Characteristics, interventions and longer-term outcomes of COVID-19 ICU patients in Denmark - a nationwide, observational study

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DR NICOLAI HAASE (Orcid ID : 0000-0002-4668-0123)

DR BODIL STEEN STEEN RASMUSSEN (Orcid ID : 0000-0003-2190-145X)

DR RICARDO SANCHEZ GARCIA (Orcid ID : 0000-0001-7131-0645)

PROFESSOR ANDERS PERNER (Orcid ID : 0000-0002-4668-0123)

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Characteristics, interventions and longer-term outcomes of COVID-19 ICU patients in Denmark – a nationwide, observational study

Nicolai Haase1, Ronni Plovsing2, Steffen Christensen3, Lone Musaeus Poulsen4, Anne Craveiro Brøchner5, Bodil Steen Rasmussen6, Marie Helleberg7, Jens Ulrik Stæhr Jensen8, Lars Peter Kloster Andersen9, Hanna Siegel10, Michael Ibsen11, Vibeke Jørgensen12, Robert Winding13, Susanne Iversen14, Henrik Planck Pedersen15, Jacob Madsen6, Christoffer Sølling16, Ricardo Sanchez Garcia17, Jens Michelsen18, Thomas Mohr19, Anne Mannering20, Ulrick Skipper Espelund21, Helle Bundgaard22, Lynge Kirkegaard23, Margit Smitt24, David Levarett Buck25, Niels-Erik Ribergaard26, Helle Scharling Pedersen27, Birgitte Viebæk Christensen28, Anders Perner1

1) Department of Intensive Care, Rigshospitalet, Copenhagen, Denmark.
2) Department of Anesthesiology and Intensive Care, Hvidovre Hospital, Copenhagen, Denmark.
3) Department of Anesthesiology and Intensive Care, Århus University Hospital, Århus, Denmark
4) Department of Anesthesiology and Intensive Care, Zealand University Hospital, Køge, Denmark
5) Department of Anesthesiology and Intensive Care, Kolding Hospital, Kolding, Denmark

6) Department of Anesthesiology and Intensive Care, Ålborg University Hospital, Ålborg, Denmark
7) Department of Infectious Diseases, Rigshospitalet, Copenhagen, Denmark
8) Department of Respiratory Medicine, Herlev-Gentofte Hospital, Copenhagen, Denmark
9) Department of Anesthesiology and Intensive Care, Bispebjerg Hospital, Copenhagen, Denmark
10) Department of Anesthesiology and Intensive Care, Herlev-Gentofte Hospital, Copenhagen, Denmark
11) Department of Anesthesiology and Intensive Care, North Zealand Hospital, Hillerød, Denmark
12) Department of Cardiothoracic Anesthesiology, Rigshospitalet, Copenhagen, Denmark
13) Department of Anesthesiology and Intensive Care, Herning Hospital, Herning, Denmark
14) Department of Anesthesiology and Intensive Care, Slagelse Hospital, Slagelse, Denmark
15) Department of Anesthesiology and Intensive Care, Zealand University Hospital, Roskilde, Denmark
16) Department of Anesthesiology and Intensive Care, Viborg Hospital, Viborg, Denmark
17) Department of Anesthesiology and Intensive Care, Esbjerg Hospital, Esbjerg, Denmark
18) Department of Anesthesiology and Intensive Care, Odense University Hospital, Odense, Denmark
19) Department of Anesthesiology and Intensive Care, Herlev-Gentofte Hospital, Copenhagen, Denmark
20) Department of Anesthesiology and Intensive Care, Svendborg Hospital, Svendborg, Denmark
21) Department of Anesthesiology and Intensive Care, Horsens Hospital, Horsens, Denmark
22) Department of Anesthesiology and Intensive Care, Randers Hospital, Randers, Denmark
23) Department of Anesthesiology and Intensive Care, Åbenrå Hospital, Åbenrå, Denmark
24) Department of Neuroanesthesiology, Rigshospitalet, Copenhagen, Denmark
25) Department of Anesthesiology and Intensive Care, Holbæk Hospital, Holbæk, Denmark
26) Department of Anesthesiology and Intensive Care, Hjørring Hospital, Hjørring, Denmark
27) Department of Anesthesiology and Intensive Care, Nykøbing Falster Hospital, Nykøbing Falster, Denmark
28) Department of Anesthesiology and Intensive Care, Glostrup Hospital, Copenhagen, Denmark

Corresponding author:
Nicolai Haase, MD PhD
Department of Intensive Care, Rigshospitalet
Blegdamsvej 9

2100 Copenhagen, Denmark
Tel. +45 5121 3390
nicolai.rosenkrantz.segelcke.haase@regionh.dk

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Background: Most data on ICU patients with COVID-19 originate in selected populations from stressed healthcare systems with shorter-term follow-up. We present characteristics, interventions and longer-term outcomes of the entire, unselected cohort of all ICU patients with COVID-19 in Denmark where the ICU capacity was not exceeded.

Methods: We identified all patients with SARS-CoV-2 admitted to any Danish ICU from March 10th to May 19th 2020 and registered demographics, chronic comorbidities, use of organ support, length of stay and vital status from patient files. Risk factors for death were analyzed by adjusted Cox regression analysis.

Results: There were 323 ICU patients with confirmed COVID-19. Median age was 68 years, 74% were men, 50% had hypertension, 21% diabetes, and 20% chronic pulmonary disease; 29% had no chronic comorbidity. Invasive mechanical ventilation was used in 82%, vasopressors in 83%, renal replacement therapy in 26% and ECMO in 8%. ICU stay was median 13 days (IQR 6-22) and hospital stay 19 days (11-30). Median follow-up was 79 days. At end of follow-up, 118 had died (37%), 15 (4%) were still in hospital hereof 4 in ICU as of June 16th 2020. Risk factors for mortality included male gender, age, chronic pulmonary disease, active cancer and number of co-morbidities.

Conclusions: In this nationwide, population-based cohort of ICU patients with COVID-19, longer-term survival was high despite high age and substantial use of organ support. Male gender, age and chronic co-morbidities, in particular chronic pulmonary disease, were associated with increased risk of death.

3-5 keywords: COVID-19, SARS-CoV-2, intensive care, comorbidities, mortality

Editorial Comment:

This nationwide population-based cohort of ICU patients with COVID-19 showed that longer-term survival was high despite high age and substantial use of organ support therapies.

Declarations:

Ethics approval Not needed according to Danish law

Consent to participate Waived according to The Danish Patient Safety Authority (ref. no. 31-1521-293)

Consent for publication All authors agreed to publish the present manuscript.

Availability of data and material Anonymized raw data may be available upon request from the corresponding author if certain legal requirements are fulfilled by the receiving party

Code availability SAS code available upon request from the corresponding author

Authors' contributions Nicolai Haase, Ronni Plovsing, Lone Musaeus Poulsen, Steffen Christensen, Anne Craveiro Brøchner, Bodil Steen Rasmussen, Marie Helleberg, Jens Ulrik Stæhr Jensen and Anders Perner contributed to the study conception and design. All authors contributed substantially to data acquisition. Data analyses were performed by Nicolai Haase. The first draft of the manuscript was written by Nicolai Haase and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Introduction

In December 2019 a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified in China as the cause of severe respiratory failure in a larger number of hospitalized patients now named coronavirus disease 2019 (COVID-19). Despite measures to contain the virus, SARS-CoV-2 spread widely across all continents in the following months and pandemic was declared on March 11th 2020 by the World Health Organization (WHO).

The first Covid-19 case in Denmark was reported on February 27th 2020 in a traveler returning from Northern Italy and soon thereafter patients with Covid-19 were admitted to Danish hospitals and Intensive Care Units (ICU). On March 11th virus transmission in Denmark was confirmed, and during the following weeks the government implemented several mitigation measures to slow the spread of the corona virus including school closures, social distancing, limits of public gatherings and closure of national borders. The restrictions imposed were eased gradually from mid-April and onwards. Healthcare capacity in Denmark was never exceeded.

Previous reported characteristics of COVID-19 patients in the ICU were mostly from selected centers with shorter-term follow-up and from countries such as China, Italy and the United States where COVID-19 has put a heavy burden on healthcare systems all of which may influence patient selection, treatment patterns and patient outcome[1-3]. Thus, population-based data from less stressed healthcare systems are needed to better inform patients, relatives, clinicians and policy-makers in case of new outbreaks of SARS-CoV-2.

In this paper we present characteristics, use of organ support and long-term outcomes in the entire, unselected cohort of all ICU patients with COVID-19 in Denmark during the first wave of the pandemic.

Methods

The present study is a nationwide, retrospective observational study with manual screening of all patients admitted to any Danish ICU and data collection from patients' files.

The Danish Patient Safety Authority granted access to the patient files and waived consent from the individual patients due to the retrospective nature of the study (ref. no. 31-1521-293). Ethical approval is not required for this type of study in Denmark. The database was designed in accordance with the European Union General Data Protection Regulation.

Setting

Denmark is a 42,000 km2 country in Northern Europe with 5.8 million citizens. Health care expenses in 2016 were 9.8% of the Danish gross national product. Health care services including hospital and ICU treatment are tax-supported and free of charge for all Danish residents. All ICUs treating COVID-19 patients are in public hospitals. Usual ICU capacity is approximately 7.5 ICU beds per 100.000 inhabitant (i.e. approximately 435 beds), but the capacity was tripled during the epidemic. Seroconversion studies performed in samples of the general population in Denmark suggest that approximately 61,000 citizens in Denmark were infected with SARS-CoV-2 until beginning of May, and approximately 2,400 of those were hospitalized. The largest burden of COVID-19 was seen in the Capital Region (the Copenhagen area), but minor outbreaks occurred throughout the country [4].

Study population

All 29 ICUs in 27 hospitals in Denmark, which received patients with COVID-19, contributed to the study. We manually screened all ICU patients from the date of the first detected case in Denmark to 19th May 2020. Patients of all ages with a positive real-time polymerase chain reaction (RT-PCR) test for SARS-CoV-2 either prior to or during ICU admission were included. The database was closed on 16th June 2020.

Data collection

Study personnel obtained the following information from the electronic patient files, which was entered into a RedCap database: Demographics: Age, gender, height, weight, time from onset of symptoms to hospital admission and to ICU admission. The following chronic comorbidities were registered: hypertension (use of antihypertensive medication), ischemic heart disease (previous myocardial infarction, coronary stenting, stable or unstable angina), heart failure (left-ventricular ejection fraction < 40% or New York Heart Association Functional Classification (NYHA) 3 or 4), chronic pulmonary disease (use of inhalers), chronic kidney disease (estimated glomerular filtration rate < 60 ml/min/1.73 m^2), diabetes (use of any antidiabetic drug (oral or injection)), active cancer, hematologic cancer (leukemia, lymphoma or myeloma) and immunocompromise (congenital immunodeficiency, human immunodeficiency virus (HIV) or use of radiotherapy, chemotherapy or systemic prednisolone or other immunosuppressive agent within the last 6 months). In the ICU, we registered daily use of mechanical ventilation, vasopressor or inotropes, renal replacement therapy (RRT) and the use of extra corporeal membrane oxygenation (ECMO). Follow-up data included ICU length of stay, hospital length of stay and mortality.

Statistics

First, we described patient and admission characteristics using common descriptive statistics. Confidence intervals of the proportion were calculated using the binomial proportion. Secondly, we analyzed the risk of death according to burden of comorbidity, organ support, body mass index (BMI) and age using Chi-square and Cochran-Armitage test for trend when appropriate. Finally, we assessed baseline risk factors for time to death using uni- and multivariate Cox regression analysis, where patients where censored at time of death or at last day of follow-up. Covariates were included in the multivariate model if the P value was less than 0.10 in the univariate analysis. All statistical analyses were performed using SAS Enterprise Edition 3.8, SAS Institute Inc., Cary, NC, USA.

Results

Three-hundred-twenty-three patients with COVID-19 were admitted to a Danish ICU from 10th March 2020 to 19th May 2020. All participating sites contributed to the study and confirmed completeness of their data giving a 100% nationwide coverage as there are no private ICUs in Denmark.

The surge of patients peaked in the last week of March 2020, where 25 patients were admitted to an ICU per day. From mid-April the number of new ICU admissions due to COVID-19 declined rapidly to a very low level (Supplemental Figure 1 in Electronic Supplement Material (ESM)).

The typical patient admitted to ICU was a 68-year-old overweight male admitted to hospital 2 days earlier following one week of COVID-19 symptoms (Table 1). The most common comorbidities were hypertension (50%), diabetes (21%), chronic pulmonary disease (20%) and ischemic heart disease (14%) (Table 1). Three out of ten patients did not have any of the registered comorbidities.

Invasive mechanical ventilation and vasopressors were used in 82% and 83% of patients, respectively, while a quarter of the population received RRT. The use of mechanical ventilation and vasopressors was initiated on the day of ICU admission and RRT was started median 6 days after ICU admission (all medians). The duration of mechanical ventilation was median 13 days (Interquartile range (IQR) 7-21) and vasopressors were used for 8 days (IQR 4-14). A total of 25 (8%) patients received ECMO. The use of organ support did not differ considerably across age groups (Figure 1). Half of the patients were in the ICU for almost two weeks and one quarter remained in ICU for three weeks or more (Table 2).

At database closure on 16th June 2020, all patients were followed-up for at least 28 days with a median follow-up of 79 days (range 28-96, IQR 71-84) of survivors: A total of 190 (59%) patients had been discharged alive from hospital, 118 (37%) had died (108 in the ICU and 10 on the ward post-ICU) and 15 (4%) patients were still in hospital of whom 4 remained in the ICU (Figure 2).Twenty-eight-day mortality was 29% (95%-CI: 24-34). Overall mortality was 35% (95%-CI: 31-48), 39% (31-48), 45% (33-57) and 51% (36-66) among patients who stayed in ICU for more than 1, 2, 3 and 4 weeks, respectively (Figure 2).

Mortality increased with the use of organ support (Figure 1) and with increasing number of comorbidities (Table 3 and Supplemental Figure 2 in ESM). Patients receiving RRT had a mortality of 65% (95%-CI 54-75). Patients without any of the registered comorbidities had a 24% (95%-CI 16-35) risk of death. All comorbidities seemed to be associated with increased risk of death. However, not all associations were statistically significant after adjustment for age and gender. The independent risk factors with the highest risk of death were higher age, chronic pulmonary disease and active cancer, while body mass index was not associated with increased risk of death (Supplemental Figure 3 in ESM).

Discussion

To the best of our knowledge this is the first description of a complete nationwide cohort of COVID-19 ICU patients. In our setting two-thirds of ICU patients with COVID-19 had comorbidity. Most patients needed substantial organ support and mortality was 37%. Half of the patients were in ICU receiving mechanical ventilation for almost two weeks and 25% for three weeks or more. Mortality increased with increased ICU length of stay, but half of the patients who remained in the ICU for 4 weeks or more survived and were discharged from hospital. The most important risk factors for fatal outcome were gender, age, burden of comorbidity and use of organ support.

The first published cohorts of patients admitted to the ICU with COVID-19 were mainly from selected hospitals in pandemic epicenters [1-3]. Compared to those studies, the Danish patients were older, but had a similar pattern of comorbidity with hypertension and overweight as most common characteristics. However, we report a considerable higher number of patients with underlying chronic pulmonary disease, which may be explained by our broad definition (all patients using inhalers). A relative consistent finding is that one-third of patients admitted to ICU do not have any chronic comorbidity [2, 5]. The underlying pathophysiology of SARS-CoV-2 infection is not yet fully elucidated, but genetics [6], viral load exposure [7-9], immunosuppression by SARS-CoV-2 itself [10] or hyperinflammation [11] may influence the degree of disease severity and explain why otherwise relatively healthy people become critically ill.

Mortality was high in our study, but similar to previous reported mortality of 35-50% in mechanically ventilated patients with acute lung injury and adult respiratory distress syndrome (ARDS) [12, 13].

Direct comparison with previous studies on mortality in COVID-19 ICU patients is hampered by many patients still being in the ICU or in hospital at time of publication of these studies, which may underestimate mortality. Still most studies report a higher death than survival rate among ICU patients [1-3, 14, 15]. In our study mortality was 37% overall and 41% among those mechanically ventilated, which is slightly lower compared with previous studies.

During a pandemic, like the present with SARS-CoV-2 a heavy burden is put on health care systems which may influence the criteria for ICU-admission, the interventions used and their duration, all of which may influence patient’s outcome. Our data underlines the substantial burden put on ICUs as many ICU patients with COVID-19 needed several weeks of mechanical ventilation. In Denmark, the overall burden of COVID-19 never exceeded hospital or ICU capacity, which may explain the relatively higher age, long duration of treatment, relatively high number of patients treated with ECMO and lower mortality. Thus, the present figures may better reflect ICU burden and patient outcome in many countries in the future as most healthcare systems are now better prepared for new outbreaks of COVID-19. On the other hand, any mortality difference may simply be a consequence of differences in health care systems around the world including varying definitions and availability of ICU beds [16]. The free access to public healthcare in Denmark for all residents may reduce the social-economic impact of COVID-19 as reported elsewhere [17].

The association of mortality in COVID-19 with burden of comorbidity and degree of organ support is a consistent finding [14, 15]. The increasing risk of death by increasing age may be more pronounced in COVID-19 patients than in the general ICU-population [18, 19], but is likely similar in those with high severity of disease.

The main strength of our study is that we present a complete nationwide cohort of COVID-19 ICU patients reflecting the total ICU burden of the first COVID-19 wave in a European country with excess health care resources. This likely increases generalizability and may inform patients, relatives, clinicians and policymakers in case of new outbreaks of SARS-CoV-2 in the future. We do not have any losses to follow-up and present high-quality data harvested manually directly from patient files.

Limitations include the limited number of variables included in this study to increase feasibility, that our sample size is relatively small increasing the risk of type II errors and that a few patients were still in hospital at database closure.

In conclusion, in this nationwide, population-based cohort of ICU patients with COVID-19, longer-term survival was high despite high age and substantial use of organ support. Male gender, age and chronic co-morbidities, in particular chronic pulmonary disease, was associated with increased risk of death.

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Table 1: Patient demographics and comorbidities

	All	Survivors	Non-survivors
Number of patients	323	190	118
Male gender, N (%)	239 (74)	132 (70)	94 (80)
Age, years	68 (59-75)	64 (54-71)	73 (67-77)
Body Mass Index	27 (24-31)	27 (25-31)	27 (24-31)
Time from initial symptom to hospital admission, days	7 (4-10)	7 (5-11)	7 (3-10)
Time from hospital to ICU admission, days	2 (1-4)	2 (0-4)	2 (1-6)
Comorbidities, N (%)			
Hypertension	160 (50)	88 (46)	67 (57)
Ischemic Heart Disease	44 (14)	22 (12)	18 (15)
Heart Failure	14 (4)	4 (2)	8 (7)
Chronic Pulmonary Disease	63 (20)	28 (15)	32 (27)
Chronic Kidney Disease	39 (12)	18 (9)	20 (17)
Liver Cirrhosis	3 (1)	1 (1)	2 (2)
Diabetes	68 (21)	38 (20)	26 (22)
Active cancer	15 (5)	5 (3)	10 (8)
Hematological malignancy	13 (4)	6 (3)	7 (6)
Immunosuppressed	34 (11)	15 (8)	18 (15)
None of the above	93 (29)	68 (36)	22 (19)

Continuous variables are medians and interquartile ranges. Fifteen patients were still in hospital at database closure and could not be classified as survivors or non-survivors. Body Mass Index and time from initial symptoms to hospital admission were missing for 32 and 25 patients, respectively.

Table 2: Outcome, organ support and length of stay

Outcome	
Discharged from hospital and alive, N (%)	190 (59)
Still in hospital at database closure, N (%)	15 (4)
In ICU	4
On general ward	11
Died, N (%)	118 (37)
In ICU	108
On general ward, post ICU	10
After hospital discharge	0
Use of organ support, N (%)	
Mechanical ventilation	250 (82)
Vasopressor or inotrope	252 (83)
Renal replacement therapy	84 (26)
ECMO	25 (8)
Duration of organ support (days), median (IQR)	
Mechanical ventilation	13 (7-21)
Vasopressor or inotrope	8 (4-14)
Renal replacement therapy	9 (4-18)
ICU length of stay, days	
All patients (N=319)	13 (6-22)
ICU survivors (N=211)	13 (7-21)
Hospital length of stay, days	
All patients (N=308)	19 (11-30)
Hospital survivors (N=190)	23 (14-32)

ECMO denotes extracorporeal membrane oxygenation.

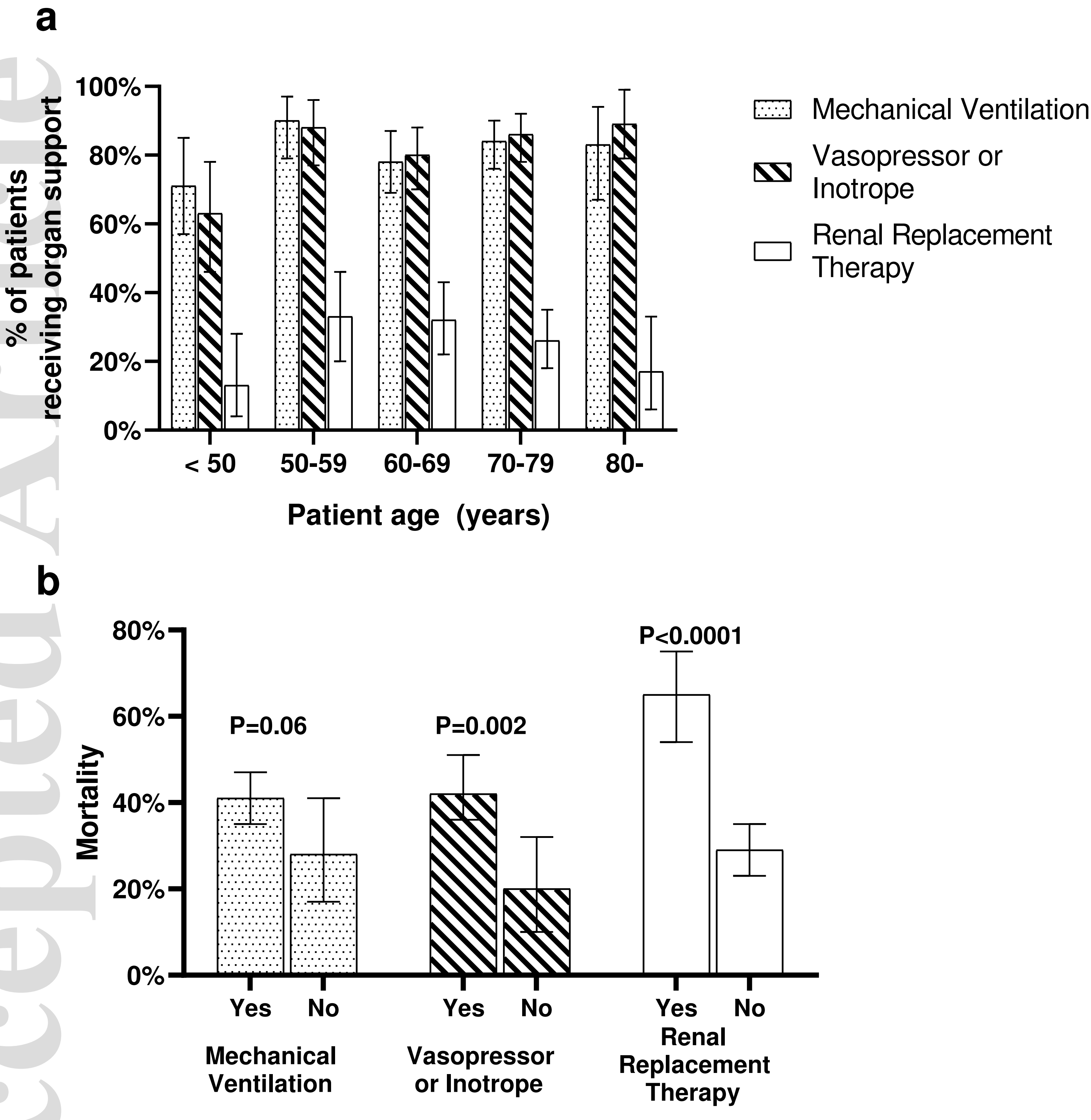
Table 3: Cox regression – risk factors for death

Univariate analysis			Multivariate analysis	
Risk factor	**HR**	**P-value**	**HR**	**P-value**
Gender (ref. female)	1.53 (0.98-2.40)	0.05	1.57 (0.99-2.48)	0.06
Ischemic heart disease	1.28 (0.77-2.11)	0.34		
Heart failure	2.10 (1.03-4.31)	0.04	1.31 (0.62-2.77)	0.47
Hypertension	1.40 (0.97-2.02)	0.07	0.94 (0.64-1.37)	0.73
Chronic pulmonary disease	1.84 (1.23-2.77)	< 0.01	1.86 (1.23-2.82)	< 0.01
Chronic kidney disease	1.80 (1.11-2.91)	0.02	1.43 (0.87-2.35)	0.16
Liver cirrhosis	2.85 (0.70-11.5)	0.14		
Diabetes	1.10 (0.71-1.70)	0.66		
Active cancer	3.18 (1.66-6.09)	< 0.001	1.92 (0.96-3.86)	0.07
Haematologic cancer	1.83 (0.85-3.92)	0.12		
Immunocompromised	1.88 (1.14-3.11)	0.01	1.55 (0.90-2.64)	0.11
Age		< 0.0001		< 0.0001
< 50	0.15 (0.04-0.64)	0.01	0.18 (0.04-0.78)	0.02
50-59	0.72 (0.36-1.43)	0.35	0.75 (0.37-1.52)	0.43
60-69	1	-	1	-
70-79	1.91 (1.19-3.05)	< 0.01	1.92 (1.19-3.08)	< 0.01
80-	2.64 (1.49-4.68)	< 0.001	2.77 (1.55-4.96)	< 0.001
Body Mass Index		0.84		
< 18	0.95 (0.51-1.76)	0.84		
18-24.9	1	-		
25-29.9	0.77 (0.49-1.22)	0.27		
30-34.9	0.71 (0.39-1.27)	0.24		
35-39.9	0.80 (0.34-1.89)	0.61		
>40	0.86 (0.38-1.93)	0.71		

A sensitivity analysis including BMI as a covariate increased the hazard ratio for being a male to 1.68 (1.05-2.68).

Figure 1 Use of organ support stratified by age (panel a) and mortality stratified by use of organ support (panel b)

Figure 2 Patients admitted to intensive care with COVID-19 stratified by age, gender and outcome (panel a) and time to outcome since ICU admission (panel b). Outcomes are death, ongoing care and discharge from hospital



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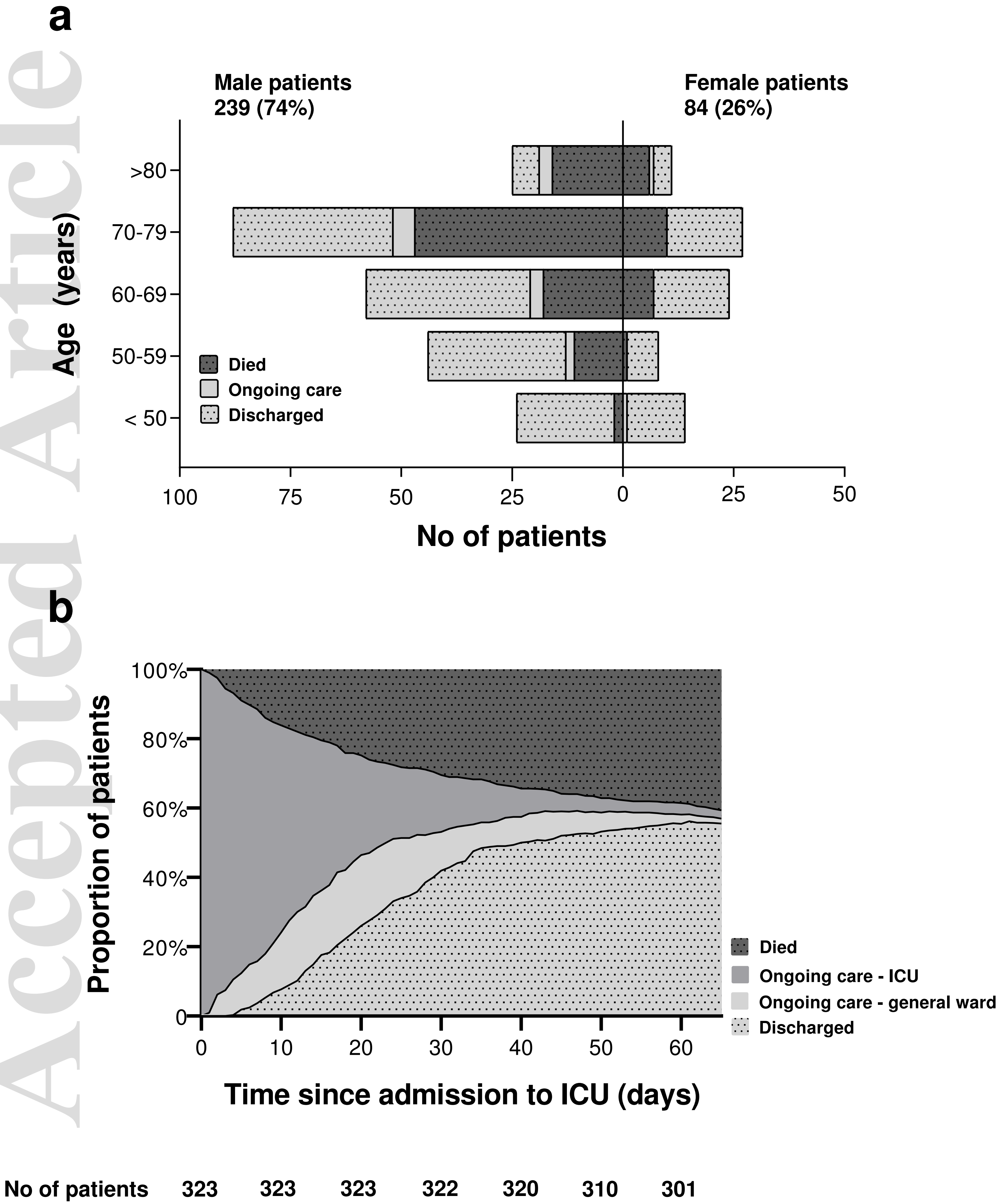
a
Male patients
239 (74%)
Female patients
84 (26%)
Age (years)
>80
70-79
60-69
50-59
< 50
Died
Ongoing care
Discharged
100
75
50
25
0
25
50
No of patients
b
Proportion of patients
100%
80%
60%
40%
20%
0
Died
Ongoing care - ICU
Ongoing care - general ward
Discharged
0
10
20
30
40
50
60
Time since admission to ICU (days)
No of patients
323
323
323
322
320
310
301