

Risk factors for mortality in a multicenter cohort of mechanically ventilated COVID-19 patients in Belgium.

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Research

Keywords: Corticosteroids, Covid-19, Intensive care, Mechanical ventilation, Prognostic factors

Posted Date: August 5th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-52427/v1>

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Abstract

Background: Considering the high mortality rate of severe Covid-19 patients, it is necessary to identify prognostic factors and therapies which could be valuable in this setting.

Methods: The method consisted in a multicentric retrospective analysis in all consecutive Covid-19 patients admitted to intensive care unit (ICU) and mechanically ventilated for more than 24 hours from March 1 to April 25, 2020.

Admission date, age, sex, body mass index, underlying conditions, treatments, physiological values, use of vasopressors, renal replacement therapy and extracorporeal membrane oxygenation, duration of mechanical ventilation, length of ICU stay, ICU and ventilator-free days at day 42 were collected. Primary outcome was survival.

Simple and multiple time-dependent Cox regression models were used to assess the effects of factors on survival.

Results: Out of 2003 patients hospitalized for SARS-CoV-2, 361 were admitted to the participating ICUs, 257 were ventilated for more than 24 hours and 247 were included in the study. The length of stay in ICU was 21 (12-32) days and the mortality rate was 45%. Using multiple regression, risk factors for mortality were age, high serum creatinine value, low mean arterial pressure, low lymphocytes count on day 0 and the absence of corticosteroid therapy during the first week of mechanical ventilation. The mortality rate of the patients who received corticosteroids was 34% and 48% for patients who did not ($p = 0.01$).

Conclusion: In this multicenter cohort, the mortality of patients with SARS-CoV-2 pneumonia treated with mechanical ventilation was high. The risk factors for mortality included age, renal and circulatory dysfunction, lymphopenia and the absence of corticosteroid therapy during the first week of mechanical ventilation.

Background

In late 2019, the virus responsible for COVID-19 was identified and called SARS-CoV-2. In China, 5% of COVID-19 patients were admitted in intensive care unit (ICU), 2,3% were ventilated and 1,4% died [1]. In early 2020, Covid-19 quickly spread in Europe and the first 9 cases were described in Belgium on February 4, 2020. In Belgium, the highest hospitalization rate was 629 patients a day on March 28 while the highest number of patients ($n = 1285$) in ICU was reached on April 8. The highest mortality rate was 340 patients a day on April 12 and on April 25, 4355 patients were still hospitalized including 970 in ICU.

Considering the high mortality rate of severe COVID-19 patients, it is necessary to identify prognostic factors and therapies which could be valuable in this setting [1]. Since the start of the SARS-CoV-2 pandemic, the need for trials to assess the benefit of antiviral treatment, anti-cytokine drugs, convalescent

plasma and hydroxychloroquine was advocated by the world health organization. However, evidence of the efficacy of such strategies is still lacking. Hydroxychloroquine was tested because of its capacity to increase endosomal pH and interfere with the glycosylation of cellular receptor of SARS-CoV-2 [2, 3] but no clinical benefit could be shown in a randomized controlled trial [4]. The main hypothesis supporting the use of anti-inflammatory drugs is the concept of “cytokine storm”, referring to an exacerbation of the host response mimicking what is observed after CAR-T cells administration for hematologic malignancies, and supposedly responsible for mortality of Covid-19 despite apparent clearance of the virus [5, 6]. Among anti-inflammatory drugs, steroids are frequently used because they are cheap and easily available around the world, and recommended use in both septic shock [7] and acute respiratory distress syndrome (ARDS) [8]. The Surviving Sepsis Campaign guidelines were recently adapted to COVID-19, despite the absence of evidence in this particular setting [9]. Eventually, a prospective before-after study suggested a beneficial effect of methylprednisolone use in patients with moderate to severe COVID-19 [10]. Other treatments, either antivirals, convalescent plasma or anti-cytokines are still marginally used because of their cost and/or low availability.

Until now, the COVID-19 patients treated with tracheal intubation and mechanical ventilation have been reported to have short-term mortality rates between 28 and 81%, depending on the patients characteristics [11–15]. Two months after the dissemination of COVID-19 in Belgium, we set up a clinical database of the patients admitted to 12 ICUs in Wallonia and requiring mechanical ventilation to describe these patients’ course and the factors associated with their outcomes.

Methods

Study design and participants

This retrospective observational cohort study was performed in the following 12 hospitals of Wallonia in Belgium: Centre Hospitalier Universitaire of Liege, Centre Hospitalier Régional of Liege, Centre Hospitalier Chrétien of Liege, Centre Hospitalier Régional of Verviers, Centre Hospitalier Chrétien of Hermalle, Centre Hospitalier Régional of Huy, Clinique Notre-Dame de Grâce of Gosselies, Centre Hospitalier Universitaire (Université Catholique de Louvain) of Dinant, Klinik St Josef VoG of St Vith, Centre Hospitalier of Malmedy, Centre Hospitalier du Bois de l’Abbaye of Seraing, and Centre Hospitalier André Renard of Herstal.

The creation of the database was planned during the study period and collection started after approval of the Ethics Committee.

The study protocol was approved by the Ethics Committee of the University Hospital of Liege on May 29, 2020. Due to the retrospective nature of the data collected, in accordance with Belgian law, no consent from the patient was required.

Procedures

We identified all consecutive adult patients admitted to the participating ICUs for acute respiratory failure due to SARS-CoV-2 pneumonia (diagnosed with a chest tomography suggestive of COVID-19 and with a positive polymerase chain reaction (PCR) for SARS-CoV-2 in nasal swab), and mechanically ventilated for at least 24 hours from March 1 to April 25, 2020. The patients were studied for their entire hospital stay or for a minimum of 42 days in case of prolonged hospital stay. The following data were retrospectively collected and entered in a clinical report form transmitted to the participating ICUs. On ICU admission, the admission date, age, gender, Body Mass Index (BMI), SARS-CoV-2 viral load (Cycles Threshold, Gene E), quantitative chest CT-scan analysis and underlying conditions (smoking, chronic kidney disease, diabetes, hypertension) were collected. During the ICU stay, diuresis, mean arterial pressure, PaO₂, FiO₂, PaO₂/FiO₂ ratio, and laboratory blood values (creatinine, bilirubin, ferritin, C-reactive protein (CRP), D-dimer, platelets count and lymphocytes count) were collected on days 0 and 7. Sequential organ failure assessment (SOFA) score and Glasgow coma score were calculated on days 0 and 7 after ICU admission. Use of drugs oriented against COVID-19 (hydroxychloroquine, azithromycin, corticosteroid and monoclonal antibodies directed against interleukin (IL)-1 or 6), use of vasopressors, renal replacement therapy (RRT), extra-corporeal membrane oxygenation (ECMO), duration of mechanical ventilation, length of ICU stay, and ICU and ventilator-free days at day 42 were collected. Patients were defined as treated with corticosteroid for COVID-19 if the corticosteroid therapy (methylprednisolone or dexamethasone) was started between day 0 and day 7 after ICU admission. In particular, corticosteroids use at a later stage of the stay, either for rescue therapy of ARDS or for prevention of extubation stridor was not considered.

Outcomes

The primary outcome was survival during the hospital stay. Secondary outcomes included use of vasopressors, RRT or ECMO, ICU and ventilator-free days at day 42, and evolution of the main physiological values between days 0 and 7.

Statistical methods

Quantitative variables are reported as median and interquartile range (Q1-Q3). Categorical variables are expressed as number (%).

A Kaplan-Meier plot was used to describe survival rate.

Simple and multiple time-dependent Cox regression models were used to assess the effects of factors on survival. All the variables which had a p-value lower than the critical level of 0.1 were selected for the multivariate model.

A p-value < 0.05 was considered significant. Missing data were not replaced. Calculations were done using SAS (version 9.4) and R (version 3.6.2) softwares.

Results

From March 1 to April 25, 2020, 2003 adult patients diagnosed with SARS-CoV-2 pneumonia were hospitalized and 361 were admitted to the 12 participating ICUs for acute respiratory failure. Of these, 257 patients were mechanically ventilated for more than 24 hours and 247 included in the data base (Fig. 1). Because of too many missing data, ten patients were not included because they were transferred to another hospital (n = 5) or from another hospital (n = 5) during their ICU stay.

The baseline characteristics of the 247 included patients are shown in Table 1. The viral load assessed in 142 patients was 31,98 (28,36 – 34,39) (Cycles Threshold, Gene E). Quantitative chest CT-scan analysis on admission showed that pneumonia extended to 25% or more in 76% of the patients (electronic supplement Table 1). Corticosteroid therapy was started in 58 (23%) patients between days 0 and 7 of ICU admission and 225 (91%) received hydroxychloroquine alone or in combination with corticosteroid and/or azythromycin (electronic supplement Table 2). Sixty-nine (28%) patients needed RRT and 215 patients (87%) were treated with norepinephrine during their ICU stay. Four patients (1,6%) were on ECMO.

Table 1

Baseline characteristics and treatment, and association with survival in mechanically ventilated COVID-19 patients.

Variable	All N = 247		Survivors N = 136		Simple Cox p- value	Multiple Cox- adjusted p-value
	N (%) or median (Q1-Q3)	N Missing	N (%) or median (Q1-Q3)	N (%) or median (Q1-Q3)		
Male sex	172 (69.6)	-	95 (69.9)	77 (69.4)	0.92	-
Age (years)	65 (57–72)	-	63 (55–69)	69 (60–77)	< 0.0001	< 0.0001
BMI (kg/m ²)	29 (26–33)	14	29 (26–33)	30 (26–33)	0.88	-
Tobacco	21 (8.5)	1	8 (5.9)	13 (11.7)	0.05	0.07
Chronic kidney disease	26 (10.5)	-	8 (5.9)	18 (16.2)	0.0007	0.71
Diabetes	88 (35.8)	1	48 (35.6)	40 (36.0)	0.98	-
Hypertension	141 (57.1)	-	77 (56.6)	64 (57.7)	0.71	-
COPD	32 (13.0)	-	13 (9.6)	19 (17.1)	0.09	0.63
Cancer	11 (6.1)	66	5 (5.3)	6 (7.0)	0.74	-
Immunodeficiency	16 (6.5)	-	6 (4.4)	10 (9.0)	0.22	-
SOFA	6 (4–8)	-	5 (3–7)	7 (5–9)	< 0.0001	0.27
PaO ₂ (mmHg)	74 (62–90)	25	72 (62–90)	75 (64–91)	0.95	-
FiO ₂ (%)	80 (60–90)	17	78 (60–90)	80 (65–100)	0.09	0.19
PaO ₂ / FiO ₂	103 (82–132)	25	108 (83–140)	96 (79–128)	0.83	-
Platelet count (10 ³ /mm ³)	207 (156–290)	-	209 (160–285)	207 (155–293)	0.79	-

Abbreviations: BMI: body mass index; COPD: chronic obstructive pulmonary disease; SOFA: sequential organ failure assessment; MAP: mean arterial pressure; CRP: C- reactive protein. *Cox model on log-transformed values.

Variable	All N = 247	N Missing	Survivors N = 136	Non- survivors N = 111	Simple Cox p- value	Multiple Cox- adjusted p-value
	N (%) or median (Q1-Q3)		N (%) or median (Q1-Q3)	N (%) or median (Q1-Q3)		
Bilirubin (mg/dl)	0.64 (0.49– 0.94)	1	0.67 (0.50– 0.97)	0.60 (0.42– 0.93)	0.42	-
Glasgow coma scale = 15	185 (77.4)	8	109 (82.6)	76 (71.0)	0.05	0.49
Creatinin (mg/dl)	1.00 (0.78– 1.37)	1	0.91 (0.71– 1.21)	1.20 (0.88– 1.73)	< 0.0001	< .0001
MAP < 70 mmHg	89 (36.0)	-	37 (27.2)	52 (46.8)	0.0004	0.01
Norepinephrin use	128 (51.8)	-	58 (42.6)	70 (63.1)	0.0021	0.41
Diuresis		1			< 0.0001	0.25
≥ 500 ml/day	226 (91.9)		132 (97.1)	94 (85.5)		
200–500 ml/day	11 (4.5)		4 (2.9)	7 (6.4)		
≤ 200 ml/day	9 (3.7)		0 (0.0)	9 (8.2)		
CRP (mg/l)	175 (108– 258)	-	172 (107– 243)	179 (109– 261)	0.33	-
D-dimer (ng/ml)*	1500 (868– 3832)	84	1305 (843– 3190)	1938 (990– 4000)	0.13	-
Lymphocyte count (10 ³ /mm ³)*	0.80 (0.55– 1.05)	2	0.84 (0.60– 1.10)	0.75 (0.51– 1.02)	0.06	0.02
Ferritin (mcg/l)*	1185 (582– 3053)	163	1281 (578– 2790)	1041 (587– 3196)	0.43	-
Hydroxychloroquin use	225 (91.1)	-	128 (94.1)	97 (87.4)	0.02	0.46

Abbreviations: BMI: body mass index; COPD: chronic obstructive pulmonary disease; SOFA: sequential organ failure assessment; MAP: mean arterial pressure; CRP: C- reactive protein. *Cox model on log-transformed values.

Variable	All N = 247		Survivors N = 136	Non- survivors N = 111	Simple Cox p- value	Multiple Cox- adjusted p-value
	N (%) or median (Q1-Q3)	N Missing	N (%) or median (Q1-Q3)	N (%) or median (Q1-Q3)		
Azythromycin use	107 (43.3)	-	59 (43.4)	48 (43.2)	0.82	-
Corticosteroids use	58 (23.5)	-	38 (27.9)	20 (18.0)	0.05	0.01
Abbreviations: BMI: body mass index; COPD: chronic obstructive pulmonary disease; SOFA: sequential organ failure assessment; MAP: mean arterial pressure; CRP: C- reactive protein. *Cox model on log-transformed values.						

Table 2

Evolution of physiological variables between Day 0 to Day 7 (day 7 – day 1 value) in 212 mechanically ventilated COVID-19 patients surviving at least 7 days.

Variable	All N = 212	N Missing	Survivors N = 136	Non- survivors N = 76	HR	IC 95%	p- value
	median (Q1; Q3)		median (Q1; Q3)	median (Q1; Q3)			
SOFA	1 (-1 ; 3)	4	0 (-2 ; 3)	2 (-1 ; 5)	1.11	1.04– 1.19	0.002
PaO ₂ / FiO ₂	26 (-14 ; 66)	28	29 (-12 ; 73)	18 (-17 ; 49)	0.77	0.55– 1.06	0.11
Platelet count (10 ³ /mm ³)	93 (10 ; 167)	3	116 (45; 194)	44 (-34; 115)	0.996	0.994– 0.998	< 0.0001
Bilirubin (mg/dl)	0.00 (-0.23; 0.30)	11	0.01 (-0.23; 0.30)	0 (-0.22; 0.41)	0.86	0.71– 1.04	0.12
Glasgow	0 (0; 0)	13	0 (0; 0)	0 (0; 0)	1.03	0.98– 1.09	0.28
Creatinin (mg/dl)	-0.03 (-0.24; 0.50)	2	-0.04 (-0.23; 0.30)	0.02 (-0.28; 1.03)	1.17	1.02– 1.34	0.03
CRP (mg/l)	-8 (-89; 65)	2	-32 (-96; 48)	27 (-57; 144)	1.003	1.001– 1.005	0.001
D-dimer (ng/ml) *	280 (-590 ; 1750)	153	0 (-933 ; 1270)	538 (-46 ; 2638)	1.31	0.79– 2.17	0.29
Lymphocytes (10 ³ /mm ³) *	-0.04 (-0.29 ; 0.35)	36	0.06 (-0.28 ; 0.40)	-0.14 (-0.30 ; 0.11)	0.57	0.37– 0.87	0.01
Ferritin (mcg/l)	-76 (-503 ; 11)	190	0 (-295 ; 28)	-539 (-1340 ; 0)	0.999	0.998- 1.000	0.23
Abbreviations: SOFA: sequential organ failure assessment; CRP: C- reactive protein.							
*Cox model on the difference of log-transformed values.							

Survival probability was 75% at 12 days and median survival time was 82 days (electronic supplement Fig. 1). Overall mortality was 111/247 (45%). Mortality of the patients who received corticosteroids was 34% (20/58) while it was 48% (91/189) in patients who did not (p = 0,01) (Fig. 2).

As opposed to survivors, non-survivors were older and suffered more often from chronic kidney disease (Table 1). On Day 0, non-survivors had higher SOFA score and serum creatinine value, lower mean arterial

pressure and diuresis. Non-survivors were also more often treated with norepinephrine during the first day in ICU. Survivors received more frequently corticosteroid and hydroxychloroquine.

Evolution for SOFA score, PaO₂/FiO₂ ratio, platelets count, bilirubin value, creatinine value, Glasgow coma score, ferritin value, CRP value, D-dimer value, and lymphocytosis during the first week of ICU stay are displayed on Table 2 (electronic supplement Table 3). In non-survivors, SOFA score, serum creatinine and CRP values increased, and lymphocytes count decreased significantly. Platelets count increased significantly less in non-survivors than in survivors.

Length of stay in hospital was 26 (13–42) days, length of stay in ICU was 21 (12–32) days, duration of ventilation 16 (9–26) days, ventilator-free days at 42 days was 0 (0.0–22.0) and ICU-free days at 42 days was 0.0 (0.0–17.0) for the entire population. Ventilator-free and ICU-free days were 21.0 (13.0–30.0) and 15.0 (3.0–25.0) in survivors, respectively (electronic supplement Table 4 and Fig. 2).

Using multiple regression, the predictors of mortality were age, creatinine value, mean arterial pressure lower than 70 mmHg, and lymphocytes count on day 0 and absence of corticosteroid use (Table 1). Survival probability was significantly higher in patients who received corticosteroids ($p = 0,01$) (Fig. 2). Survival probability was 75% at 23 days in patients who received corticosteroids versus at 10 days for those who did not (Fig. 2).

Discussion

In this retrospective multicenter study of 247 consecutive patients with SARS-CoV-2 pneumonia mechanically ventilated more than 24 hours, we observed that mortality was as high as 45% and that the factors associated with mortality were age, high creatinine value, low mean arterial pressure, low lymphocytes count and absence of corticosteroid use.

The characteristics of our cohort are consistent with what was observed by previous authors [11–15]. These series assessed 37 to 1150 mechanically ventilated patients and reported 28 to 81% mortality rates. However, these studies had only short-term follow-up, while we could study our patients for their entire hospital stay or for a minimum of 42 days in case of prolonged hospital stay.

The therapies used in our patients were consistent with those used during this phase of the pandemic. Regular use of hydroxychloroquine was based on initial observational studies [16], but its efficacy was not confirmed in subsequent randomized controlled trials [4, 17]. No recommendation prompted adjunctive treatments as no specific treatment had been proven to decrease mortality of Covid-19 critically ill patients on mechanical ventilation [18]. The “Recovery” trial recently demonstrated a beneficial effect of steroids in the most severe patients, but was going on at that time and is still being under reviewing assessment [19].

The outcomes of our patients indicate that death may occur at a late stage of the ICU stay. In fact, the length of organ support and ICU stay were particularly high in survivors. This may be explained by the

therapeutic obstinacy that has been commonly developed because the disease was not known and the potential for new treatments was real [20]. This also invites to coordinate long-term physical and psychological evaluation and rehabilitation in survivors of severe SARS-CoV-2 pneumonia [21].

The risk factors for mortality that we found included age, severity at ICU admission, as assessed by low mean arterial pressure or high creatinine values, lower lymphocyte count, and absence of corticosteroid therapy before day 7. When associated with acute respiratory failure, circulatory shock and acute renal failure are indicative of multiple organ dysfunction due to the severity of the disease [22]. Acute renal failure has been recognized as a major issue in COVID-19, and may reflect direct invasion of SARSCoV-2 into kidney tissue in most severe cases [23]. A reduction and exhaustion of the T lymphocytes has been observed in COVID-19, and particularly marked in patients requiring ICU admission [24]. The beneficial role of corticosteroids is consistent with what was recently anticipated by Fadel et al. in a before-after study [10] and observed in the “Recovery” multicenter randomized controlled trial performed in the United Kingdom [19], indicating that corticosteroid use was associated with a better prognosis mostly in those patients with severe disease. In Fadel’s study, a short course of methylprednisolone was associated with a reduction of the primary composite endpoint from 54 to 35%. Early released results of the Recovery trial showed that day 28 mortality decreased from 40 to 28% in patients receiving dexamethasone [19]. We also observed that mortality decreased from 48–34% in ICU patients on mechanical ventilation who received corticosteroid therapy.

Corticosteroids may act by controlling the intensity of the immune response to SARS-CoV-2 infection. At the start of the SARS-CoV-2 pandemic, based on prior literature about other respiratory viruses, several authors argued against the use of steroids outside research trials in COVID-19 patients because their use was associated with delay in the clearance of viral RNA from respiratory tract [25]. On the opposite, steroids have been shown to improve outcome in ARDS secondary to *Pneumocystis Carinii* pneumonia [26] and recently in ARDS of various causes [8]. Additionally, despite concerns that corticosteroids increase the risk of secondary infections, their use was also shown beneficial as an adjunctive treatment of septic shock [27]. The response to SARS-CoV-2 infection has recently been described as “cytokine storm” [28] which is defined as an excessive production of immune mediators. This excessive production of cytokines is a rationale to assess the efficacy of IL-6 and/or IL-1 blockade [29, 30].

Our study has several limitations. First, it was a retrospective analysis. This was due to the rapidity of occurrence of the COVID-19 in our country. This mode of spread precluded the possibility to homogenize the therapy protocols and data assessment. The retrospective nature of our study was attenuated by the fact that the study was decided while most patients were still in the hospital, resulting in very few missing data, and treated with conventional intensive care guidelines, in accordance with international guidelines. Second, the study was performed in one part of the country and our results may not be applicable to other regions. This was a multicenter study and we estimate that our hospitals did not suffer shortage of human or material resources in significantly different proportions than others Western countries, which could largely influence the mortality rate of the cohort. Third, at the time of the study, there was no

coercive guidelines for specific treatments or protocols. This may have led to different practices than in other regions of the world and reduced external validity of our results.

Conclusion

Retrospectively analyzing the data of a multicenter cohort, we observed that mortality of patients with SARS-CoV-2 pneumonia treated with mechanical ventilation was as high as 45% and median survival time was 82 days. In this series, the risk factors for mortality included age, renal and circulatory dysfunction, lymphopenia and the absence of corticosteroid use during the first week of mechanical ventilation. These findings support the continuing research for effective treatments in these particularly severe patients, as well as applying effective follow-up programs for those patients surviving intensive care for COVID-19.

Abbreviations

ARDS: acute respiratory distress syndrome; BMI:body mass index; CRP:C-reactive protein; ECMO:extracorporeal membrane oxygenation; ICU:intensive care unit; IL:interleukin; PCR:polymerase chain reaction; RRT:renal replacement therapy; SOFA:sequential organ failure assessment.

Declarations

Acknowledgements: not applicable

Authors' contributions:

All authors contributed to the study conception and design.

Data collection was performed by: Bernard Lambermont¹, Marie Ernst², Sandrine Boccar⁴, Pierre Demaret³, Christine Gurdebeke⁵, Cedric Van Brussel⁶, Manuel Quinonez⁷, Christophe J.J.Dubois⁸, Thierry Lemineur⁹,Thierry Njambou¹⁰, Benoit Akando¹¹, Damien Wertz¹², Julien Higny¹³, Marie Thys¹⁵, Nathalie Maes², François Lejeune⁶, Pierre François³, Vincent Fraipont⁴, Thierry Sottiaux⁶, Frédéric Foret¹³.

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The first draft of the manuscript was written by Bernard Lambermont¹ and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding None

Availability of data and material: The data used and/or analyzed in the present study are available from the corresponding author on reasonable request.

Ethics approval Study protocol was approved by Ethics Committee of the University Hospital of Liege on May 29, 2020.

Consent to participate Study protocol was approved by Ethics Committee of the University Hospital of Liege on May 29, 2020. Due to the retrospective nature of the data collected, in accordance with Belgian law, no consent of the patient was required.

Conflicts of interest/Competing interests None

Consent for publication Not applicable

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Figures

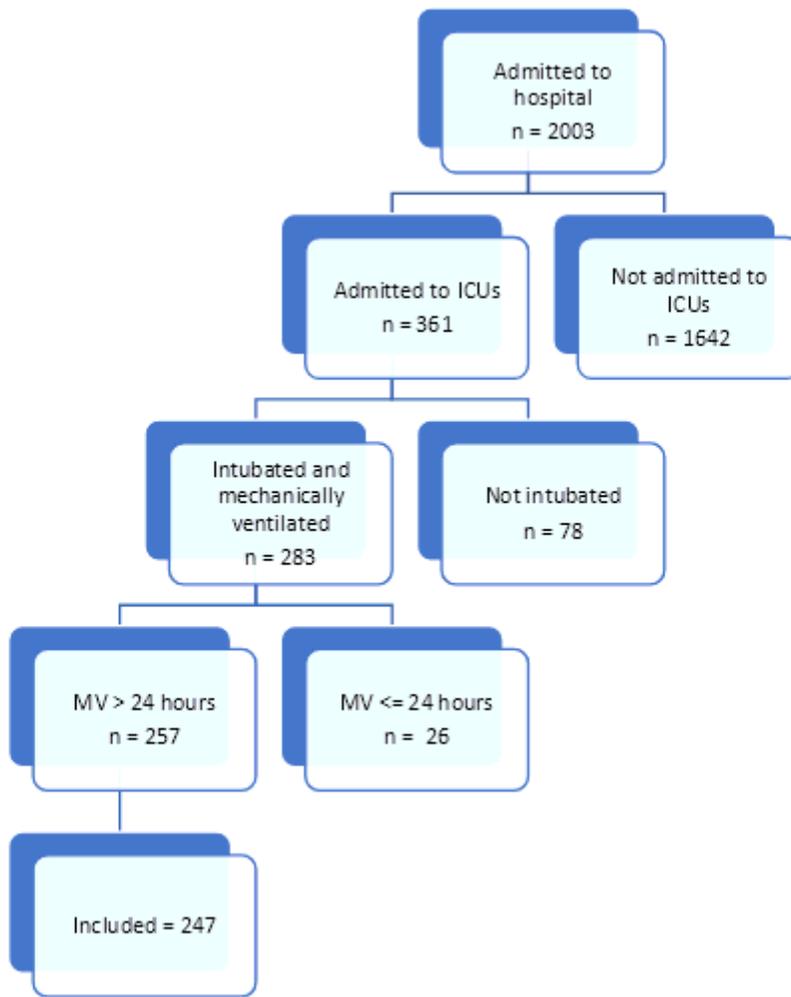


Figure 1

Flowchart of the patients admitted to the hospital for SARS-CoV-2 pneumonia. Abbreviation: MV: mechanical ventilation. Ten patients ventilated for more than 24 hours and transferred to another hospital (n = 5) or from another hospital (n=5) during their ICU stay were not included in the study because of too many missing data.

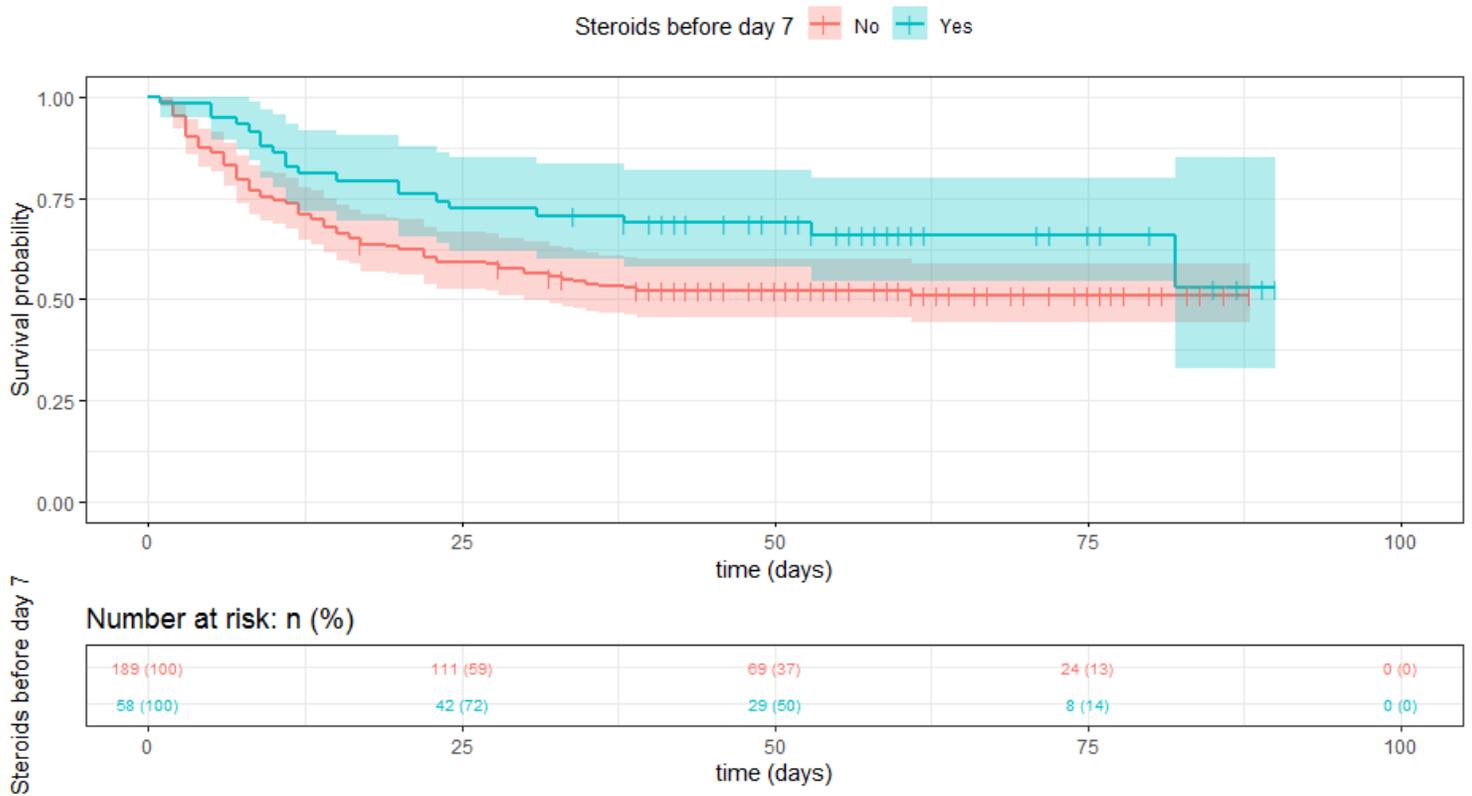


Figure 2

Kaplan-Meier survival probability plot of COVID-19 patients treated with and without corticosteroids during their first week of mechanical ventilation (adjusted p value = 0,01).

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