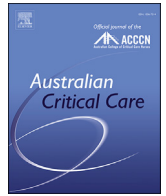




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Research paper

Mechanical ventilation and mortality among 223 critically ill patients with coronavirus disease 2019: A multicentric study in Germany

Kevin Roedl, MD ^{a,*}, ¹Dominik Jarczak, MD ^{a,1}Liina Thasler, MD ^aMartin Bachmann, MD ^bFrank Schulte, MD ^cBerthold Bein, MD ^dChristian Friedrich Weber, MD ^eUlrich Schäfer, MD ^fCarsten Veit, MD ^gHans-Peter Hauber, MD ^hSebastian Kopp, MD ⁱKarsten Sydow, MD ^jAndreas de Weerth, MD ^kMarc Bota, MD ^lRüdiger Schreiber, MD ^mOliver Detsch, MD ⁿJan-Peer Rogmann, MD ^oDaniel Frings, MD ^aBarbara Sensen, MD ^aChristoph Burdelski, MD ^aOlaf Boenisch, MD ^aAxel Nierhaus, MD ^aGeraldine de Heer, MD ^{a,1}Stefan Kluge, MD ^{a,1}

^a Department of Intensive Care Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

^b Department of Intensive Care and Respiratory Medicine, Clinic for Airway-, Thorax and Respiratory Medicine, Asklepios Hospital Harburg, Hamburg, Germany

^c Department of Pneumology and Intensive Care Medicine, Weaningcenter, Asklepios Hospital Barmbek, Hamburg, Germany

^d Department of Anaesthesiology, Intensive Care, Emergency Medicine and Pain Medicine, Asklepios Hospital St. Georg, Hamburg, Germany

^e Department of Anaesthesiology, Intensive Care and Emergency Medicine, Asklepios Hospital Wandsbek, Hamburg, Germany

^f Department of Cardiology, Angiology and Intensive Care Medicine, Marien Hospital, Hamburg, Germany

^g Department of Interdisciplinary Intensive Care Medicine, Bundeswehr Hospital, Hamburg, Germany

^h Department of Cardiology, Pneumology and Intensive Care Medicine, Asklepios Hospital Altona, Hamburg, Germany

ⁱ Department of Anaesthesiology and Intensive Care Medicine, Amalie Sieveking Hospital, Hamburg, Germany

^j Department of Cardiology, Albertinen Hospital, Hamburg, Germany

^k Department of Internal Medicine, Agaplesion Diakonie Hospital Hamburg, Hamburg, Germany

^l Department of Internal Medicine, Bethesda Hospital Bergedorf, Hamburg, Germany

^m Department of Anaesthesiology, Intensive Care and Emergency Medicine, Asklepios West Hospital Hamburg, Hamburg, Germany

ⁿ Department of Anaesthesiology, Intensive Care, Emergency Medicine and Pain Medicine, Asklepios Hospital Nord, Hamburg, Germany

^o Department of Anaesthesiology and Intensive Care Medicine, Israelitic Hospital, Hamburg, Germany

* Corresponding author. Department of Intensive Care Medicine, University Medical Center Hamburg-Eppendorf, Martinistraße 52, 20246, Hamburg, Germany. Tel.: +49 40 7410 57020; fax: +49 40 7410 57011.

E-mail address: k.roedl@uke.de (K. Roedl).

¹ Authors contributed equally.

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ABSTRACT

Background: There are large uncertainties with regard to the outcome of patients with coronavirus disease 2019 (COVID-19) and mechanical ventilation (MV). High mortality (50–97%) was proposed by some groups, leading to considerable uncertainties with regard to outcomes of critically ill patients with COVID-19.

Objectives: The aim was to investigate the characteristics and outcomes of critically ill patients with COVID-19 requiring intensive care unit (ICU) admission and MV.

Methods: A multicentre retrospective observational cohort study at 15 hospitals in Hamburg, Germany, was performed. Critically ill adult patients with COVID-19 who completed their ICU stay between February and June 2020 were included. Patient demographics, severity of illness, and ICU course were retrospectively evaluated.

Results: A total of 223 critically ill patients with COVID-19 were included. The majority, 73% (n = 163), were men; the median age was 69 (interquartile range = 58–77.5) years, with 68% (n = 151) patients having at least one chronic medical condition. Their Sequential Organ Failure Assessment score was a median of 5 (3–9) points on admission. Overall, 167 (75%) patients needed MV. Noninvasive ventilation and high-flow nasal cannula were used in 31 (14%) and 26 (12%) patients, respectively. Subsequent MV, due to noninvasive ventilation/high-flow nasal cannula therapy failure, was necessary in 46 (81%) patients. Renal replacement therapy was initiated in 33% (n = 72) of patients, and owing to severe respiratory failure, extracorporeal membrane oxygenation was necessary in 9% (n = 20) of patients. Experimental antiviral therapy was used in 9% (n = 21) of patients. Complications during the ICU stay were as follows: septic shock (40%, n = 90), heart failure (8%, n = 17), and pulmonary embolism (6%, n = 14). The length of ICU stay was a median of 13 days (5–24), and the duration of MV was 15 days (8–25). The ICU mortality was 35% (n = 78) and 44% (n = 74) among mechanically ventilated patients.

Conclusion: In this multicentre observational study of 223 critically ill patients with COVID-19, the survival to ICU discharge was 65%, and it was 56% among patients requiring MV. Patients showed high rate of septic complications during their ICU stay.

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1. Background

Originating from China, a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in December 2019.^{1,2} SARS-CoV-2 was detected as a cause of coronavirus disease 2019 (COVID-19) in lower respiratory tract samples.³ The virus spread is causing an ongoing global pandemic.⁴ COVID-19 led to high hospitalisation rates worldwide and confronted the healthcare systems with an enormous challenge.^{5,6} The clinical spectrum of COVID-19 ranges from asymptomatic to severe illness, with development of acute respiratory distress syndrome (ARDS) and multiple organ failure.^{1–3} About 17% of hospitalised patients with COVID-19 need admission to the intensive care unit (ICU). Certain clinical characteristics and risk factors have been previously reported to be associated with worse outcomes, especially in patients with pre-existing medical conditions and older patients.^{7–9}

Patients with COVID-19 treated at the ICU suffer from high mortality; in patients with invasive mechanical ventilation (MV), rates from 50% to 97% have been reported.^{6,10–12} However, some studies were preliminary and included patients without a completed ICU stay. Furthermore, numerous studies were conducted in regions with overwhelmed healthcare systems, which possibly led to a resource limitation as a result of higher mortality rates.¹³ Furthermore, owing to high risk of infection via respiratory aerosols, potential aerosol-generating procedures such as noninvasive ventilation (NIV) or high-flow nasal cannula (HFNC) therapy are a matter of concern.¹⁴ Avoidance of NIV/HFNC therapy and early tracheal intubation has been suggested as a management strategy for COVID-19; however, this is controversial owing to the worse outcomes reported with tracheal intubation.^{15,16} Data on outcomes after critical illness in patients with COVID-19 and outcomes of patients requiring MV are limited. Therefore, the aim of this study

was to investigate clinical characteristics and outcomes of MV in critically ill patients with COVID-19 in a large cohort in Germany.

2. Methods

2.1. Study design, setting, and ethics

We conducted a retrospective multicentre observational study and included all critically ill adult patients with COVID-19 who completed an ICU stay and who were treated in the ICUs of the University Medical Center Hamburg-Eppendorf and 14 teaching hospitals in Hamburg (the second largest city in Germany, with 1.8 million inhabitants) between February 1, 2020, and June 3, 2020. The participating hospitals were Agaplesion Diakonie Hospital, Albertinen Hospital, Amalie-Siebeking Hospital, Asklepios Hospital Altona, Asklepios Hospital Barmbek, Asklepios Hospital Harburg, Asklepios Hospital North, Asklepios Hospital St. Georg, Asklepios Hospital Wandsbek, Asklepios West Hospital Hamburg, Bethesda Hospital Bergedorf, Bundeswehr Hospital Hamburg, Israelitic Hospital, and Marien Hospital. Furthermore, epidemiological data about the number of hospitalised patients were enquired at the Hamburg health authorities for the aforementioned time frame. The study was approved by the local clinical institutional review board and complies with the Declaration of Helsinki. The Ethics Committee of the Hamburg Chamber of Physicians was informed about the study (no.: WF-107/20). Owing to retrospective and de-identified data collection, the need for informed consent was waived.

2.2. Inclusion and exclusion criteria

We included all consecutive adult patients (≥ 18 years) with confirmed COVID-19 and COVID-19-associated critical illness

admitted to one of the ICUs in the participating hospitals. Confirmed COVID-19 was defined as at least one positive result on reverse transcriptase polymerase chain reaction obtained from nasopharyngeal swabs and/or bronchial secretions. Patients with noncompleted ICU stay (ongoing ICU treatment) were excluded.

2.3. Data collection

The data were collected through a predefined case report form (CRF) in electronic or paper form. Each hospital enrolled all patients with confirmed COVID-19 and who completed an ICU stay. The individual patient data were recorded retrospectively after the end of the ICU stay, and the de-identified CRFs were collected until June 3, 2020. The collected data included age, gender, comorbidities, reason of admission, length of ICU stay, treatment modalities, organ support (MV, vasopressor support, renal replacement therapy [RRT], blood transfusions, antibiotics, antivirals, and so on), procedures, complications, and laboratory parameters during the ICU stay. Pre-existing medication was recorded on the basis of known regular medications and medication on admission.

2.4. Study definitions

ARDS was defined as per the Berlin definition.¹⁷ Sepsis and septic shock were defined as per the 2016 Third International Consensus Definition for Sepsis and Septic Shock.¹⁸ Severity of illness was evaluated using Sequential Organ Failure Assessment (SOFA).¹⁹ Charlson Comorbidity Index (CCI)²⁰ was calculated in all patients. For management and therapy of critically ill patients with COVID-19, national and international recommendations were followed.^{21–23}

2.5. Statistical analysis

Data are presented as count and relative frequency or median and interquartile range. The distribution of variables was graphically assessed using histograms. Binary variables were compared using chi-square analysis or Fisher's exact test, as appropriate. Metric variables were compared using the Mann–Whitney U test. Binary logistic regression analysis and Cox regression analysis were performed, and factors that were considered clinically relevant and did not fulfil the criteria for multicollinearity were included in the model. We used a hierarchical backward stepwise approach. The initial model was gradually reduced. Variables that caused a change in parameter estimates by >10% or were statistically significant at a 0.05 level remained in the model. Missing values were addressed by using the multiple imputation method. Statistical analysis was conducted using IBM SPSS Statistics Version 24.0 (IBM Corp., Armonk, NY). Generally, a p-value <0.05 was considered statistically significant.

The study was prepared in accordance with the Strengthening of Reporting of Observational studies in Epidemiology recommendations (see [supplementary material](#)).²⁴

3. Results

3.1. Study population

Until June 3, 2020, 5096 people were tested positive for SARS-CoV-2 in the city of Hamburg. Overall, 996 (20%) patients with COVID-19 were hospitalised, and of those, 261 (26%) needed intensive care therapy. During the study period, we could include 223 patients with a completed ICU stay, which illustrates a representative sample (85%) of all ICU-treated patients with COVID-19 in the city of Hamburg.

3.2. Baseline characteristics of the study population

Detailed demographic and baseline characteristics are shown in [Table 1](#). Comorbidities, represented by the CCI, were a median of 1 (0–2) point. arterial hypertension was the leading comorbidity (49%, n = 108). Forty-five (20%) patients had ongoing treatment with angiotensin-converting-enzyme (ACE) inhibitors, and 42 (19%) patients had treatment with angiotensin receptor blockers. Further common comorbidities were diabetes mellitus (type II), history of active haematologic or oncologic disease, and chronic respiratory disease in 27% (n = 59), 20% (n = 44), and 18% (n = 40) of patients, respectively. The majority of patients were admitted to the ICU owing to respiratory deterioration. Most common symptoms on ICU admission were shortness of breath and fever in 124 patients (56%) each. Further symptoms were productive cough in 55 (25%), fatigue in 49 (22%), nonproductive cough in 34 (15%), and myalgia in 11 (5%) patients. Seventy-five patients (34%) needed vasopressor support on the day of admission to the ICU.

3.3. Ventilatory support, ARDS management, and COVID-19 therapy

Of 223 patients, 167 (75%) received MV during the ICU stay. The median time from admission to initiation of invasive MV was 1 (0–2) day. Eighty-nine (40%) patients required invasive MV within the first day of ICU admission. Furthermore, NIV and HFNC therapy were used in 18 (8%) and 22 (10%) patients, respectively, within the first day, and in 31 (14%) and 26 (12%) patients during their ICU stay. Subsequent invasive MV due to NIV/HFNC therapy failure was necessary in 23 of 31 (74%) patients who underwent NIV and 23 of 26 (88%) patients who underwent HFNC therapy. One hundred sixty-three (73%) developed ARDS. As per the PaO₂:FiO₂ ratio, ARDS was diagnosed as mild (4%, n = 12), moderate (42%, n = 70), and severe (49%, n = 81). Owing to severe ARDS, 20 patients received extracorporeal membrane oxygenation (ECMO). Initial mechanical ventilator settings were a positive end-expiratory pressure (PEEP) of 12 (10–15) cmH₂O, respiratory rate of 22 (20–28), FiO₂ of 0.6 (0.5–0.8), and inspiratory pressure of 25 (19–29) cmH₂O (median values). For further ARDS treatment, 108 (65%) mechanically ventilated patients were placed in prone position, 37 (22%) received neuromuscular blockade, and 19 (11%) patients inhaled nitric oxide. In patients receiving prone positioning with the first days of the ICU stay, 62% responded; the median PaO₂ before and after prone positioning was 73.3 (64.2–78.7) and 78.7 (68.3–97.9) mmHg in responders and 72.8 (62.5–77.5) and 62.4 (59.3–73) mmHg in nonresponders, respectively. The median duration of MV was 15 (8–25) days. Self-proning was performed in four patients in the non-MV group. In 73 (33%) patients, RRT was initiated. Systemic glucocorticoid treatment was initiated in 51 (23%) of patients. Experimental antiviral treatment with hydroxychloroquine was used in 11 (5%) patients and lopinavir–ritonavir treatment was initiated in 10 (4%) patients.

3.4. Differences between patients with and without MV

Clinical findings concerning baseline characteristics, interventions, and complications are summarised in [Table 2](#). No differences were observed in age and gender; body mass index was significantly higher (p < 0.05) in mechanically ventilated patients. Severity of illness represented by a median SOFA score on admission and after 24 h was 5 (3–9) and 9 (4–12), respectively. The SOFA score on admission and after 24 h was significantly higher in the MV group (both p < 0.001). Vasopressor use within the first 24 h after admission was significantly higher in patients with MV (71% vs. 5%, p < 0.001). RRT was initiated in 73 (33%) patients in the whole cohort and was used more frequently in mechanically

Table 1
Baseline characteristics of the study cohort stratified as per mechanical ventilation (MV) and no MV.

| Parameters | All (n = 223) | MV (n = 167) | No MV (n = 56) | p-value |
|---|------------------|------------------|------------------|------------------|
| Demographics | | | | |
| Age (years) | 69 (58–77.5) | 70 (60–77.5) | 63 (50–75) | 0.056 |
| Sex | | | | 0.435 |
| - Men (%) | 163 (73) | 123 (74) | 40 (71) | |
| - Women (%) | 60 (27) | 44 (26) | 16 (29) | |
| Height (cm) | 175 (170–180) | 175 (170–180) | 175 (170–180) | 0.970 |
| Weight (kg) | 80 (72–93) | 82 (72–95) | 75 (72–84) | 0.042 |
| BMI (kg/m ²) | 26.3 (24.1–30.7) | 26.7 (24.3–31.1) | 24.5 (23.1–27.9) | 0.022 |
| Disease severity | | | | |
| SOFA, admission (points) | 5 (3–9) | 7 (4–10) | 3 (0.8–4) | <0.001 |
| SOFA, 24 h (points) | 9 (4–12) | 10 (7.5–12) | 2 (0–4) | <0.001 |
| Comorbidities | | | | |
| Charlson Comorbidity Index (points) | 1 (0–2) | 1 (0–2) | 1.5 (0–3) | 0.591 |
| ≥one chronic medical condition | 151 (68) | 115 (69) | 36 (64) | 0.243 |
| Arterial hypertension | 108 (49) | 86 (51) | 22 (39) | 0.076 |
| Obesity (BMI > 30 kg/m ²) | 52 (23) | 44 (26) | 8 (14) | 0.045 |
| Diabetes | 59 (27) | 50 (30) | 9 (16) | 0.036 |
| Immunosuppression | 38 (17) | 25 (15) | 13 (23) | 0.114 |
| Coronary heart disease | 18 (8) | 15 (9) | 3 (5) | 0.329 |
| Congestive heart disease | 15 (7) | 11 (7) | 4 (7) | 0.508 |
| Connective tissue disease | 6 (3) | 6 (4) | 0 (0) | 0.187 |
| Chronic kidney disease | 26 (12) | 20 (12) | 6 (11) | 0.559 |
| Chronic respiratory disease | 40 (18) | 24 (14) | 16 (29) | 0.013 |
| Chronic liver disease | 5 (2) | 5 (3) | 0 (0) | 0.329 |
| <i>Malignant condition</i> | | | | |
| - Lymphoma | 12 (5) | 8 (5) | 4 (7) | 0.320 |
| - Leukaemia | 17 (7) | 10 (6) | 7 (13) | 0.082 |
| - Solid organ tumour | 15 (7) | 11 (7) | 4 (7) | 0.564 |
| COVID-19 symptoms | | | | |
| Nonproductive cough | 34 (15) | 25 (15) | 9 (16) | 0.423 |
| Productive cough | 55 (25) | 44 (26) | 11 (20) | 0.405 |
| Shortness of breath | 124 (56) | 104 (62) | 20 (36) | 0.281 |
| Fever | 124 (56) | 94 (56) | 30 (54) | 0.529 |
| Fatigue | 49 (22) | 34 (20) | 15 (27) | 0.527 |
| Myalgia | 11 (5) | 9 (5) | 2 (4) | 0.654 |
| Characteristics at ICU admission | | | | |
| Heart rate (per minute) | 90 (77–104) | 91 (75–104) | 90 (81–98) | 0.927 |
| Mean arterial pressure (mmHg) | 84 (72–98) | 81 (70–97) | 90 (78–99) | 0.059 |
| Vasopressor therapy | 75 (34) | 72 (43) | 3 (5) | <0.001 |
| <i>Noninvasive and invasive ventilation</i> | | | | |
| - Respiration rate (per minute) | 23 (20–29) | 22 (20–28) | 25 (20–34) | 0.080 |
| - Invasive mechanical ventilation | 80 (36) | 80 (48) | 0 (0) | <0.001 |
| - Noninvasive ventilation | 18 (8) | 16 (10) | 2 (4) | 0.041 |
| - High-flow nasal cannula (HFNC) | 22 (10) | 18 (11) | 4 (7) | 0.591 |
| <i>Oxygen support</i> | | | | |
| - Low oxygen | 38 (17) | 20 (12) | 18 (32) | 0.207 |
| - High oxygen | 32 (14) | 22 (13) | 10 (18) | 0.569 |
| Outcome | | | | |
| ICU mortality | 78 (35) | 74 (44) | 4 (7) | – |
| Duration of ICU stay (days) | 13 (5–24) | 18 (9–27.5) | 3 (2–6) | <0.001 |

Data are expressed as n (%) or median (interquartile range).

Bold intends a significant p-value in the far right column.

cm, centimetre; kg, kilogram; COVID-19, coronavirus disease 2019; SOFA, Sequential Organ Failure Assessment; ICU, intensive care unit; BMI, body mass index.

ventilated patients ($p < 0.001$). Therapeutic anticoagulation was used in 121 (54%) patients overall and was distributed equally in both groups. Use of antibiotic, antifungal, and antiviral therapy was common in both groups; use of antibiotic therapy was significantly more frequent in mechanically ventilated patients ($p < 0.001$). Pre-existing obesity (body mass index $> 30 \text{ kg/m}^2$) and diabetes mellitus type II were significantly higher in patients with MV ($p = 0.045$ and 0.036 , respectively). Patients with chronic respiratory disease were more frequent among patients in the non-MV group. Laboratory and blood gas analyses are summarised in [Supplementary Table 1](#). Significant differences were found in admission in terms of PaO_2 , PaCO_2 , and pH after 24 h. As to clinical chemistry, we observed significantly higher values in creatinine and liver function parameter (including bilirubin, Aspartat-Aminotransferase (ASAT), Alanin-Aminotransferase (ALAT)) in the MV group. Markers of

inflammation were significantly lower in the patients in the non-MV group. Logistic regression analysis revealed that the SOFA score on admission (odds ratio [OR] = 1.360; 95% confidence interval [CI] = 1.184–1.562; $p < 0.001$), septic shock (OR = 3.946; 95% CI = 1.005–9.231; $p = 0.049$), and RRT (OR = 4.909; 95% CI = 1.319–18.275; $p = 0.018$) were significantly associated with the need for MV after adjusting for confounders (see [Supp. Table 2a](#)).

3.5. Overall outcome and complications

In our cohort of 223 critically ill patients with COVID-19, 78 patients died, resulting in an overall ICU mortality rate of 35%. We observed a mortality rate of 44% ($n = 74$) in mechanically ventilated patients and 7% ($n = 4$) in patients in the non-MV group. All four patients dying in the non-MV group had severe hypoxaemia and/or

Table 2

Differences between therapies and complications in ICU patients with COVID-19 in the mechanical ventilation (MV) group and non-MV group during the ICU stay.

| Parameters | All (n = 223) | MV (n = 167) | No MV (n = 56) | p-value |
|--|---------------|--------------|----------------|--------------|
| Procedures/therapies | | | | |
| Vasopressors (first 24 h) | 123 (55) | 119 (71) | 4 (5) | <0.001 |
| Renal replacement therapy | 73 (33) | 70 (42) | 3 (5) | <0.001 |
| Therapeutic anticoagulation | 121 (54) | 102 (61) | 19 (34) | 0.185 |
| Antibiotic therapy | 197 (8) | 161 (96) | 36 (64) | <0.001 |
| Antifungal therapy | 25 (11) | 20 (12) | 5 (9) | 0.363 |
| Antiviral therapy | 42 (19) | 32 (19) | 10 (18) | 0.504 |
| <i>Experimental therapy</i> | | | | |
| - Hydroxychloroquine | 11 (5) | 11 (7) | 0 (0) | 0.038 |
| - Specific antiviral therapy | 10 (4) | 8 (5) | 2 (4) | 0.520 |
| - Glucocorticoid therapy | 51 (23) | 46 (28) | 5 (9) | 0.012 |
| Complications during ICU stay | | | | |
| Heart failure | 17 (8) | 15 (9) | 2 (4) | 0.151 |
| Pulmonary embolism | 14 (6) | 13 (8) | 1 (2) | 0.092 |
| Deep vein thrombosis | 18 (8) | 12 (7) | 6 (11) | 0.280 |
| Cardiac arrest | 25 (11) | 23 (14) | 2 (4) | 0.048 |
| Myocardial infarction | 7 (3) | 3 (2) | 4 (7) | 0.068 |
| DIC | 5 (2) | 5 (3) | 0 (0) | 0.232 |
| Septic shock | 90 (40) | 85 (51) | 5 (9) | <0.001 |
| Ventilation/ventilatory support | | | | |
| Mechanical ventilation | 167 (75) | 167 (100) | – | – |
| ECMO | 20 (9) | 20 (12) | – | – |
| <i>Other ventilation support</i> | | | | |
| - High-flow nasal cannula | 31 (14) | 23 (14) | 8 (14) | 0.540 |
| - Noninvasive ventilation | 26 (12) | 23 (14) | 3 (5) | 0.066 |
| Duration of ventilation (days) | 15 (8–25) | 15 (8–25) | – | – |

Data are expressed as n (%) or median (interquartile range); p-value: MV vs. non-MV.

Bold intends a significant p-value in the far right column.

BMI, body mass index; kg, kilogram; m, metre; DIC, disseminated intravascular coagulation; SOFA, Sequential Organ Failure Assessment; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit.

multiple organ failure; therapy was limited based on the existing advance directive. The mortality of patients receiving ECMO was 65% (n = 13). Overall, the median length of ICU stay was 13 (5–24) days. The following complications were observed during the ICU stay: 90 (40%) patients suffered from septic shock, and 17 (8%) patients had heart failure. Deep vein thrombosis or pulmonary embolism was detected in 18 (8%) and 14 (6%) of patients.

3.6. Factors associated with mortality in mechanically ventilated patients

Findings concerning survival and nonsurvival of mechanically ventilated patients are shown in Table 3 and Fig. 1. Of 167 patients, 93 (56%) survived the ICU stay. Survivors after MV were significantly younger (65 vs. 72 years; p = 0.001). Severity of illness, represented by the SOFA score and CCI, was significantly higher in nonsurvivors. Regarding ventilatory settings, we did not find significant differences. Use of ECMO and adjunctive therapies (glucocorticoid treatment, inhaled vasodilatory treatment) were more common in nonsurvivors. Need for RRT was frequent in nonsurvivors compared with survivors (62% vs. 26%, respectively; p < 0.001). Complications during the ICU stay were more common in nonsurvivors receiving MV. Cox regression analysis reveals that age (hazard ratio [HR] = 1.037; 95% CI = 1.013–1.062; p = 0.003), CCI (HR = 1.121; 95% CI = 1.006–1.249; p = 0.039), and pulmonary embolism (HR = 2.376; 95% CI = 1.218–4.635; p = 0.011) were significantly associated with mortality after adjusting for confounders (see Supp. Table 2b).

4. Discussion

We hereby report on a large observational cohort study on critically ill patients with COVID-19 from Germany. To our knowledge, this is the first reported study on a cohort of critically ill

patients with COVID-19 in whom clinical characteristics and outcomes after MV were investigated, including only patients with a completed ICU stay. We demonstrated an overall ICU mortality rate of 35% and a mortality rate of 44% among patients who received MV.

In our representative cohort, 75% of patients required invasive MV. Overall, NIV and HFNC therapy was used in 12% and 14% of patients, respectively. Eighty-one percent (46 of 57) of patients needed MV after NIV or HFNC therapy. However, a previous small study reported a rate of 41% HFNC therapy failure in patients with COVID-19.²⁵ Recently, a meta-analysis compared different forms of respiratory support in patients without COVID-19 and with respiratory failure, which encompassed 25 trials. In this analysis, NIV was associated with lower mortality than standard oxygen therapy. Furthermore, NIV and HFNC therapy were associated with lower rates of endotracheal intubation.²⁶ Nevertheless, it is unclear whether the application of HFNC therapy/NIV or early intubation and subsequent MV is preventing COVID-19 progression.¹⁵

In our cohort, we observed that 40% of patients required MV within the first day of ICU admission. Furthermore, NIV was used in 11% and HFNC therapy in 13% of patients within the first day after admission. In spontaneously breathing patients with an indication for HFNC therapy or NIV immediately after admission, the time to intubation was a median of only 1 day. Overall, 75% of admitted patients received MV, which is higher than that in other studies recently reported.^{27,28} However, our findings are comparable with two large trials in Germany on MV recently reported.^{29,30} But differences may be explained by different ICU admission strategies and some of the hospitals serving as ARDS referring centres specialised in treatment of ARDS and providing ECMO support. The median duration of invasive MV was 15 days comparable with previous reports on patients with ARDS of non-COVID-19 origin.³¹ Richardson et al.⁶ demonstrated a rather low mortality of 25%, in patients with COVID-19 who received MV, but more than 70% of

Table 3
Differences between survivors and nonsurvivors among ICU patients with COVID-19 and who received mechanical ventilation.

| Parameters | Mechanically ventilated survivors (n = 93) | Mechanically ventilated nonsurvivors (n = 74) | p-value |
|--|--|---|------------------|
| Demographics | | | |
| Age (years) | 65 (58–74) | 72 (63–79) | 0.001 |
| Gender | | | 0.078 |
| - Male | 64 (69) | 59 (80) | |
| - Female | 29 (31) | 15 (20) | |
| BMI (kg/m ²) | 26.9 (24.7–31.2) | 26.2 (23.9–30.9) | 0.267 |
| Disease severity | | | |
| CCI (pts.) | 1 (0–2) | 2 (1–3) | 0.024 |
| SOFA, admission (pts.) | 6 (4–10) | 7 (4–10) | 0.412 |
| SOFA, 24 h (pts.) | 10 (7–11) | 11 (8–13) | 0.020 |
| ARDS | | | |
| No ARDS | 4 (4) | 0 (0) | 0.093 |
| Mild | 8 (9) | 4 (5) | 0.287 |
| Moderate | 47 (51) | 23 (31) | 0.007 |
| Severe | 34 (37) | 47 (64) | <0.001 |
| Mechanical ventilation | | | |
| On admission | 40 (43) | 26 (35) | 0.191 |
| Beginning of MV (days) | 1 (1–2) | 1 (0–2) | 0.398 |
| Duration of MV (days) | 16 (8–32) | 14 (6–12) | 0.027 |
| PEEP, adm. (cmH ₂ O) | 11 (10–15) | 13.5 (10–15) | 0.504 |
| PEEP, 24 h (cmH ₂ O) | 13 (10–15) | 13 (10–15) | 0.400 |
| pInsp, adm. (cmH ₂ O) | 25 (19–29) | 26 (20–29) | 0.733 |
| pInsp, 24 h (cmH ₂ O) | 24 (19–27) | 24 (19–28) | 0.590 |
| Compliance, adm. (l/bar) | 50.2 (36.7–58.8) | 34.5 (23.2–38.4) | 0.150 |
| Compliance, 24 h (l/bar) | 46.3 (34.3–57.4) | 31.5 (26.4–47.4) | 0.194 |
| Tidal volume, adm. (ml) | 494 (417–559) | 370 (338–403) | 0.182 |
| Tidal volume, 24 h (ml) | 473 (409–579) | 443 (418–521) | 0.917 |
| Respiratory rate, adm. (per minute) | 23 (20–27) | 22 (20–30) | 0.834 |
| Respiratory rate, 24 h (per minute) | 21 (18–25) | 21 (18–24) | 0.839 |
| Noninvasive ventilation | 12 (13) | 11 (15) | 0.442 |
| High flow nasal cannula | 14 (15) | 9 (12) | 0.380 |
| ARDS management | | | |
| ECMO | 7 (8) | 13 (18) | 0.041 |
| Prone positioning | 55 (59) | 53 (72) | 0.065 |
| Neuromuscular blockade | 21 (23) | 16 (22) | 0.540 |
| Inhaled vasodilatory treatment | 3 (3) | 16 (22) | <0.001 |
| Glucocorticoid therapy | 16 (17) | 30 (41) | <0.001 |
| Blood gas analysis | | | |
| PaO ₂ , adm. (mmHg) | 70 (57–86.7) | 64 (57.9–75.3) | 0.152 |
| PaO ₂ , 24 h (mmHg) | 76.6 (68.5–87.1) | 74 (60.1–84) | 0.033 |
| PaCO ₂ , adm. (mmHg) | 36.6 (32.6–43.5) | 36 (31–50) | 0.867 |
| PaCO ₂ , 24 h (mmHg) | 42 (36.7–48.2) | 42.2 (34.4–49.8) | 0.861 |
| Lactate, adm. (mmol/l) | 1.2 (0.09–1.7) | 1.45 (0.9–1.98) | 0.109 |
| Lactate, 24 h (mmol/l) | 1.3 (0.9–1.6) | 1.2 (1.1–2.1) | 0.022 |
| Lactate, max. (mmol/l) | 2.5 (1.7–3.5) | 5.8 (3–11.6) | <0.001 |
| pH, adm. | 7.44 (7.37–7.48) | 7.43 (7.34–7.48) | 0.438 |
| pH, 24 h | 7.38 (7.32–7.44) | 7.39 (7.30–7.45) | 0.677 |
| pH, nadir | 7.26 (7.2–7.32) | 7.15 (7.08–7.25) | <0.001 |
| Procedures/therapies | | | |
| Vasopressors (first 24 h) | 66 (71) | 53 (72) | 0.450 |
| Renal replacement therapy | 24 (26) | 46 (62) | <0.001 |
| Therapeutic anticoagulation | 57 (61) | 45 (61) | 0.538 |
| Length of stay in the ICU | 22 (13–36) | 14 (7–23) | <0.001 |
| SARS-CoV-2–positive patients to the ICU (days) | 1 (0–5) | 2 (0–8) | 0.961 |
| Complications during the ICU stay | | | |
| Heart failure | 8 (9) | 7 (9) | 0.528 |
| Pulmonary embolism | 2 (3) | 11 (15) | 0.003 |
| Deep vein thrombosis | 6 (6) | 6 (8) | 0.452 |
| Cardiac arrest | 5 (5) | 18 (24) | <0.001 |
| Myocardial infarction | 2 (3) | 1 (1) | 0.585 |
| DIC | 1 (1) | 4 (5) | 0.121 |
| Septic shock | 41 (44) | 44 (59) | 0.034 |

Data are expressed as n (%) or median (interquartile range); *p*-value: mechanically ventilated survivors vs. mechanically ventilated nonsurvivors.

Bold intends a significant *p*-value in the far right column.

BMI, body mass index; kg, kilogram; m, metre; pts., points; DIC, disseminated intravascular coagulation; SOFA, Sequential Organ Failure Assessment; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; MV, mechanical ventilation; adm., admission; max., maximum; CCI, Charlson Comorbidity Index; ARDS, acute respiratory distress syndrome; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.; *p*-value: MV-survivors vs. MV-non survivors; PEEP, positive end-expiratory pressure.

* Data cohort of 66 patients.

reported patients were undergoing ICU treatment at the end of the study period, resulting in a biased outcome with regard to mortality. One recent study reporting of 165 critically ill mechanically ventilated patients with COVID-19 observed a mortality rate of 36%,

with only a small number of patients still ventilated.³² In our cohort, we observed a mortality rate of 44% among mechanically ventilated patients. The differences in mortality between studies can be explained by several observations. First, several studies

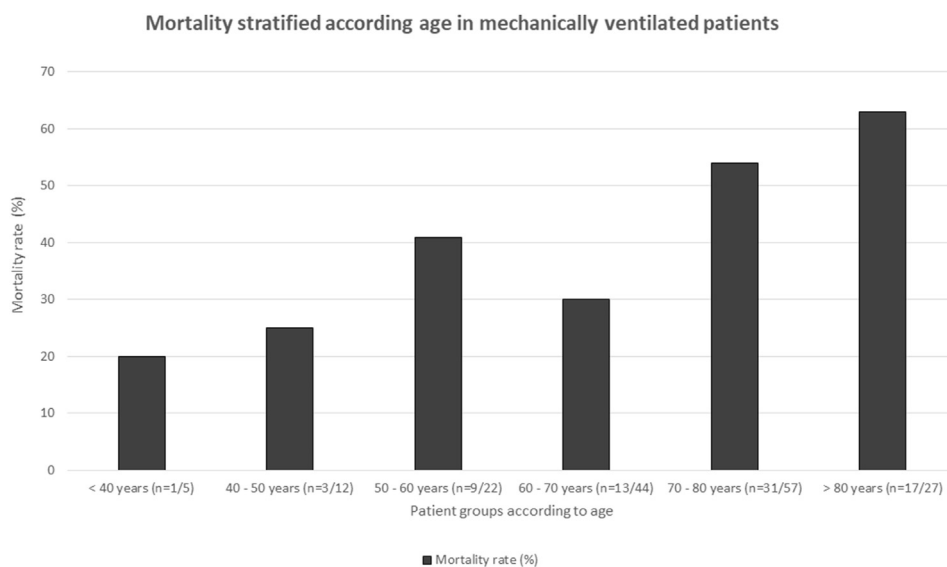


Figure 1. Mortality stratified as per age in mechanically ventilated patients.

report on cohorts with incomplete outcomes for large proportions of patients, when the studies were submitted. This prevents an actual statement on mortality. Second, to date, many studies have been reported from regions that have seen a rapid rise in SARS-CoV-2–positive patients, leading to significant resource limitation. Owing to the overwhelming number of patients admitted to hospitals in China (Wuhan), Italy (Lombardi Region), and the US (New York), local healthcare systems were over their maximal capacities, possibly leading to intubation avoidance and rationing of medical therapies.^{3,6,7} Hereby, we report on a region with overall 5096 cases during the study period and 996 being hospitalised. The total number of ICU beds was increased by 57% in the city of Hamburg. Luckily, the region of northern Germany was not overwhelmed with COVID-19 cases, so we were able to prepare sufficiently and systematically for the pandemic. Patients were likely admitted early to ICU facilities and received early ventilatory support in a sufficiently staffed intensive care setting without shortage of ventilators. However, in a setting without resource limitations, we could show that the observed mortality rate is comparable with patients without COVID-19 and with ARDS.³¹

Several studies have reported on use of ECMO in patients with COVID-19. However, the outcome of patients treated with ECMO owing to ARDS caused by COVID-19 is unclear. A recent report from China with 21 of 129 (16%) critically ill patients receiving ECMO reported a mortality of 57%.³³ In our study, 9% of our patients received ECMO. The mortality among patients receiving ECMO in our cohort was 65% and considerably higher than previous studies on ARDS.³⁴ This may be explained by different management strategies and reporting of patients with virus-induced ARDS only.

In our cohort, we observed different parameters potentially associated with mortality. Both older age and comorbidities were associated with mortality as previously reported.^{7,8} Furthermore, as expected, patients with more severe ARDS had worse outcomes. Furthermore, we observed no differences in outcomes with regard to time of initiation of invasive MV. However, mortality was associated with use of adjunctive therapies—glucocorticoid treatment, inhaled vasodilatory treatment—but not prone positioning or neuromuscular blockade for ARDS treatment. The neuromuscular blockade rate in our cohort was rather low, and national guidelines suggest the use of neuromuscular blockade in selected cases only. Our study found that higher lactate, lower pH, and lower PaO₂ values after 24 h were associated with worse outcomes. Procedures

and complications during the ICU stay were frequent: necessity of RRT, septic shock, and cardiac arrest were significantly associated with mortality. These findings are in line with previous studies.^{6,35} Twelve percent of patients suffered from clinically detected pulmonary embolism, and this was also related to mortality in mechanically ventilated patients. Thromboembolic events are frequently observed in autopsy studies, representing yet another potentially life-threatening complication in critically ill patients with COVID-19.³⁶ These findings led to recommendation of, at least, prophylactic anticoagulation in critically ill patients with COVID-19.³⁷

This study has several strengths. First, we exclusively report on patients with a completed ICU stay, which allows firm conclusions regarding outcomes to be drawn. Second, we report on a representative sample of critically ill patients with COVID-19 treated during the study period. Some limitations should be mentioned. First, data derived from an observational cohort from different hospitals. Different management and therapy strategies of patients with COVID-19 requiring MV and influence on outcomes cannot be entirely excluded. Second, some cases had incomplete documentation based on missing laboratory testing. Third, we observed a rather high rate of complications (e.g., septic shock, cardiac arrest), and a more detailed analysis could not be performed as per retrospective data collection using the CRF. Fourth, residual confounding of unmeasured covariates is a matter of concern and cannot be entirely excluded.

5. Conclusions

In a large multicentre observational cohort study of 223 critically ill patients with COVID-19, we observed an ICU mortality of 35%, an MV rate of 75%, and a mortality rate of 44% in patients receiving MV. Septic shock was a common complication in this cohort. Future randomised trials should focus on the impact of NIV strategies and on the application of adjunctive therapies in patients with COVID-19.

Availability of data and materials

The data sets supporting the conclusions of this article are included within the article.

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Conflict of Interest

K.R., D.J., L.T., M.B., F.S., C.F.W., U.S., C.V., H.-P.H., S.Ko., K.S., A.d.W., M.B., R.S., O.D., J.-P.R., B.S., C.B., O.B., B.B., and G.d.H. do not report any conflicts of interest. S.K. received research support from Ambu, E.T.View Ltd., Fisher & Paykel, Pfizer, and Xenios; lecture honoraria from ArjoHuntleigh, Astellas, Astra, Basilea, Bard, Baxter, Biotest, CSL Behring, CytoSorbents, Fresenius, Gilead, MSD, Orion, Pfizer, Philips, Sedana, Sorin, Xenios, and Zoll; and consultant honorarium from AMOMED, Astellas, Baxter, Bayer, Fresenius, Gilead, MSD, Pfizer, and Xenios. A.N. received research funds, lecture honoraria, and travel reimbursement within the last 5 years from CytoSorbents Europe, Biotest AG, and Thermo Fisher Scientific. D.F. reports lecture honoraria within the last 5 years from Xenios AG.

CRediT authorship contribution statement

KR, DJ, GdH, LT and SK participated in study conception and design. KR, DJ, LT, MB, FS, CFW, US, CV, HPH, SKo, KS, AdW, MB, RS, OD, JPR, BS, CB, OB, DF, AN, SK and GdH were involved in acquisition of data. KR, DJ, GdH and SK contributed to analysis and interpretation of data. KR drafted the manuscript. KR, DJ, CFW, AN, SK and GdH were involved in critical revision of the manuscript for important intellectual content. SK participated in supervision. All authors read and approved the final manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.aucc.2020.10.009>.

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