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COVID-19 Induced Acute Respiratory Distress Syndrome—A Multicenter Observational Study

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Background: Proportions of patients dying from the coronavirus disease-19 (COVID-19) vary between different countries. We report the characteristics; clinical course and outcome of patients requiring intensive care due to COVID-19 induced acute respiratory distress syndrome (ARDS).

Methods: This is a retrospective, observational multicentre study in five German secondary or tertiary care hospitals. All patients consecutively admitted to the intensive care unit (ICU) in any of the participating hospitals between March 12 and May 4, 2020 with a COVID-19 induced ARDS were included.

Results: A total of 106 ICU patients were treated for COVID-19 induced ARDS, whereas severe ARDS was present in the majority of cases. Survival of ICU treatment was 65.0%. Median duration of ICU treatment was 11 days; median duration of mechanical ventilation was 9 days. The majority of ICU treated patients (75.5%) did not receive any antiviral or anti-inflammatory therapies. Venovenous (vv) ECMO was utilized in 16.3%. ICU triage with population-level decision making was not necessary at any time. Univariate analysis associated older age, diabetes mellitus or a higher SOFA score on admission with non-survival during ICU stay.

Conclusions: A high level of care adhering to standard ARDS treatments lead to a good outcome in critically ill COVID-19 patients.

Keywords: COVID−19, ARDS (acute respiratory distress syndrome), intensive care medicine, pandemia, Germany

BACKGROUND

Following the first outbreak of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) in December 2019, the virus has spread worldwide. The coronavirus disease-19 (COVID-19) currently affects 188 countries and territories (1).

In Germany the first case of a SARS-CoV2 infection was diagnosed on February 27, 2020 (2). Although means of social distancing helped to contain virus transmission more than 175 000 people were infected (1). SARS-CoV2 was suggested to elicit a new ARDS-subphenotype, where hypoxemia often does not match lung compliance and ventilator responsiveness (3). The observed case-fatality ratios differ among countries, with the United States reporting 3.8% and Germany reporting 4.5%,respectively. This is lower compared to other European countries, for example, Italy (14.3%), United Kingdom (15.3%) or France (14.2%) (4). Understanding the specific characteristics of severe and fatal disease, as well as the therapeutic approaches to COVID-19 induced ARDS remains an urgent need to provide a basis for best practice models of standardized ARDS treatment.

In the current study, we report the epidemiologic features, clinical course, treatment patterns and outcome of patients requiring intensive care due to COVID-19 induced ARDS in five German centers.

METHODS

This is a retrospective, observational multicenter study at the University Hospital Würzburg and University Hospital Frankfurt, as well as the municipal hospitals of Kassel, Offenbach and Aschaffenburg. Würzburg, Frankfurt, and Kassel are referral centers for adult extracorporeal membrane oxygenation (ECMO) and part of the German ARDS network. To guarantee an individual high level of ICU care all participating hospitals immediately improved ICU infrastructure by adding extra ICU nurses, physicians, medical students and other support workers to the COVID-19 ICUs.

The institutional ethic boards of the University of Würzburg and Frankfurt, as well as the medical association of Bavaria ethics board (Aschaffenburg) and Hessen (Offenbach, Kassel), respectively, approved the study. The need for informed consent from individual patients was waived due to the context of sole retrospective chart review within standard care.

Patient Selection

We included all patients consecutively admitted to the ICU in any of the participating hospitals due to an acute respiratory distress syndrome between March 12 and May 4, 2020. All patients submitted to the ICU had received the diagnosis of a SARS-CoV2 infection or were tested positive for COVID-19 during ICU treatment. SARS-CoV2 infection was detected with real-time reverse transcriptase polymerase chain reaction (RT-PCR) testing based on the recommended World Health Organization standards. No patient tested positive for other respiratory viruses in primary diagnostics. All patients received venous thromboembolism (VTE) prophylaxis with pharmacologic anticoagulation according to the German guidelines on VTE (5). In case of contraindications against pharmacological anticoagulation, mechanical prophylaxis (intermittent pneumatic compression) was conducted. Follow-up ended with ICU discharge or death during ICU treatment, respectively.

Data Collection

Specific treatment protocols were not defined. Routine clinical data were continuously recorded using patient data management systems (PDMS) (University of Würzburg: COPRA6 RM1.0, COPRA System GmbH, Berlin, Germany; University of Frankfurt: Metavision 5.0, imd soft, Dusseldorf, Germany) or assessed via handwritten records (Aschaffenburg, Offenbach, Kassel). The data were retrieved according to the diagnostic standards of the individual centers. Demographic data, pre-existing medical conditions and medications were gathered from prior written records or discharge letters, questionnaires at the time of hospital admission, as well as personal communication with family members. Lung edema on chest radiographs was evaluated via the Radiographic Assessment of Lung Edema (RALE) score (6) in all patients admitted to the ICU in Würzburg. Severity of ARDS was categorized in line with the Berlin definition (mild: 200 mm Hg $< PaO_2/FIO_2 \leq$ 300 mm Hg; moderate: 100 mm Hg $< PaO_2/FIO_2 <$ 200 mm Hg and severe $PaO_2/FIO_2 <$ 100 mm Hg) (7). Since treatment and data acquisition were conducted according to the standard procedures of the respective hospital, diagnostics and reported parameters varied to some degree between the centers. Hence, if applicable the nominators and denominators are reported for each parameter separately, since not all parameters could be retrieved in the whole cohort of patients. All participating hospitals reported their data via a unified sheet (Microsoft® Excel 2019, Version 16.41, Microsoft® Corporation, Redmond, WA).

Statistical Analysis

Median and interquartile range (25–75%) were reported for continuous data, absolute and relative frequencies for categorical variables. Percentages are based on the total number of patients with complete information in the respective category. Continuous variables were tested for normality using histogram and QQ-plot. To compare differences between survivors and non-survivors in continuous variables the Mann-Whitney rank-sum test or the Wilcoxon matched-pairs signed rank test, respectively, was used as appropriate, as most of the variables were not normally distributed. The Chi^2-Test or Fisher exact test was used to assess the association of dichotomous variables and the outcome. Age-adjusted logistic regression analyses were

Abbreviations: COVID-19, coronavirus disease-19; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ARDS, acute respiratory distress syndrome; ICU, intensive care unit; vvECMO, venovenous extracorporeal membrane oxygenation; RT-PCR, real-time reverse transcriptase polymerase chain reaction; SOFA, sepsis-related organ failure assessment; F_iO_2, fraction of inspired oxygen; p_aO_2/F_iO_2, arterial partial pressure of oxygen/fraction of inspired oxygen oxygenation index; PEEP, positive end-expiratory pressure; P_{Plat}, maximum airway plateau pressure; P_{mean}, mean airway pressure; RALE, radiographic assessment of lung edema; IQR, interquartile range (25–75%); PCT, procalcitonin; IL-6, interleukin 6; VTE, venous thromboembolism.

performed to identify factors associated with death during ICU treatment. Wilson score method was used to estimate 95%-confidence intervals for the crude proportion of survival during ICU stay; Kaplan-Meier estimates were used for estimating survival probability. All tests were two-tailed, a p-value <0.05 was considered as statistically significant. The univariate p-values were based on Mann-Whitney U Test, Chir²-Test or Fisher's exact Test as appropriate. The adjusted p-values are based on a logistic regression adjusted for age.

Data were analyzed using SAS® Software, Version 9.4. Copyright© SAS Institute Inc. Cary, NC, USA, R, R Version 3.6.2., Prism 5 for Mac OS X (GraphPad Software, San Diego, CA), Stata version 14.2 (Stata Corp, College Station, TX) or SigmaPlot®, version 10.0 (Systat Software, Erkrath, Germany).

RESULTS

A total of 106 ICU patients were treated for COVID-19 induced ARDS. None of these patients remained in ICU care at the end of the study period. Three patients were transferred from Italy to the ICU in Würzburg. Two of these patients were excluded from the analysis due to an advanced clinical course at the time of their transfer, as well as incomplete records and short-term ICU stay.

Epidemiologic Characteristics and Outcome

Median age of the patients was 64 (IQR 54–76) years, 70.5% were males. Median time from hospital to ICU admission was 2 (IQR 1–4) days. Overall, 37 patients died during ICU stay, constituting an overall survival of 65.0% (95% CI 55.6–73.5) (**Figure 1**). Considering only severe ARDS (P_aO_2/F_iO_2 < 100) (7), survival in critical care was 59.7% (CI 46.7–71.4) (**Supplementary Table 1**). Median duration of ICU treatment was 11 (IQR 7–19) days. Reported comorbidities were present in 79.3% of the cases, with arterial hypertension as most common comorbidity followed by diabetes mellitus (**Table 1**). Patients surviving ICU treatment were significantly younger. Although the majority of patients were male, a gender difference with respect to survival was not observed. Diabetes mellitus [age-adjusted Odds Ratio (OR) 3.4; 95-CI 1.3–8.7] and a higher SOFA score on admission (age-adjusted OR 1.2; 95%-CI 1.1–1.4) were associated with non-survival in univariate and age-adjusted analyses.

Laboratory Findings

Laboratory findings are presented in **Table 2**. Patients who survived ICU treatment had lower levels of inflammatory markers on admission and during the course of therapy. A near

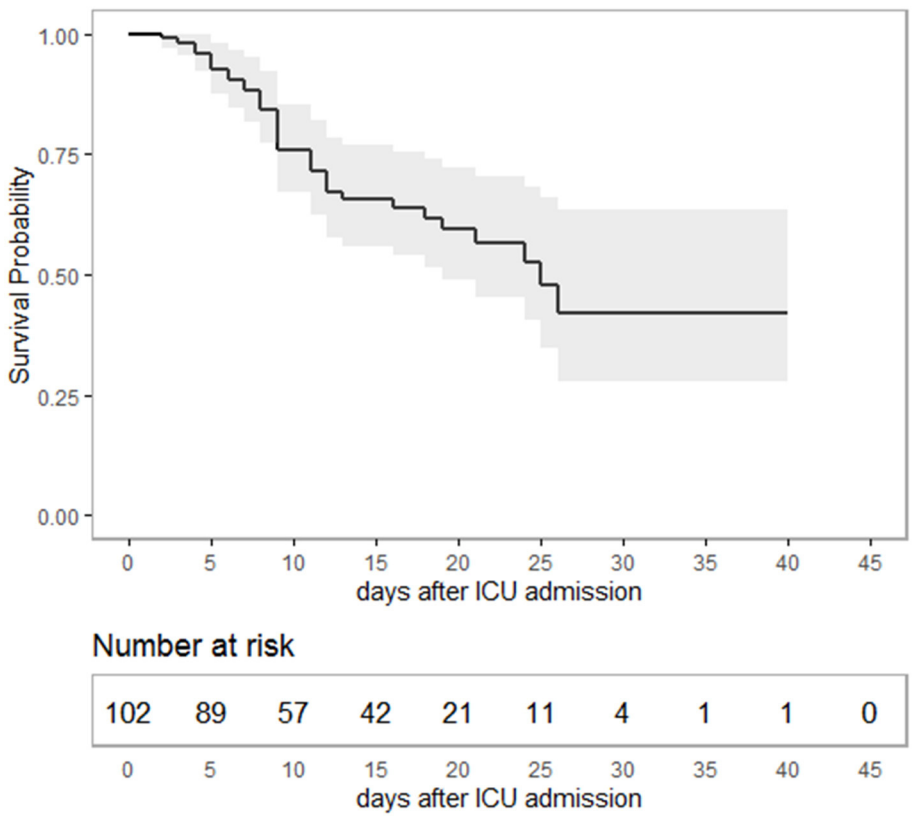

FIGURE 1 | Kaplan-Meier-plot showing survival probability as a function of time in intensive care. Overall, 65% (95%-CI 55.6–73.5) of the patients survived ICU treatment with a median duration of 11 (IQR: 7–19) days. The study period ended with ICU discharge or death, respectively. Hence, survival data are terminally censored resulting in a horizontal line on the far right.

TABLE 1 | Epidemiologic characteristics.

Characteristic	All patients (*N* = 106)	Survivors (*N* = 69)	Non-survivors (*N* = 37)	*P*-value*	Adjusted *p*-value**
Demographics					
Age (years)	64 (54–76)	61 (51–71)	70 (60–78)	0.0029	
Male—no. patients (%)	74(70.5)	50 (72.5)	24 (66.7)	0.5365	0.8194
BMI—median	27.8 (24.9–32.0)	27.8 (24.9–32.0)	27.4 (25.0–31.7)	0.9385	0.8029
Co-morbidities					
Arterial hypertension—no. patients (%)	71 (67.0)	44 (63.8)	27 (73.0)	0.3368	0.6103
Diabetes mellitus—no. patients (%)	26 (24.5)	11 (15.9)	115 (40.5)	0.0050	0.0133
COPD/asthma bronchiale—no. patients (%)	16 (15.1)	7 (10.1)	9 (24.3)	0.0519	0.1192
Coronary artery disease—no. patients (%)	20 (18.9)	9 (13.0)	11 (29.7)	0.0363	0.2236
Heart failure—No. patients (%)	15 (14.2)	7 (10.2)	8 (21.6)	0.1061	0.4755
Stroke—no. patients (%)	13 (12.3)	7 (10.1)	6 (16.2)	0.3637	0.6759
Chronic renal failure—no. patients (%)	16 (15.1)	8 (11.6)	8 (21.6)	0.1692	0.5348
Cancer—no. patients (%)	12 (11.3)	8 (11.6)	4 (10.8)	>0.900	0.3842
Duration prior to ICU admission—days in hospital	2 (0–4) (*N* = 51)	2 (0–4) (*N* = 33)	2 (1–4) (*N* = 18)	0.6519	0.9821
Body temp. > 37.5°C at time of ICU admission (%)	54 (71.0) (*N* = 76)	41 (68.9) (*N* = 52)	13 (54.2) (*N* = 24)	0.0274	0.0098
Scores					
SOFA at time of ICU admission	9 (4–14) (*N* = 78)	5 (4–11) (*N* = 49)	13 (9–16) (*N* = 29)	0.0002	0.0003
Highest SOFA	13 (7–18) (*N* = 69)	10 (5–15) (*N* = 45)	18 (14–21) (*N* = 24)	<0.0001	0.0010

**P-values based on Mann-Whitney, Chi²-Test or Fisher exact test as appropriate.*

***P-values adjusted for age in a logistic regression.*

ICU, intensive care unit; Covid-19, Corona virus disease 2019; No. patients, number of patients; BMI, body mass index; SOFA, Sepsis-related organ failure assessment score. Data are shown as median and interquartile range (25%-75%) or absolute numbers and percentage of patients, respectively. The data represent the analysis of 106 patients, unless otherwise specified via the n-number in the respective row.

three-fold difference in interleukin-6 (IL-6) was present between survivors and non-survivors at the time of ICU admission. 58.3% percent of the non-survivors had IL-6 levels >400 pg/ml. Bacterial specimens were found in 12.3% of the patients with no significantly differences between survivors or non-survivors. Nevertheless, a high percentage was already treated with antibiotics prior to ICU admission.

Respiratory Support

The median arterial oxygenation index (P_aO_2/F_iO_2) at the time of admission was 120 (IQR 88–164), indicating moderate to severe ARDS in the majority of patients. Overall, 55.6% had a moderate ARDS at admission; 35.8% of all patients and 63.8% of the non-survivors already suffered from a severe ARDS ($P_aO_2/F_iO_2 < 100$) at the time of ICU admission. Pulmonary gas exchange worsened in both populations. Prone positioning was performed in 78.9% of the cases. However, comparing the P_aO_2 at the time of ICU discharge or death, respectively, there was no significant difference. Median duration of mechanical ventilation was 9 (IQR 5.5–15.5) days and not significantly different between survivors and non-survivors. The same applies to lung mechanics or radiographic findings (**Table 3**). Chest X-ray pathologies were relatively minor compared to the degree of hypoxemia at admission. While deteriorating during the course of therapy, RALE scores were never significantly different between survivors and non-survivors. Moreover, RALE scores recovered in both groups toward the end of therapy.

Extracorporeal Membrane Oxygenation (ECMO)

Venovenous (vv) ECMO was utilized in 16.3% ($n = 17$) of the patients with a median age of 58 (IQR 51–63) years. Two patients received venoveno-arterial (vva) support due to acute cor pulmonale. ECMO patients had been on mechanical ventilation for a median of two (IQR 1–6) days. In three quarters of all cases, the use of ECMO was indicated due to refractory hypoxemia. Median P_aO_2/F_iO_2 at the time of ECMO commencement was 58 (IQR 51–66). Six patients (35.3%; 95%-CI 17.3–58.7) survived until ICU discharge.

TABLE 2 | Laboratory and microbiological findings.

	All patients (*N* = 106)	Survivors (*N* = 69)	Non-survivors (*N* = 37)	*P*-value*	Adjusted *p*-value**
Laboratory data					
Lactate on Admission (mmol/l)	1.3 (0.9–1.8) (*N* = 72)	1.2 (0.9–1.4) (*N* = 44)	1.7 (1.3–3.2) (*N* = 28)	0.0002	0.0025
Ferritin (μg/l) on Admission	1,917 (1,310–3,166) (*N* = 26)	1,563 (1,013–2,453) (*N* = 17)	2,794 (1,483–3,487) (*N* = 9)	0.1693	
Highest D-dimers (mg/l) during ICU stay	5.7 (2.1–15.6) (*N* = 74)	4.4 (1.4–15.6) (*N* = 51)	7.1 (3.6–15.7) (*N* = 23)	0.0768	0.0502
Infection analyses					
IL-6 (pg/ml) on admission	236.0 (80.3–608.0) (*N* = 64)	146 (49.8–374.5) (*N* = 40)	501.5 (236.0–1,019.5) (*N* = 24)	0.0004	0.0985
IL-6 > 400 pg/ml on Admission- No. patients (%)	23 (35.9)	9 (22.5)	14 (58.3)	0.0038	0.0046
IL-6 (pg/ml) at discharge or death	47 (18.8–447.5) (*N* = 72)	22.8 (11.0–44.8) (*N* = 43)	550.0 (200.0–2,957.0) (*N* = 29)	<0.0001	0.0440
White blood cell count (*n**1000/μl) on admission	9.2 (6.3–11.8) (*N* = 104)	8.1 (5.6–11.3) (*N* = 67)	10.0 (7.4–12.7) (*N* = 37)	0.0111	0.0290
Lymphocyte count (*n**1000/μl) at discharge or death	1.5 (0.8–8.4) (*N* = 76)	1.5 (0.8–9.0) (*N* = 53)	1.6 (0.8–6.0) (*N* = 23)	0.4386	0.1760
PCT (ng/ml) on admission	0.5 (0.3–2.0) (*N* = 99)	0.5 (0.2–0.9) (*N* = 65)	1.3 (0.5–5.5) (*N* = 34)	0.0029	0.1001
PCT (ng/ml) at discharge or death	0.8 (0.1–4.1) (*N* = 80)	0.2 (0.1–0.8) (*N* = 48)	3.9 (1.6–7.4) (*N* = 32)	<0.0001	0.0273
Pos. bacterial culture (all sources of culture)—no. patients (%)	13 (12.3)	5 (7.3)	8 (21.6)	0.0582	0.0741
Antibiotic treatment no. patients (%)	57 (64.8) (*N* = 88)	31 (56.4) (*N* = 55)	26 (78.8) (*N* = 33)	0.0397	
Antiviral therapy—no. patients (%)	26 (24.5)	17 (24.6)	9 (24.3)	0.9715	0.8392

*P-values based on Mann-Whitney,Chi²-Test or Fisher exact test as appropriate.

**P-values adjusted for age in a logistic regression.

IL-6, interleukin-6; PCT, procalcitonin; No. patients, number of patients.

Data are shown as median and interquartile range (25%-75%) or absolute numbers and percentage of patients, respectively. The data represent the analysis of 106 patients, unless otherwise specified via the n-number in the respective row.

Antiviral Therapies

The majority of patients (75.5%) did not receive any antiviral or anti-inflammatory therapy, while 24.5% received adjunct therapies including oseltamvir ($n = 10$), remdesivir ($n = 1$), chloroquins ($n = 10$) or tocilizumab ($n = 3$). However, as the choice and duration of therapy was purely at the discretion of the attending physicians, a large number of heterogeneous substances and protocols were used. Hence, no further analyses were performed due to the small sample sizes.

DISCUSSION

The current study focused on the characteristics and outcome of COVID-19 patients admitted to the ICU in five German centers. Our study population mainly consisted of high-risk patients, where ARDS mortality rates of 40 to 46% can be expected (8). Half of our patients suffered from severe ARDS. Major findings include the identification of age, diabetes mellitus and higher SOFA scores on admission as factors associated with non-survival during ICU treatment. Furthermore, our observations indicate that standard ARDS treatment resolves acute hypoxemia in the majority of cases.

The proportion of patients surviving ICU care was 65.0% with a corresponding 95% CI of 55.6–73.5. Survival rates of ICU patients varied substantially between previous studies and different countries, for example, between 22 to 84% in China (9–12), 50% in Seattle (13), 33% in Washington State (14) and 61% in New York (15). In a retrospective cohort study from Italy only 46.6% of the patients requiring hospital admission survived (16). The ICNARC currently reports a survival of 60% in intensive care from the United Kingdom (17). A recent analysis of COVID-19 patients via the claims of the German Local Health Care Funds revealed an overall mortality of 22% and a mortality of 53% in patients requiring invasive ventilation. However, ARDS subtypes were not classified and risk factors of non-survival were not identified (18). Differences between countries may be due to variations in patient characteristics, as well as ICU admission criteria, criteria for ECMO, or availability of ICU capacities. All of the participating hospitals had sufficient resources to provide the best available standard care at any time. The workforce on the ICU of the participating hospitals was actually increased

TABLE 3 | Characteristics of pulmonary function and outcome.

	All patients (*N* = 106)	Survivors (*N* = 69)	Non-survivors (*N* = 37)	*P*-value*	Adjusted p-value**
Pulmonary gas exchange (on admission)					
P_aO_2/F_iO_2	120 (88–164) (*N* = 83)	121 (88–167) (*N* = 56)	120 (88–156) (*N* = 27)	0.8269	0.5717
P_aO_2 (mmHg)	74.1 (61.0–90.0) (*N* = 103)	76.0 (61.0–88.1) (*N* = 69)	67.4 (59.4–104.0) (*N* = 34)	0.6259	0.2783
P_aCO_2 (mmHg)	39.0 (34.2–47.5) (*N* = 104)	38.1 (33–43.6) (*N* = 69)	44.8 (37–49.4) (*N* = 34)	0.0072	0.0287
s_aO_2 (%)	94.0 (91.1–97.1) (*N* = 102)	94.6 (91.7–97.0) (*N* = 68)	93.6 (89.0–98.0) (*N* = 34)	0.8230	0.1693
Lung compliance (ml/cmH_2O)	43.1 (32.0–59.8) (*N* = 42)	43.2 (36.4–55.4) (*N* = 21)	41.2 (30.7–59.8) (*N* = 21)	0.6781	0.7680
RALE score	12.0 (5.5–28.5) (*N* = 28)	12.5 (8.0–28.0) (*N* = 18)	8.5 (4.0–29.0) (*N* = 10)	0.3368	0.9313
Pulmonary gas exchange (during ICU stay)					
Lowest P_aO_2/F_iO_2	100. (75–131.) (*N* = 61)	110 (81–142) (*N* = 42)	89 (60–111) (*N* = 19)	0.0437	0.0256
Lowest p_aO_2 (mmHg)	57 (49.8–66.5) (*N* = 72)	61.9 (53.8–68.0) (*N* = 46)	51.7 (45.0–59.0) (*N* = 26)	0.0082	0.0064
P_aO_2 (mmHg)—at ICU-Discharge/Death	73.0 (66.0–89.8) (*N* = 95)	73.0 (67.0–92.0) (*N* = 62)	75.0 (66.0–86.5) (*N* = 33)	0.7337	0.5492
Highest p_aCO_2 (mmHg)	56.0 (45.0–72.0) (*N* = 98)	52.0 (41.0–62.8) (*N* = 67)	71.4 (53.1–81.5) (*N* = 31)	0.0005	0.0045
RALE score day 7	16 (5–36) (*N* = 27)	16 (7–36) (*N* = 17)	13 (2–33) (*N* = 10)	0.4204	0.6911
RALE score at time of discharge/death	6 (3–18) (*N* = 28)	7 (4–12) (*N* = 18)	4.5 (2.0–33.0) (*N* = 10)	0.8101	
Mechanical ventilation					
Highest F_iO_2 (%)	90 (65.0–100) (*N* = 103)	85 (60–100) (*N* = 67)	100 (90–100) (*N* = 36)	0.0012	0.0018
Highest peep (cmH_2O)	15 (11–16) (*N* = 95)	12 (10–15) (*N* = 59)	15 (14–17) (*N* = 36)	0.0016	0.0058
Highest P_{Plat} (cmH_2O)	31 (26–34) (*N* = 92)	29.5 (24.0–33) (*N* = 58)	32 (31–36) (*N* = 34)	0.0013	0.0054
Prone positioning—no. patients (%)	76 (71.7) (*N* = 104)	45 (65.2) (*N* = 69)	31 (88.6) (*N* = 35)	0.0111	
ECMO (*N* = 17)					
Age	58 (51–63)	50 (47–52)	62 (57–67)	0.0137	
Mode—no. patients (%)					
vvECMO	17 (16.0)	6 (8.7)	11 (29.7)		
vvaECMO	2 (1.9)	0 (0.0)	2 (5.4)		
P_aO_2/F_iO_2–prior to ECMO start	58 (51–66)	58.0 (56.3–69)	59.6 (55–80)	0.8548	
P_aCO_2–prior to ECMO start	70.5 (60.5–77.7)	71.3 (60.5–77.7)	67.3 (60.5–76.5)	0.7963	
Duration—hours	164.5 (126.7–369.3)	164.5 (126.7–225.4)	217.7 (126.5–444.6)	0.6605	
Duration mechanical ventilation prior to ECMO—days	2 (1–6)	1.5 (1.0–2.0)	5 (2–6)	0.0961	
Survival (%)	35.3 (95%-CI 17.3–58.7)				
Outcome					
Duration of ICU treatment–days	11 (7–19) (*N* = 102)	15 (7–20) (*N* = 67)	9 (6.5–12) (*N* = 35)	0.0540	
Duration of mechanical ventilation—days	9 (4.5–15.5) (*N* = 100)	9 (4–17) (*N* = 65)	9 (5–15) (*N* = 35)	0.6795	
Survival—(%)	65 (95%-CI 55.6–73.5)				

**P-values based on Mann-Whitney,Chi²-Test or Fisher exact test as appropriate.*

***P-values adjusted for age in a logistic regression.*

P_aO_2, arterial partial pressure of oxygen; F_iO_2, fraction of inspired oxygen; s_aO_2, arterial saturation of hemoglobin; PEEP, positive end-expiratory pressure, P_{Plat}, plateau airway pressure; SOFA, sepsis-related organ failure assessment score; vvECMO, venovenous extracorporeal membrane oxygenation; vaECMO, venoarterial extracorporeal membrane oxygenation; ICU, intensive care unit; No. patients, number of patients.

Data are shown as median and interquartile range (25%-75%) or absolute numbers and percentage of patients, respectively. The data represent the analysis of 106 patients, unless otherwise specified via the n-number in the respective row.

to counteract the big challenges associated with COVID-19, including a high number of patients requiring prone positioning, as well as time and effort associated with the use of personal protective equipment.

Advanced age has been uniformly reported as a risk factor for severe disease (12, 19) and was also associated with a worse outcome in our study. Diabetes mellitus was also reported as a factor associated with death from COVID-19 in critically ill in New York City and Lombardy (15, 16). It was associated with an approximately three-fold increased risk of death in our study. Arterial hypertension on the other hand was the most frequent comorbidity. Nevertheless its presence was not associated with a worse outcome and likely only represents the overall disease frequency (20). Although previously reported as a predictor of sepsis mortality (21), lymphocytopenia was not a distinctive feature in our ICU population. We did observe differences in SOFA scores and IL-6. IL-6 is perceived to be the central mediator of a cytokine release syndrome (22) and survivors had significantly lower IL-6 levels at the time of ICU admission. In this regard, preliminary data indicate that the administration of dexamethasone could improve survival in patients receiving respiratory support (23). Nevertheless, in our study treatment protocols for the use of glucocorticoids were not defined and dexamethasone was not utilized in any of the patients. Moreover, due to the small sample size, no multivariable prediction model to identify potential predictors of survival could be build.

The standards of ARDS treatment consist of prone positioning and protective mechanical ventilation with higher PEEP levels. All centers adhered to these guideline recommended therapies (24), although P_{Plat} values indicate difficulties in maintaining lung protective ventilation at all times. Both survivors and non-survivors had worsening lung injury during the course of treatment with a high percentage of prone positioning. Patients dying during ICU treatment suffered from a worse pulmonary function at time of ICU admission, however, interestingly the duration of mechanical ventilation was not significantly different to patients surviving ICU care. Furthermore, p_aO_2 values do not indicate hypoxemia at the time of death. The same applies to the RALE score or lung compliance, emphasizing that radiographic findings and lung mechanics often do not match the severity of disease (3). Antiviral or anti-inflammatory treatments were only utilized in a minority of the patients. The use of remdesivir was recently associated with faster COVID-19 recovery times, whereupon beneficial effects could not be shown in patients receiving mechanical ventilation or ECMO (25). In our cohort, approximately one fourth received antiviral treatment, whereas no significant difference in survival was observed.

Seventeen patients (16.3%) received vvECMO therapy. The overall rate of vvECMO treatment was higher compared to what has been reported from China (11, 12), the United States (15) and Italy (26). German Local Health Care Fund data recorded ECMO treatment in 7% of all ventilated patients in 920 German hospitals (18). The high ECMO rate in our study population emphasizes the severity of disease and that mainly specialized centers participated in the study. Nevertheless, the survival rate was lower in these patients and worse compared to other causes of ARDS.

Taken together, standard ARDS treatment according to published guidelines resolved acute hypoxemia in the majority of cases. Advanced age and diabetes mellitus increased the risk of non-survival. ICU triage with population-level decision making was not necessary and sufficient ICU equipment and personnel resources were available at any time. If the number of COVID-19 ICU patients re-increases, standard ARDS treatment provides a strong basis to ensure a good outcome in critically ill COVID-19 ARDS patients.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Würzburg and Frankfurt, as well as the medical association of Bavaria ethics board (Aschaffenburg) and Hessen (Offenbach, Kassel). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

JH, EA, KZ, and CL contributed substantially to the conception and design of the study, the acquisition, analysis, interpretation of the data, and drafted the article. PM, QN, PHel, MS, PU-P, AS, IT, CaR, ChR, MK, JS, and DG-S contributed substantially to the acquisition and analysis of the data. PK, AB, ToS, BS, DW, HK, TW, SF, GE, RM, HM, and YZ contributed substantially to the acquisition of data, the interpretation of the data and provided critical revision of the article. ThS contributed substantially to the critical revision of the article. PHeu contributed substantially to the analysis, interpretation of the data and provided critical revision of the article. VR contributed substantially to the analysis of the data. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2020.599533/full#supplementary-material

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