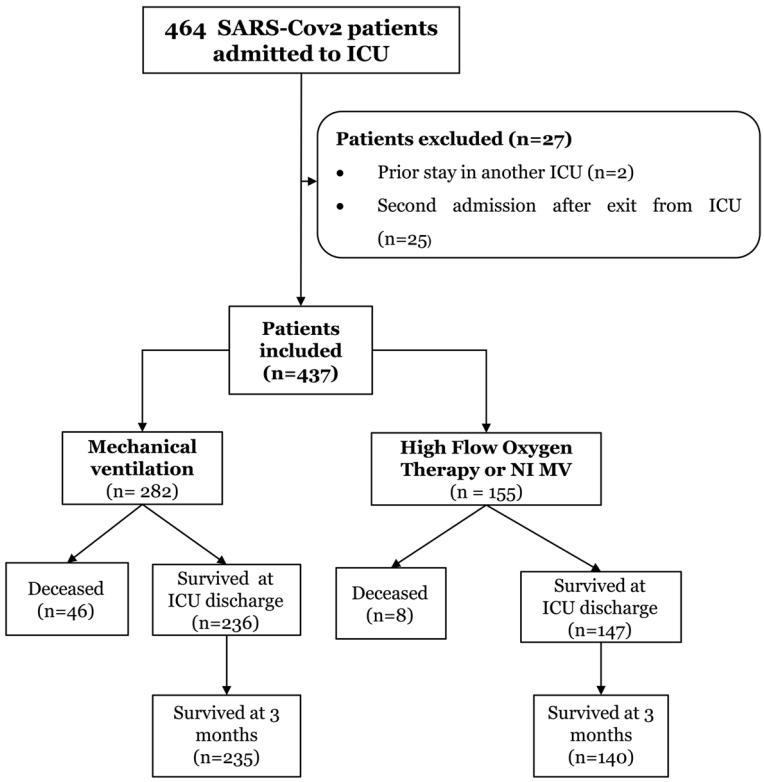

Fig. 1 Flowchart of the studied population. ICU, intensive care unit; NI MV, non invasive mechanical ventilation

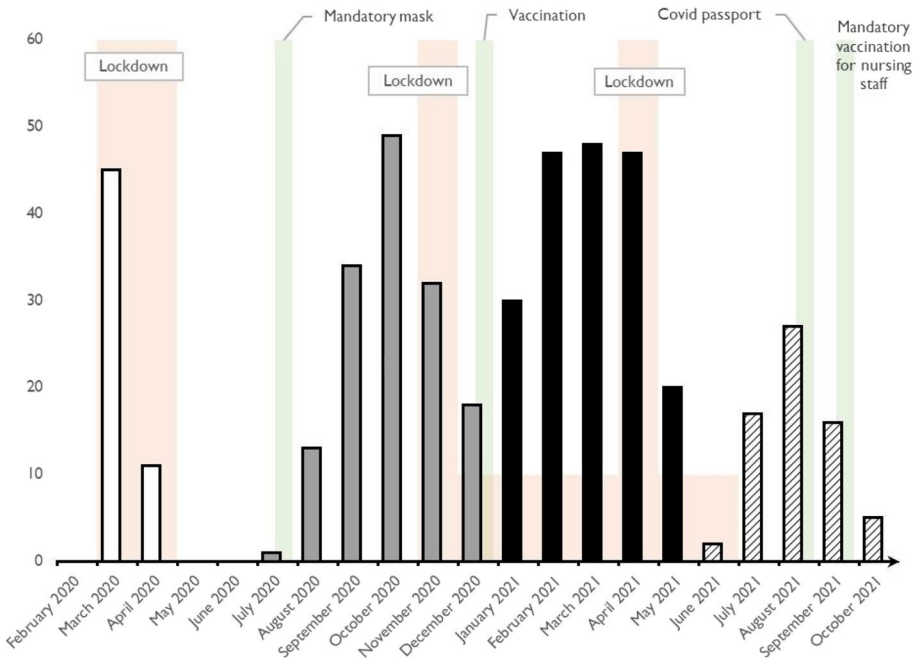

Fig. 2 Distribution of patients according to the 4 successive waves. The various events (lockdown, mask, vaccination, etc.) are shown on the figure according to their date of application

Table 1 Baseline characteristics at admission, interventions, and mortality of patients admitted to ICU with SARS-Cov 2 pneumonia. Differences between patients according to each wave

Characteristics	All Patients	Wave 1 (*N* = 51)	Wave 2 (*N* = 133)	Wave 3 (*N* = 191)	Wave 4 (*N* = 62)	*P*-value
Patients						
Age, years, median (Q1;Q3)	65 (55;72)	65 (56;72)	68 (60;75)	66 (56;72)	57 (45;65)	< 0.001
Male, n (%)	309 (71%)	36 (71%)	107 (81%)	124 (65%)	42 (68%)	0.0241
Charlson score, median (Q1;Q3)	1 (0;2)	1 (0;3)	1 (0;3)	1 (0;3)	0 (0;1)	0.0085
Chronic kidney disease, n(%)	39 (9%)	10 (20%)	9 (7%)	18 (9%)	2 (3%)	0.0129
BMI, kg/m2, median (Q1;Q3)	28 (25;32)	26 (23;29)	28 (25;33)	28 (26;31)	29 (27;33)	0,00109
ICU admission						
SAPS II, median (Q1;Q3)	32 (22;44)	41 (31;49.5)	40 (29;51)	30 (21;40)	24 (17;30.5)	< 0.001
SOFA, median (Q1;Q3)	4 (2;7)	7 (4.5;9)	4 (2;7)	3 (2;7)	3 (2;6)	< 0.001
PaO2/FiO2 ratio, median (Q1;Q3)	147 (106;182)	146 (110;164)	160 (113;200)	137 (100;174)	150 (116;165)	0,09
D-dimer, ng/mL, median (Q1;Q3)	990 (594;1867)	1138 (787;1774)	865 (492;1626)	1041 (681;1963)	899 (527;1480)	0.0246
Lactates, mmol/L, median (Q1;Q3)	1,3 (1,0;1,7)	1,3 (1,0;1,7)	1,3 (1,0;1,7)	1,3 (1,0;1,7)	1,3 (1,0;1,5)	0,618
CRP, mg/L, median (Q1;Q3)	141 (84;216)	238 (152;303)	160 (93;228)	123 (77;199)	120 (73;178)	$8{,}35.10^{-8}$
Lymphocytes, 10^9/L, median (Q1;Q3)	0,7 (0,5;0,92)	0,68 (0,5;0,98)	0,69 (0,46;0,86)	0,71 (0,51;0,92)	0,77 (0,59;1)	0,119
ICU stay						
MV, n (%)	282 (65%)	46 (90%)	87 (65%)	114 (60%)	35 (57%)	< 0.001
duration (*n* = 280), days, median (Q1;Q3)	9 (5;20)	6 (3;11)	9 (5;19)	12 (6;22)	11 (7;28)	< 0.001
Vasopressors [a], *n* (%)	48 (11%)	15 (30%)	4 (8%)	4 (8%)	5 (10%)	< 0.001
Dexamethasone, n (%)	357 (82%)	0 (0%)	133 (98%)	167 (87%)	60 (97%)	< 0.001
AKI, n (%)	135 (31%)	26 (51%)	49 (37%)	49 (26%)	12 (19%)	< 0.001
RRT, n (%)	54 (12%)	16 (31%)	9 (7%)	24 (13%)	5 (8%)	< 0.001
ECMO, n (%)	8 (2%)	2 (4%)	1 (1%)	4 (2%)	1 (2%)	0,534
VAP, n (%)	170 (39%)	13 (26%)	55 (41%)	76 (40%)	26 (42%)	0,795
CAPA, n (%)	22 (5%)	3 (6%)	8 (6%)	7 (4%)	4 (7%)	0,717
ICU LOS, days, median (Q1;Q3)	8 (4;15)	8 (4;14)	8 (4;15)	8 (4;16)	7 (4;15)	0,945
Hospital LOS, days, median (Q1;Q3)	20 (12;33)	18 (10;39)	18 (11;29)	22 (14;34)	19 (12;35)	0,19
Mortality, n (%)						
In ICU	53 (12%)	13 (26%)	13 (10%)	20 (11%)	7 (11%)	0.0209
In-hospital	68 (16%)	17 (33%)	15 (12%)	28 (15%)	8 (14%)	0.0037

SAPSII simplified acute physiologic score, *SOFA* sequential organ failure assessment, *AKI* acute kidney injury, *MV* mechanical ventilation, *RRT* renal replacement therapy, *ECMO* extracorporeal membrane oxygenation, *VAP* ventilated associated pneumonia, *CAPA* covid19 associated pulmonary aspergillosis, *LOS* length of stay

[a] norepinephrine > 0.3µg/kg/min

ICU and hospital lengths of stay were 8 (4;15) and 20 (12;33) days respectively. The ICU mortality rate was 12% (53 patients), rising to 16% (68 patients) at discharge (Table 1). Of the 53 ICU deaths, 34 (64%) were the result of treatment limitation. At 90 days, the survival rate remained at 84 (82;88) % (Fig. 3).

Comparison of patient groups corresponding to each wave (Table 1)

Mortality was 26% in the first wave, then fell and stabilized at around 10% in subsequent waves ($p = 0.02$). In the first wave, patients had a higher Charlson index, higher rates of chronic kidney disease (20%) and a higher incidence of AKI, with a consequent higher use of RRT (31%). A greater proportion of these patients were ventilated, but for a shorter duration. In contrast, patients in the fourth wave were younger (median age 57 (45;65) years).

Predictive factors of mortality

Univariate analysis of surviving and deceased ICU patients showed that higher age, higher Charlson index, higher SAPSII and SOFA severity scores, lower PaO_2/FiO_2 ratio and higher blood lactate and D-dimer levels were associated with mortality (Table 2). The need for mechanical ventilation, vasopressor drugs and/or RRT was also associated with mortality. Multivariate analysis retained only age (OR 1.09 (1.04;1.15), $p = 0.001$), high Charlson index (OR 1.23 (1.02;1.48), $p = 0.028$), SOFA score (OR 1.40 (1.19;1.66), $p < 0.001$), and lactatemia on admission (OR 1.61 (1.15;2.40), $p = 0.011$), and need for

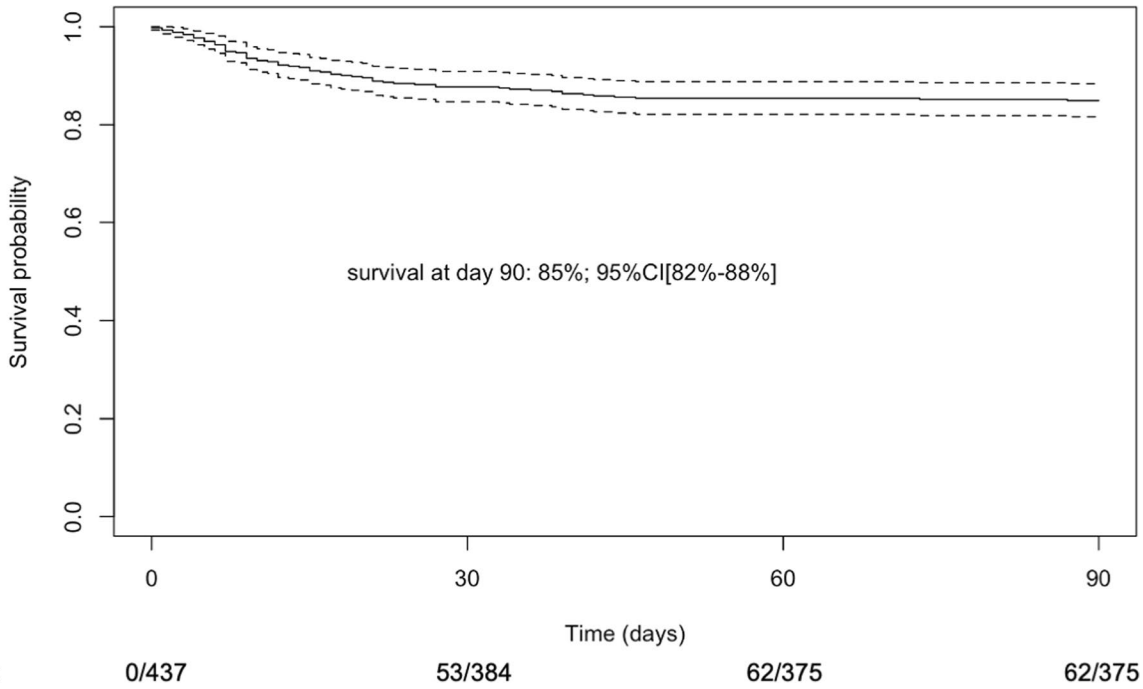

Fig. 3 Overall survival by Kaplan–Meier analysis at 90 days

prone positioning (Table 2). The occurrence of CAPA was also associated with mortality (Fig. 5).

Predictive factors of nosocomial infection

Of the 282 patients who required ventilation, more than half (167) developed VAP. Microbiological data were as follows: enterobacteria (90, 54%), pseudomonas (25, 15%), staphylococcus aureus (12, 7%), other gram positives (25, 15%) and unidentified (15, 9%).

The comparative univariate analysis of patients with and without VAP identified the following factors as being associated with its occurrence: longer duration of ventilation (16 (9;28) vs. 5 (3;8) days, $p<0.001$), longer duration of curarization (4 (2;7) vs. 1(1;3) days, $p<0.001$), and higher proportion of patients requiring prone position (69% vs. 40%, $p<0.001$) and receiving Dexamethasone (86% vs 64%, $p<0.001$) (Table 3). Multivariate analysis retained only the following factors (Table 3): prolonged mechanical ventilation (OR 1.12 (1.08;1.18), $p<0.001$) and Dexamethasone administration (OR 2.97 (1.46;6.25), $p=0.003$).

We observed and diagnosed 22 cases of pulmonary aspergillosis in the entire cohort. In all cases, plasma or bronchoalveolar lavage (BAL) fluid galactomannan was > 1.0. In some cases (5), the diagnosis was confirmed by the presence of aspergillus in BAL culture.

In univariate analysis, the occurrence of CAPA was associated with the duration of mechanical ventilation, the need for RRT and with respiratory co-infection (Table 4). In multivariate analysis, only the presence of an initial respiratory co-infection (OR 2.92 (0.98;8.30), $p=0.046$) and the requiring of RRT (OR 1.58 (0.99;2.46), $p=0.046$) were associated with the occurrence of CAPA.

Survival to 90 days was not significantly different according to whether or not a VAP had occurred during the stay (Fig. 4). On the other hand, the occurrence of a CAPA in mechanically ventilated patients prolonged the ICU length of stay and significantly worsened mortality (8 (36%) vs. 38 (15%), $p=0.0114$) and was associated with lower survival at 3 months, 64% (95% CI (46;87), $p=0.001$) (Fig. 5).

Discussion

In this study, we report a comprehensive analysis of the characteristics of 437 patients with severe SARS-CoV-2 who were admitted to the ICU during 4 successive waves. Our population was characterized by its severity, as evidenced by severity scores and a PaO_2/FiO_2 ratio below 150. Overall mortality in intensive care was 12%, rising to 16% at hospital discharge, but this decreased significantly (26 vs. 10% in intensive care; 33 vs. 14% in hospitalization) over the waves. Factors associated with mortality were advanced age, high Charlson and SOFA scores, high blood lactate levels, and the need for prone position. Over half the patients (55%) developed VAP, and 5% pulmonary aspergillosis. Prolonged mechanical ventilation and dexamethasone administration were associated with the occurrence of VAP, while respiratory co-infection and

Table 2 Comparison by univariate and multivariate analysis of deceased and surviving patients

	Alive (*N* = 384)	Deceased (*N* = 53)	*p*-value	Multivariate analysis OR (95%IC) *p*-value
Characteristics				
Age, years, median (Q1;Q3)	64 (55;72)	71 (66;77)	< 0.001	1.09 (1.04;1.15), *p* = 0.001
Smoking, n (%)	84 (22%)	16 (31%)	NS	-
Coronary artery disease, n (%)	36 (9%)	15 (29%)	0.001	-
Hypertension, n (%)	158 (41%)	31 (60%)	0.013	-
Chronic kidney disease, n (%)	26 (7%)	13 (25%)	< 0.001	-
Diabete mellitus, n (%)	38 (10%)	10 (19%)	0.048	-
Chronic pulmonary disease, n (%)	76 (20%)	18 (35%)	0.0165	-
Charlson score, median (Q1;Q3)	1 (0;2)	2 (1;5)	< 0.001	1.23 (1.02;1.48), *p* = 0.028
ICU admission				
SAPS II, median (Q1;Q3)	31 (21;42)	49 (40;63)	< 0.001	-
SOFA score, median (Q1;Q3)	3 (2;7)	8 (6;10)	< 0.001	1.40 (1.19;1.66), *p* < 0.001
PaO2/FiO2 ratio, median (Q1;Q3)	150 (110;188)	130 (90;168)	0,039	-
CRP, mg/L, median (Q1;Q3)	140 (81.2;212.5)	173.4 (121.5;258.4)	0.0337	-
Lactates, mmol/L, median (Q1;Q3)	1.2 (1;1.6)	1.6 (1.2;2)	< 0.001	1.61 (1.15;2.40), *p* = 0.011
D-dimer, ng/mL, median (Q1;Q3)	943 (573;1739)	1447 (811;4000)	0.0066	-
Lymphocytes 10^9/L, median (Q1;Q3)	0.71 (0.52;0.93)	0.585 (0.4;0.76)	0.0273	-
ICU stay				
MV, n (%)	236 (61%)	46 (87%)	< 0.001	-
Delay admission-MV, days, median (Q1;Q3)	0;1 (0)	0 (0;1)	NS	-
Prone position, n (%)	127 (33%)	35 (66%)	< 0.001	4.25 (1.62;12.65),,*p* = 0.005
Duration of MV, days, median (Q1;Q3)	9 (5;19)	11 (5;26)	NS	-
Vasopressors[a], n (%)	29 (8%)	19 (36%)	< 0.001	-
AKI, n (%)	106 (28%)	29 (56%)	< 0.001	-
Dexamethasone, n (%)	322 (84%)	35 (66%)	0.0022	-
RRT, n (%)	29 (8%)	25 (47%)	< 0.001	-
ICU LOS, days, median (Q1;Q3)	8 (4;14.3)	9 (5;20)	NS	-

SAPSII simplified acute physiologic score, *SOFA* sequential organ failure assessment, *MV* mechanical ventilation, *AKI* acute kidney injury, *VAP* ventilated associated pneumonia, *CAPA* Covid19 associated pulmonary aspergillosis, *RRT* renal replacement therapy, *LOS* length of stay, *ICU* intensive care unit

[a] norepinephrine > 0.3µg/kg/min

Table 3 Factors associated with the occurrence of VAP (univariate and multivariate analysis)

ICU management	Ventilated patients (*n* = 282)	No VAP (*n* = 115)	VAP (*n* = 167)	*p*-value	Multivariate OR (95%IC), *p*-value
Curarisation, days, median (Q1;Q3)	2 (1;6)	1 (1;3)	4 (2;7)	< 0.001	-
Prone position, n (%)	162 (57%)	46 (40%)	116 (69%)	< 0.001	-
MV, days, median (Q1;Q3)	9 (5;20.3)	5 (3;8)	16 (9;27.8)	< 0.001	1.12 (1.08;1.18), *p* < 0,001
Dexamethasone, n (%)	217 (77%)	74 (64%)	143 (86%)	< 0.001	2.97 (1.46;6.25), *p* = 0,003

MV mechanical ventilation, *VAP* ventilated associated pneumonia

the need for RRT were associated with the occurrence of pulmonary aspergillosis, significantly worsening the outcome.

ARDS, the most severe form of Covid-19, is the leading cause of ICU admission, as reported here. We observed an overall mortality rate of 12%, which is in the lower range of those reported by various published series [6, 19–24]. Indeed, reported mortality rates range from 18 to 40%. Our results are similar to those of the AZUREA group which, in a prospective multicenter French study conducted from March to July 2020, found a mortality rate at D28 of 18% [25]. The 2 populations were fairly comparable in terms of age (66 vs. 65 years), Charlson and IGS II scores (37 vs. 32). Moreover, the percentage

Table 4 Factors associated with the occurrence of CAPA (univariate and multivariate analysis)

	No CAPA ($n=415$)	CAPA ($n=22$)	*p*-value	Multivariate OR (95%IC), *p*-value
MV, days, median (Q1;Q3)	9 (5;19)	21.5 (10.3;36.8)	0.0027	
RRT, n (%)	37 (9%)	9 (41%)	0.0023	1,58 (0.99–2.46. $p=0.046$)
VAP associated, n (%)	39/260 (15%)	8/22 (36%)	0.0136	2.92 (0.98–8.30. $P=0.046$)
Mortality, n (%)				
In ICU	38 (9%)	8 (36%)	0.0114	
In hospital	51 (12%)	9 (41%)	0.0238	
LOS, days, median (Q1;Q3)				
In ICU	12 (7;21)	21.5 (10.3;31.8)	0.0062	
In Hospital	24 (16.8;40)	51 (22.3;69.5)	0.0028	

MV mechanical ventilation, *CAPA* Covid associated pulmonary aspergillosis, *RRT* renal replacement therapy, *VAP* ventilated associated pneumonia, *LOS* length of stay

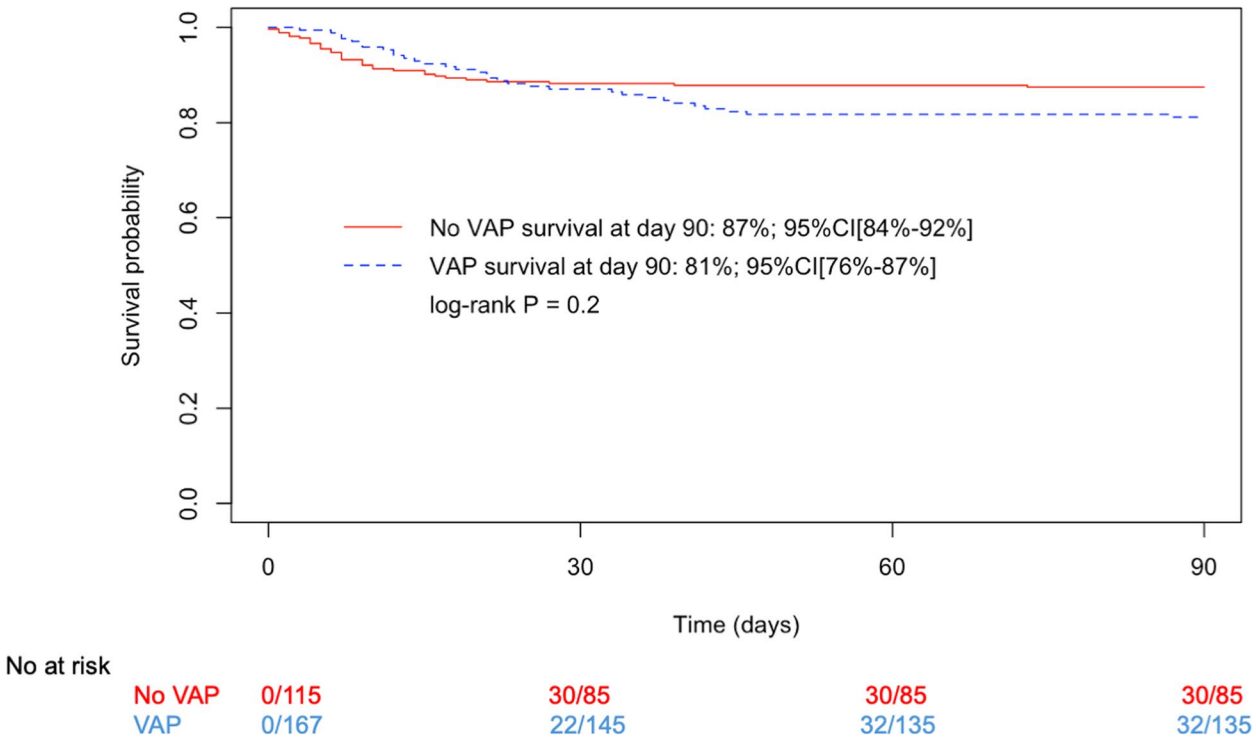

Fig. 4 Kaplan–Meier survival according to the occurrence of ventilator associated pneumonia. VAP, ventilator associated pneumonia.–- VAP,—no VAP

of patients assisted by mechanical ventilation was 75% vs. 65% in our cohort. However, higher mortality rates have been reported, such as that observed by Grasselli et al. in Lombardy in February 2020, i.e. 44.3% with 88% of patients on mechanical ventilation [6]. While the prospective multicenter European COVID-ICU study, conducted from February to May 2020, observed a mortality rate at D28 of 26% in a population of similar severity to ours [19]. In contrast, Gupta et al. [20] reported, in a North American multicenter study, a higher mortality at D28 of 35.4%, but the patients suffered more marked respiratory failure, with a median PaO_2/FiO_2 ratio of 124 (86–188) mmHg. In fact, our patients admitted in the first wave had similar severity, notably in terms of frailty scores and the number of patients ventilated (90%) and had a mortality rate of 26%. The reduction in mortality we observed in subsequent waves (10–11%) was also observed by the COVID-ICU team. In this study, the downward trend observed was attributed to less use of mechanical ventilation [19]. From the second wave onwards, we observed lower and stable mortality rates at 10–11%, with a longer duration of mechanical ventilation

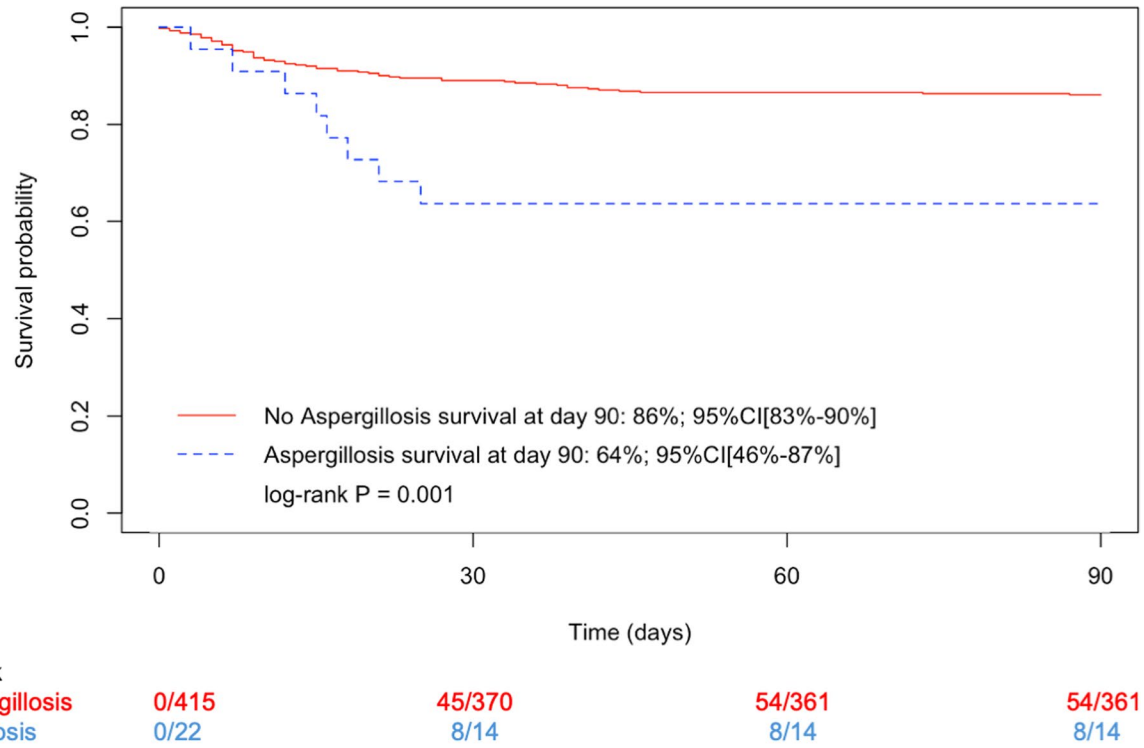

Fig. 5 Kaplan–Meier survival according to the occurrence of Covid associated pulmonary aspergillosis. CAPA, Covid associated pulmonary aspergillosis

and a higher incidence of VAP. However, mortality rates of 30% have been reported as early as autumn 2020, despite lower patient severity (lower severity scores and less frequent use of ventilatory support) [21–25]. Only Kurtz et al. reported a mortality rate of 11% but this series included a population (13,301 patients from February to December 2020) with a median age of 54 (41;69) years, a median PaO_2/FiO_2 ratio of 221 (108;357) mmHg, and a low rate of invasive and non-invasive mechanical ventilation (31%) [26]. The differences in mortality between the different series could be linked to different sanitary measures and care logistics, and to the geographical progression of the new emerging SARS-CoV-2 variants. Because of its temporality (occurring after the first patients in Eastern France and Ile de France), better anticipation of the crisis in Occitanie probably also contributed.

The Occitanie region seems to have a resuscitation capacity above the French average [27], bearing in mind that fairly significant disparities are reported in Europe. In the Dutch cohort of 7,000 patients recruited between February 2020 and June 2021 with characteristics similar to ours and a rate of mechanical ventilation decreasing from 79 to 58%, ICU mortality was 24.2%, with no improvement between the 3 waves [21]. The authors highlighted the low intensive care bed capacity in the Netherlands (6.4 per 100,000 inhabitants). In addition, the multicenter studies were carried out in a number of hospitals whose quality of care may have been uneven or at least inhomogeneous (e.g. AZUREA, 16 University Hospitals and 13 Hospital Centers). The improved prognosis we observed cannot be linked to earlier management, since the time from first symptoms to admission to intensive care was comparable (9 (7;12) days). However, patients admitted after the first wave were younger and significantly less severe, which at least partly explains this reduction in mortality. In addition, the recommendations of learned societies and medical experience over time have helped optimize management [28, 29]. For example, early intubation, initially recommended, is now postponed as long as possible. A meta-analysis published in March 2021, comparing the mortality of "early intubated" patients (within 24 h of ICU admission) with that of "late intubated" patients (more than 24 h after admission), showed no difference in mortality [30]. In addition, the use of systemic corticosteroids in patients requiring oxygen therapy will become routine from June 2020, following publication of the results of the randomized RECOVERY trial [15]. This was the first treatment to demonstrate a reduction in mortality in SARS-CoV-2.

Our analysis identified risk factors for mortality. These were age, number of comorbidities and overall severity on admission (SOFA and lactatemia), in line with

previously published results. A later admission to critical care from the onset of symptoms is protective in our study. This finding was confirmed by the results of the COVID ICU study [19]. Of note, PaO_2/FiO_2 ratios were not associated with mortality, unlike the SOFA score.

In our cohort, almost 2/3 of ventilated patients were treated for an episode of VAP, corroborating the rate reported in the COVID ICU study: 58% [19]. This incidence seems particularly and significantly higher in the case of SARS-CoV-2 than for other causes of mechanical ventilation (48% vs. 13%) [31]. The role of immunosuppression induced by the immune dysregulation of SARS-CoV-2 [32] seems to explain this fact, as well as a systematic screening effort in the management of patients ventilated for SARS-CoV-2. Vacheron et al., in a large-scale multicenter French study, also found this contrast (29% of VAPs in SARS-CoV-2-positive ventilated patients versus 13% in SARS-CoV-2-negative ventilated patients) [33]. Like Grasselli et al., we were unable to prove an association between the occurrence of a VAP and mortality, but an association with prolonged hospital stay [6]. Vacheron et al. [11] did, however, find an increase in mortality attributed to the occurrence of VAP. Anyway, the longer hospital stay could be linked to the greater difficulty of treating these pneumonias [33]. Our results reflect the factors associated with the occurrence of VAP identified in the analysis by Reyes et al. in which Dexamethasone was an independent risk factor for VAP [34]. The effect of corticosteroids must be analyzed with caution, given that patients in the first wave did not benefit from this therapeutic option. The duration of mechanical ventilation is an independent factor in the occurrence of VAP, a factor widely reported in general ICU studies.

Incidence rates of CAPA are highly variable, ranging from 0 to 30% of ventilated patients, depending on the series, despite recent clarifications in the microbiological definition of bronchopulmonary aspergillosis [35–37]. In a multicenter retrospective study conducted in 2020, Dellière et al. found a CAPA rate similar to our own, with a probable diagnosis in 8% of ventilated patients [38]. Higher incidence rates have been reported, such as 27.7% by Bartoletti et al. bearing in mind that bronchial fibroscopy was routinely performed for deep respiratory sampling at D0 and D7 [39]. It is possible that our incidence rate was underestimated due to undiagnosed disease. However, a galactomannan blood test was regularly performed, and respiratory sampling was undertaken in cases of clinical or radiological suspicion or unexplained persistent fever [35].

The susceptibility of immunocompetent patients to develop CAPA is probably multifactorial, including immune dysregulation, ARDS-induced lung injury, invasive ventilation, and lymphopenia [38]. In univariate analysis, neither Dexamethasone nor immunosuppressive treatments were associated with the occurrence of CAPA in our cohort. The combination of Dexamethazone and Tocilizumab has, however, been reported as a risk factor for CAPA [37, 40]. We observed that the occurrence of CAPA was associated with higher mortality (36% vs. 15% $p=0.0114$), but lower than that reported: 60%, or even 80%-100% in immunocompromised patients [41]. The occurrence of CAPA is to be compared with the mortality of bronchopulmonary aspergillosis in influenza, which is 36% [42]. An observational multicenter study, including 295 Cov2 SARS with CAPA, failed to show any benefit of preventive screening by measuring galactomannan in BAL to improve disease outcome [43].

Our work has several limitations. This was an observational study, with its advantages and disadvantages. Despite the size of our cohort, our results must be extrapolated to a larger scale with caution, especially as inter-regional disparities are significant during a pandemic. Lastly, we have had to interrupt inclusions in October 2021, and so miss out on an exhaustive analysis of all 5 waves. Data concerning vaccination, new treatments with Tocilizumab and the emergence of new variants could not be processed in this study.

Conclusion

The overall mortality of severe SARS Cov2 patients is 12%, with a significant drop over successive waves. Age, physiological frailty and severity of clinical status on admission (SOFA and lactatemia) are associated with the outcome. Healthcare-associated infections are responsible for a significant increase in ICU- and hospital-length of stay while the occurrence of CAPA is predictive of reduced survival to D90. The lessons learnt from these last few years of prolific research give us the means to face, better armed, a possible resurgence of cases, or the emergence of new variants, or even the evolution of this pathology towards a seasonal flu-like epidemic.

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Authors' contributions
ST: data curation, methodology, writing, review and editing; RL: formal analysis, methodology, validation, review and editing: N B, V B, V M, N Benchabane, L P, D D, P C, S M, B J, E B, L L, C P: data curation, formal analysis and methodology; KK: conceptualization, formal analysis, investigation, methodology, supervision, writing, review and editing.

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Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The ethics committee from the institutional review board (IRB) of the Montpellier University Hospital approved the study (approval number: IRB-MTP_2022_04_202201037) and waived the need for informed consent. No data allowing patient identification were collected. Clinical investigations were conducted in accordance with both French law and the 2008 Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou C-Q, He J-X, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382:1708–20.
2. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese center for disease control and prevention. JAMA. 2020;323:1239–42.
3. COVID-19 cases | WHO COVID-19 dashboard. datadot. Available from: https://data.who.int/dashboards/covid19/cases. Cited 2024 Feb 22.
4. Rosenthal N, Cao Z, Gundrum J, Sianis J, Safo S. Risk factors associated with in-hospital mortality in a US national sample of patients with COVID-19. JAMA Netw Open. 2020;3:e2029058.
5. Gao M, Piernas C, Astbury NM, Hippisley-Cox J, O'Rahilly S, Aveyard P, et al. Associations between body-mass index and COVID-19 severity in 6·9 million people in England: a prospective, community-based, cohort study. Lancet Diabetes Endocrinol. 2021;9:350–9.
6. Grasselli G, Greco M, Zanella A, Albano G, Antonelli M, Bellani G, et al. Risk factors associated with mortality among patients with COVID-19 in intensive care units in lombardy. Italy JAMA Intern Med. 2020;180:1345–55.
7. Kim L, Garg S, O'Halloran A, Whitaker M, Pham H, Anderson EJ, et al. Risk factors for intensive care unit admission and in-hospital mortality among hospitalized adults identified through the US coronavirus disease 2019 (COVID-19)-associated hospitalization surveillance network (COVID-NET). Clin Infect Dis. 2021;72:e206–14.
8. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature. 2020;584:430–6.
9. Deng G, Yin M, Chen X, Zeng F. Clinical determinants for fatality of 44,672 patients with COVID-19. Crit Care. 2020;24:179.
10. Aziz S, Arabi YM, Alhazzani W, Evans L, Citerio G, Fischkoff K, et al. Managing ICU surge during the COVID-19 crisis: rapid guidelines. Intensive Care Med. 2020;46:1303–25.
11. Vacheron CH, Lepape A, Savey A, Machut A, Timsit JF, Comparot S, et al. attributable mortality of ventilator-associated pneumonia among patients with COVID-19. Am J Respir Crit Care Med. 2022;206:61–169.
12. 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;40:373–83.
13. Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the infectious diseases society of america and the American thoracic society. Clin Infect Dis. 2016;63:e61-111.
14. WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Sterne JAC, Murthy S, Diaz JV, Slutsky AS, Villar J, et al. Association between administration of systemic corticosteroids and mortality among critically Ill patients with COVID-19: a meta-analysis. JAMA. 2020;324:1330–41.
15. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med. 2021;384:693–704.
16. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Crit Care Med. 2021;49:e1063–143.
17. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2021;397:1637–45.
18. Langford BJ, So M, Raybardhan S, Leung V, Westwood D, MacFadden DR, et al. Bacterial co-infection and secondary infection in patients with COVID-19: a living rapid review and meta-analysis. Clin Microbiol Infect. 2020;26:1622–9.
19. COVID-ICU Group on behalf of the REVA Network and the COVID-ICU Investigators. Clinical characteristics and day-90 outcomes of 4244 critically ill adults with COVID-19: a prospective cohort study. Intensive Care Med. 2021;47:60–73.
20. Gupta S, Hayek SS, Wang W, Chan L, Mathews KS, Melamed ML, et al. Factors associated with death in critically Ill patients with coronavirus disease 2019 in the US. JAMA Intern Med. 2020;180:1436–47.
21. Dongelmans DA, Termorshuizen F, Brinkman S, Bakhshi-Raiez F, Arbous MS, de Lange DW, et al. Characteristics and outcome of COVID-19 patients admitted to the ICU: a nationwide cohort study on the comparison between the first and the consecutive upsurges of the second wave of the COVID-19 pandemic in the Netherlands. Ann Intensive Care. 2022;12:5.
22. Carbonell R, Urgelés S, Rodríguez A, Bodí M, Martín-Loeches I, Solé-Violán J, et al. Mortality comparison between the first and second/third waves among 3,795 critical COVID-19 patients with pneumonia admitted to the ICU: A multicentre retrospective cohort study. Lancet Reg Health Eur. 2021;11:100243.
23. Auld SC, Harrington KRV, Adelman MW, Robichaux CJ, Overton EC, Caridi-Scheible M, et al. Trends in ICU mortality from coronavirus disease 2019: a tale of three surges. Crit Care Med. 2022;50:245–55.
24. Dennis JM, McGovern AP, Thomas NJ, Wilde H, Vollmer SJ, Mateen BA. Trends in 28-day mortality of critical care patients with coronavirus disease 2019 in the United Kingdom: a national cohort study, March 2020 to January 2021. Crit Care Med. 2021;49:1895–900.
25. Roger C, Collange O, Mezzarobba M, Abou-Arab O, Teule L, Garnier M, et al. French multicentre observational study on SARS-CoV-2 infections intensive care initial management: the FRENCH CORONA study. Anaesth Crit Care Pain Med. 2021;40:100931.
26. Kurtz P, Bastos LSL, Dantas LF, Zampieri FG, Soares M, Hamacher S, et al. Evolving changes in mortality of 13,301 critically ill adult patients with COVID-19 over 8 months. Intensive Care Med. 2021;47:538–48.
27. Fiche 13 - Les capacités d'accueil en soins critiques.pdf. Available from: https://drees.solidarites-sante.gouv.fr/sites/default/files/2021-07/Fiche%2013%20-%20Les%20capacit%C3%A9s%20d%E2%80%99accueil%20en%20soins%20critiques.pdf. Cited 2024 Feb 23.
28. Bartoletti M, Azap O, Barac A, Bussini L, Ergonul O, Krause R, et al. ESCMID COVID-19 living guidelines: drug treatment and clinical management. Clin Microbiol Infect. 2022;28:222–38.
29. WHO-2019-nCoV-therapeutics-2022.2-eng.pdf. Available from: https://iris.who.int/bitstream/handle/10665/352285/WHO-2019-nCoV-therapeutics-2022.2-eng.pdf. Cited 2024 Feb 23.
30. 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;25:121.

31. Maes M, Higginson E, Pereira-Dias J, Curran MD, Parmar S, Khokhar F, et al. Ventilator-associated pneumonia in critically ill patients with COVID-19. Crit Care. 2021;25:25.
32. Jamilloux Y, Henry T, Belot A, Viel S, Fauter M, El Jammal T, et al. Should we stimulate or suppress immune responses in COVID-19? Cytokine and anti-cytokine interventions. Autoimmun Rev. 2020;19:102567.
33. Vacheron C-H, Lepape A, Savey A, Machut A, Timsit JF, Vanhems P, et al. Increased incidence of ventilator-acquired pneumonia in coronavirus disease 2019 patients: a multicentric cohort study. Crit Care Med. 2022;50:449–59.
34. Reyes LF, Rodriguez A, Bastidas A, Parra-Tanoux D, Fuentes YV, García-Gallo E, et al. Dexamethasone as risk-factor for ICU-acquired respiratory tract infections in severe COVID-19. J Crit Care. 2022;69:154014.
35. Koehler P, Bassetti M, Chakrabarti A, Chen SCA, Colombo AL, Hoenigl M, et al. Defining and managing COVID-19-associated pulmonary aspergillosis: the 2020 ECMM/ISHAM consensus criteria for research and clinical guidance. Lancet Infect Dis. 2021;21:e149–62.
36. Verweij PE, Brüggemann RJM, Azoulay E, Bassetti M, Blot S, Buil JB, et al. Taskforce report on the diagnosis and clinical management of COVID-19 associated pulmonary aspergillosis. Intensive Care Med. 2021;47:819–34.
37. Hurt W, Youngs J, Ball J, Edgeworth J, Hopkins P, Jenkins DR, et al. COVID-19-associated pulmonary aspergillosis in mechanically ventilated patients: a prospective, multicentre UK study. Thorax. 2024;79:75–82.
38. Dellière S, Dudoignon E, Fodil S, Voicu S, Collet M, Oillic P-A, et al. Risk factors associated with COVID-19-associated pulmonary aspergillosis in ICU patients: a French multicentric retrospective cohort. Clin Microbiol Infect. 2020;27(790):e1-5.
39. Bartoletti M, Pascale R, Cricca M, Rinaldi M, Maccaro A, Bussini L, et al. Epidemiology of invasive pulmonary aspergillosis among intubated patients with COVID-19: a prospective study. Clin Infect Dis. 2021;73:e3606–14.
40. Calderón-Parra J, Mills-Sanchez P, Moreno-Torres V, Tejado-Bravo S, Romero-Sánchez I, Balandin-Moreno B, et al. COVID-19-associated pulmonary aspergillosis (CAPA): Risk factors and development of a predictive score for critically ill COVID-19 patients. Mycoses. 2022;65:541–50.
41. Contou D, Dorison M, Rosman J, Schlemmer F, Gibelin A, Foulet F, et al. Aspergillus-positive lower respiratory tract samples in patients with the acute respiratory distress syndrome: a 10-year retrospective study. Ann Intensive Care. 2016;6:52.
42. Coste A, Frérou A, Raute A, Couturaud F, Morin J, Egreteau P-Y, et al. The extent of aspergillosis in critically ill patients with severe influenza pneumonia: a multicenter cohort study. Crit Care Med. 2021;49:934–42.
43. Van Grootveld R, Van der Beek MT, Janssen NAF, Ergün M, van Dijk K, Bethlehem C, et al. Incidence, risk factors and pre-emptive screening for COVID-19 associated pulmonary aspergillosis in an era of immunomodulant therapy. J Critical Care. 2023;76:154272.

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