




Clinical and virological characteristics of hospitalised COVID-19 patients in a German tertiary care centre during the first wave of the SARS-CoV-2 pandemic: a prospective observational study

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Abstract

Purpose Adequate patient allocation is pivotal for optimal resource management in strained healthcare systems, and requires detailed knowledge of clinical and virological disease trajectories. The purpose of this work was to identify risk factors associated with need for invasive mechanical ventilation (IMV), to analyse viral kinetics in patients with and without IMV and to provide a comprehensive description of clinical course.

Methods A cohort of 168 hospitalised adult COVID-19 patients enrolled in a prospective observational study at a large European tertiary care centre was analysed.

Results Forty-four per cent (71/161) of patients required invasive mechanical ventilation (IMV). Shorter duration of symptoms before admission (aOR 1.22 per day less, 95% CI 1.10–1.37, $p < 0.01$) and history of hypertension (aOR 5.55, 95% CI 2.00–16.82, $p < 0.01$) were associated with need for IMV. Patients on IMV had higher maximal concentrations, slower decline rates, and longer shedding of SARS-CoV-2 than non-IMV patients (33 days, IQR 26–46.75, vs 18 days, IQR 16–46.75, respectively, $p < 0.01$). Median duration of hospitalisation was 9 days (IQR 6–15.5) for non-IMV and 49.5 days (IQR 36.8–82.5) for IMV patients.

Conclusions Our results indicate a short duration of symptoms before admission as a risk factor for severe disease that merits further investigation and different viral load kinetics in severely affected patients. Median duration of hospitalisation of IMV patients was longer than described for acute respiratory distress syndrome unrelated to COVID-19.

Keywords Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) · Coronavirus disease 2019 (COVID-19) · Viral concentration · COVID-19 nucleic acid testing · Respiratory distress syndrome · Mechanical ventilation · Artificial respiration · Prospective study · Symptom assessment

Introduction

The ongoing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic places an unprecedented burden on healthcare systems worldwide. Host factors predictive of severe clinical course and adverse outcome in patients with coronavirus disease 2019 (COVID-19) include older age, male gender, and pre-existing chronic comorbidities [1–6]. Several risk scores containing clinical characteristics, laboratory assessments, and biomarkers have been proposed for improved patient management and resource allocation [5, 7].

Victor M. Corman, Florian Kurth have contributed equally.

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Reported proportions of hospitalised patients requiring invasive mechanical ventilation (IMV) vary considerably between 2.3% [8] and 23.6% [2]. In-hospital case fatality rates of 20–30% have been described in China, Germany, Italy, the UK, and the US [1, 6, 9–11]. In Germany, shortages of inpatient beds and intensive care unit (ICU) capacity were largely avoided during the first pandemic wave, contributing to a comparatively low overall case fatality rate [1, 12].

Here, we report clinical characteristics, laboratory and virological parameters, clinical course, and outcome of 168 COVID-19 patients included in a prospective observational cohort study conducted at Charité-Universitätsmedizin Berlin, Germany. The study was designed for deep clinical, molecular, and immunological phenotyping of COVID-19 [13–17].

The data reflect the situation in a tertiary care referral centre for the treatment of patients with acute respiratory distress syndrome (ARDS), including veno-venous extracorporeal membrane oxygenation (vvECMO) therapy, and an associated certified weaning centre during the first months of the COVID-19 pandemic, before treatment with dexamethasone became standard of care [18]. Specific aims of this work were to identify risk factors associated with need for IMV, to analyse viral kinetics in patients with and without IMV, and to provide a comprehensive description of clinical course and outcome.

Methods

Study cohort and data collection

Data collection was performed within the Pa-COVID-19 study, a prospective observational cohort study conducted at Charité-Universitätsmedizin Berlin, as described [13]. Adult patients admitted between March 1st and June 30th, 2020, with PCR-confirmed SARS-CoV-2 infection were included if patients or their legal representatives gave informed consent. We recorded epidemiological and demographic data, medical history, history of present illness, symptoms, clinical course, treatment, and outcomes upon enrolment and longitudinally during hospitalisation. The study was approved by the ethics committee of Charité-Universitätsmedizin Berlin (EA2/066/20), conducted according to the Declaration of Helsinki and Good Clinical Practice principles (ICH 1996) and is registered in the German and WHO international clinical trials registry (DRKS00021688).

The primary objective of this first analysis of the Pa-COVID-19 cohort was to identify risk factors and virological and laboratory parameters associated with need for IMV. Comorbidities were classified using the Charlson comorbidity Index (CCI) [19]. ARDS was defined according

to the Berlin definition of ARDS [20]. Sequential Organ Failure Assessment (SOFA) score [21] was calculated from data recorded in the ICU data management system. The following predefined events were assessed in all patients: (1) sepsis (defined according to sepsis-3 criteria [22]), (2) venous thromboembolic events (VTE; pulmonary embolism or deep vein thrombosis), (3) neurologic events (haemorrhagic/ischaemic stroke, delirium, intensive care unit-acquired weakness, ICUAW), epileptic seizure, meningitis and encephalitis). Treatment was unaffected by participation in the study. Patient allocation was performed according to structured regional processes [23] and management of critically ill patients following current guidelines as described [24, 25]. Duration of symptoms was only analysed for patients with reliable information on symptom onset in the patient chart given by patients themselves or relatives.

All laboratory assessments were carried out in accredited laboratories at Charité- Universitätsmedizin Berlin. SARS-CoV-2 viral concentration was measured in respiratory samples (naso- or oropharyngeal swabs) by real-time RT-PCR [26]. Viral concentration is given as \log_{10} genome copies per swab or initial 1 mL sampling buffer.

Statistical analyses

Distribution of continuous variables was summarised by median and interquartile range (IQR) values or mean and standard deviation (SD), as appropriate. The differences of continuous variables between groups were examined by Welch's *t* test or, in absence of normal distribution, by Mann–Whitney *U* test. Categorical variables were compared using Chi-square tests. For all analyses, complete cases were used for the respective evaluation.

We conducted a multiple logistic regression with “need for invasive mechanical ventilation” as a binary dependent variable and age, BMI, hypertension, diabetes, and time between symptom onset and admission to hospital as independent variables. The covariates were chosen taking into account current evidence, results from univariate testing, and sample size. We performed univariate tests regarding all available patient factors and association with organ support treatment, complications, and outcome. Continuous variables were treated as follows: age was categorized in accordance with other reports on patients with COVID-19 [1], BMI and CCI were dichotomized at the median. Patients with therapy limitations (Do Not Intubate (DNI) or Do Not Resuscitate (DNR) orders) at the respective time point were excluded for comparison between non-IMV and IMV patients, and for analyses of course-of-organ support and mortality. Non-survivors were excluded from comparison between short- (< 15 days) or long-term (\geq 15 days) IMV. For analysis of SOFA score, scores were extracted from electronic patient charts and the highest score per day was

included for calculation of means. The neurological component of the SOFA score was not taken into consideration due to patient sedation and incomplete documentation during daily discontinuation of sedation. Patients who died or were transferred to other centres were excluded from calculation of length of hospital stay. For analyses of routine laboratory parameters within 72 h of first admission, first-available parameters were included.

We compared viral concentration between non-IMV and IMV patients, and regressed viral concentration on the duration from symptom onset to admission using both the first positive RT-PCR result and the RT-PCR with the highest viral concentration. For the calculation of viral concentration decline, we estimated the slope parameter from a linear regression of at least four viral concentration measurements over time for each patient. If available, the first of at least two final negative RT-PCR results was included, in which case the viral concentration of the negative RT-PCR was set to 2.0 in accordance with the RT-PCR limit of detection and sample dilution factor of ~ 20 [26, 27]. We calculated shedding duration as the time from symptom onset to the date of the first of at least two final negative RT-PCR results.

Analyses were conducted with R (version 3.6.1), JMP (version 14.2.0), and statsmodels (version 0.12.0) in Python 3.7.9. A p value < 0.05 indicates statistical significance, although all results have to be considered as non-confirmatory. For this reason, no adjustment for multiple testing was done.

Results

Baseline characteristics

Between March 1st and June 30th 2020, a total of 347 adult patients with COVID-19 were hospitalised at Charité-Universitätsmedizin Berlin. This analysis includes 168 adult patients who consented to participation in the prospective observational study (Fig. 1). Sixty-five per cent (110/168) were directly admitted to our centre, whereas 29.8% (50/168) were referred due to ARDS or other conditions requiring tertiary care. Four per cent (7/168) were hospitalised for other reasons and coincidentally diagnosed with SARS-CoV-2 infection during routine screening, and one patient (0.6%) was admitted due to a late complication of COVID-19.

Baseline characteristics are shown in Table 1. Median patient age was 61 years (IQR 49.3–72), and 66.1% (111/168) were male. Median CCI was 3 (IQR 1–4). Most prevalent comorbidities were hypertension (53.6%, 90/168), diabetes (19.6%, 33/168), and chronic pulmonary disease (16.7%, 28/168). Median time from symptom onset until diagnosis was 4 days (IQR 1–7), and from symptom onset until admission to hospital was 6 days (IQR 3–10).

ARDS and organ support treatment

Fifty-two per cent (88/168) of patients developed ARDS. One of them was already dependent on long-term

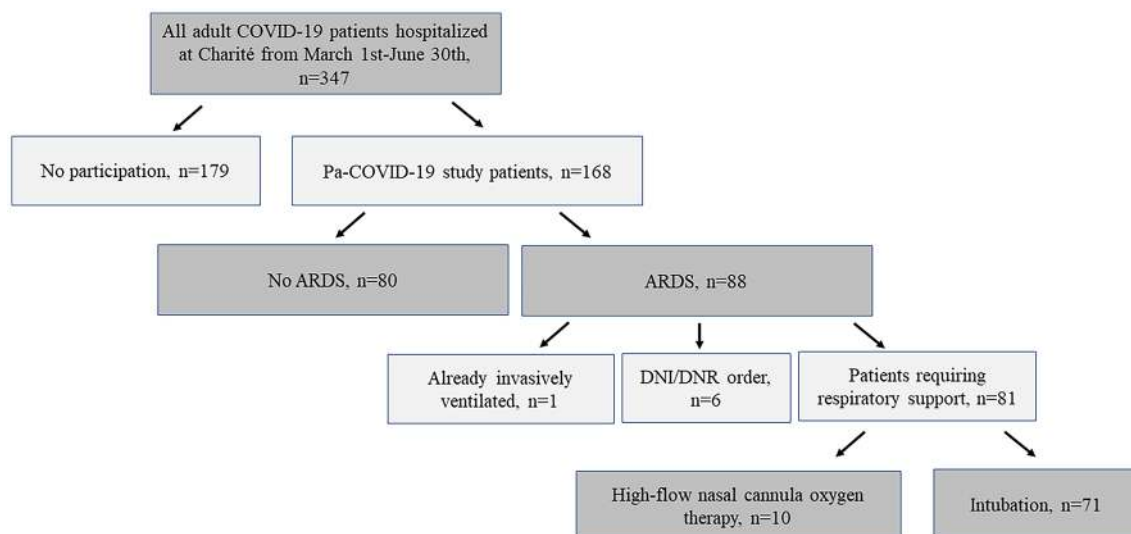


Fig. 1 Study cohort flowchart. A total of 347 adult patients were hospitalised with COVID-19 during the study period from March 1st until June 30th at Charité-Universitätsmedizin Berlin. Of these, 168 patients could be enrolled in the prospective observational study, whereas 179 denied. Among the included patients, 88 had acute res-

piratory distress syndrome (ARDS). One patient with ARDS was already invasively ventilated and six of them had DNI/DNR (do not intubate/do not resuscitate) orders in place, resulting in 81 patients requiring respiratory support. Of those, 71 patients were intubated and ten required only high-flow nasal cannula oxygen therapy

Table 1 Baseline patient characteristics, unadjusted and adjusted odds ratios and 95% confidence intervals for need of mechanical ventilation

	All patients	Non-IMV	IMV	Unadjusted OR (95% CI); <i>p</i> value Chi-square test	Adjusted OR (95% CI); <i>p</i> value
Total number of patients	168	55.9%, 90/161	44.1%, 71/161		
Age in years (median, (IQR))	61 (49.3–72)	59 (42–72)	62 (54–72)		
18–59	46.4%, 78/168	54.4%, 49/90	40.8%, 29/71	Reference group	Reference group
60–69	21.4%, 36/168	15.6%, 14/90	31.0%, 22/71	2.66 (1.18–5.89); 0.02	4.33 (1.07–20.10); 0.05
70–79	20.8%, 35/168	21.1%, 19/90	19.7%, 14/71	1.24 (0.54–2.85); 0.60	0.55 (0.14–1.91); 0.36
≥ 80	11.3%, 19/168	8.9%, 8/90	8.5%, 6/71	1.26 (0.40–4.02); 0.69	0.26 (0.04–1.54); 0.15
Gender					
Female	33.9%, 57/168	38.9%, 35/90	29.6%, 21/71	Reference group	
Male	66.1%, 111/168	61.1%, 55/90	70.4%, 50/71	1.51 (0.78–2.94); 0.22	
BMI (kg/m ² , median, (IQR), available <i>n</i>)	27.8 (24.6–31.4), <i>n</i> = 156	26.9 (23.4–30.5), <i>n</i> = 81	29.06 (25.68–33.83), <i>n</i> = 69		
≥ 30 kg/m ²	33.3%, 52/156	28.4%, 23/81	39.1%, 27/69	1.62 (0.81–3.21); 0.16	1.27 (0.46–3.47); 0.63
Major comorbidities					
CCI median, (IQR)	3 (1–4)	2 (0–4)	3 (1–4)		
< 3	49.4%, 83/168	60.0%, 54/90	40.8%, 29/71	Reference group	
≥ 3	50.6%, 85/168	40.0%, 36/90	59.2%, 42/71	2.17 (1.15–4.09), 0.02	
Hypertension	53.6%, 90/168	42.2%, 38/90	63.4%, 45/71	2.37 (1.25–4.49); < 0.01	5.55 (2.00–16.82); < 0.01
Diabetes	19.6%, 33/168	13.3%, 12/90	23.9%, 17/71	2.05 (0.90–4.63); 0.08	1.5 (0.42–5.49); 0.53
Chronic pulmonary disease	16.7%, 28/168	13.3%, 12/90	21.1%, 15/71	1.74 (0.77–4.00); 0.19	
Chronic kidney disease	13.7%, 23/168	15.6%, 14/90	8.5%, 6/71	0.50 (0.18–1.38); 0.17	
Disorder of lipid metabolism	13.7%, 23/168	15.6%, 14/90	9.9%, 7/71	0.79 (0.30–2.10); 0.63	
Cardiac arrhythmia	13.7%, 23/168	13.3%, 12/90	12.7%, 9/71	0.94 (0.37–2.83); 0.90	
Chronic myocardial infarction	7.7%, 13/168	3.3%, 3/90	12.7%, 9/71	4.21 (1.09–16.18), 0.03	
Congestive heart failure	5.4%, 9/168	4.4%, 4/90	5.6%, 4/71	1.28 (0.30–5.32); 0.73	
Chronic neurological disease	9.5%, 16/168	6.7%, 6/90	9.9%, 7/71	1.81 (0.58–5.69); 0.31	
Total number of substances as concomitant medication, median (IQR), available <i>n</i>	2 (1–3) <i>n</i> = 143	2 (0–3) <i>n</i> = 89	2 (1–4) <i>n</i> = 54		
ARB	20.2%, 29/143	15.7%, 14/89	24.1%, 14/58	1.77 (0.77–4.09); 0.18	
ACE-i	18.9%, 27/143	13.5%, 12/89	19.0%, 11/58	1.53 (0.62–3.78); 0.35	
Lipid lowering agents	18.9%, 27/143	15.7%, 14/89	20.7%, 12/58	1.44 (0.61–3.42); 0.44	
Antibiotics last 90 days	20.2%, 29/143	19.1%, 17/89	20.7%, 12/58	1.09 (0.47–2.53); 0.83	
Number of symptoms median (IQR), available <i>n</i>	3 (2–4), <i>n</i> = 163	3 (2–5), <i>n</i> = 85	3 (2–4), <i>n</i> = 71		
Fever	63.8%, 104/163	69.4%, 59/85	63.4%, 45/71		
Dry cough	53.4%, 87/163	57.6%, 49/85	52.1%, 37/71		
Dyspnea	48.5%, 79/163	42.4%, 36/85	53.5%, 38/71		
Fatigue	27.6%, 45/163	29.4%, 25/85	25.4%, 18/71		

Table 1 (continued)

	All patients	Non-IMV	IMV	Unadjusted OR (95% CI); <i>p</i> value Chi-square test	Adjusted OR (95% CI); <i>p</i> value
Diarrhoea	12.9%, 21/163	17.7%, 15/85	8.5%, 6/71		
Vomitus	7.4%, 12/163	9.4%, 8/85	5.6%, 4/71		
Stomach pain	4.9%, 8/163	7.1%, 6/85	2.8%, 2/71		
Impaired consciousness	1.8%, 3/163	1.2%, 1/85	2.8%, 2/71		
Olfactory/gustatory dysfunction	2.5%, 4/163	2.4%, 2/85	2.8%, 2/71		
Indication for admission					
Primary COVID-19 diagnosis	65.5%, 110/168	87.8%, 79/90	39.4%, 28/71		
Referral from other hospitals	29.8%, 50/168	5.5%, 5/91	60.6%, 43/71		
a) ARDS	17.9%, 30/168		42.3%, 30/71		
b) Other critical medical condition	3.6%, 6/168	1.1%, 1/91	7.0%, 5/71		
c) Other reason for referral	8.3%, 14/168	4.4%, 4/91	11.3%, 8/71		
Other primary reason for admission	4.2%, 7/168	5.5%, 5/91	2.8%, 2/71		
Late admission	0.6%, 1/168	1.1%, 1/91	–		
Time between symptom onset and admission in days median (IQR), available <i>n</i>	6 (3–10), <i>n</i> = 131	8 (5–12) <i>n</i> = 72	5 (2–7) <i>n</i> = 55		1.22 (1.10–1.37)^a; < 0.01
≤ 5 days	41.2%, 54/131	27.8%, 20/72	56.4%, 31/55	3.36, (1.60–7.10), < 0.01	
> 5 days	58.8%, 77/131	72.2%, 52/72	43.6%, 24/55	Reference group	

Bold values indicate statistically significant difference between IMV and non-IMV patients

Patients with therapy limitations were excluded from comparison and statistical analysis of IMV versus non-IMV patients. Asymptomatic patients were excluded from analyses of symptom characterisation. Independent variables incorporated into the multiple logistic regression model: Age, BMI, hypertension, diabetes, and length between symptom onset and admission

IMV invasive mechanical ventilation, OR odds ratio, CI confidence interval, IQR interquartile range, BMI body mass index, CCI Charlson comorbidity index, ARB angiotensin II receptor blockers, ACE-i angiotensin-converting enzyme inhibitor, ARDS acute respiratory distress syndrome

^aInverse adjusted OR and confidence interval

intermittent invasive ventilation and six had DNI orders in place. Of the remaining 81 patients with ARDS, 87.6% (71/81) required IMV whereas 12.3% (10/81) could be managed with HFNC oxygen only (Fig. 1). Median time from hospital admission to intubation was 2 days (IQR 0–4). Among all patients without therapeutic limitations, 44.1% (71/161) required IMV, 9.9% (16/161) could be treated with HFNC oxygen only, 24.2% (39/161) required oxygen via nasal prongs, and 22% (35/161) were not in need of supplemental oxygen.

Age between 60 and 69 years as compared to 18 to 59 years (adjusted OR 4.33, 95% CI 1.07–20.10, *p* = 0.05) and pre-existing hypertension (adjusted OR 5.55, 95% CI

2.00–16.82, *p* < 0.01) were independent risk factors for IMV requirement in multivariable analysis. Requirement for IMV increased with shorter duration of symptoms before hospital admission (adjusted OR 1.22 per day less, 95% CI 1.10–1.37, *p* < 0.01, Table 1). To account for the possible impact of less accurate information on duration of symptoms in patients transferred from other hospitals, we performed a sensitivity analysis by excluding patients with > 1 day stay in an external hospital (*n* = 45). This analysis yielded a similar result of increased need of IMV with shorter duration of symptoms (adjusted OR 1.18 95% CI 1.04–1.35, *p* = 0.015).

Seventy-nine per cent (56/71) of all intubated patients required long IMV. Need for long IMV was associated

with a short (≤ 1 day) duration from admission until intubation (20.0% (3/15) of patients with short IMV vs 53.6% (30/56) patients with long IMV, unadjusted OR (uOR) 4.6, 95% CI 1.17–18.16, $p=0.02$). Other factors associated with long IMV were transferral from other centres (28.6% (4/14) of patients with short IMV were transferred vs 69.6% (39/56) of patients with long IMV, uOR 5.73, 95% CI: 1.58–20.87, $p < 0.01$), a higher total mean SOFA score during the second week after initial admission (8.4, 95% CI 5.83–10.9 in patients with short IMV vs 11.2, 95% CI 10.1–12.3, $p=0.04$ in patients with long IMV) as well as differences in SOFA score components (coagulation, hepatic impairment; for details see Supplementary Table 1).

IMV patients had a significantly higher risk of death from COVID-19 compared to non-IMV patients (1.1% (1/90) of non-IMV patients died vs 29.6% (21/71) of IMV patients, uOR 37.38, 95% CI 4.88–286.26, $p < 0.01$). Sixty-three per cent (44/70) of IMV patients underwent tracheotomy at a median time of 15 days (IQR 12–20) from intubation. Weaning from IMV was successfully concluded in 76.0% (38/50) of surviving IMV patients after a median of 42 days (IQR 16–66) from intubation. Eighteen per cent (9/50) of patients remained dependent on intermittent IMV and 6.0% (3/50) on long-term oxygen therapy (LTOT) upon discharge or transferral.

Thirty-one per cent (22/71) of all IMV patients required vvECMO (hereafter termed “ECMO”) treatment. ECMO was initiated a median of 9 days (IQR 5.3–18.5) from intubation and continued for a median of 18 days (IQR 7.8–35.5). All ECMO patients required haemodialysis, 86.4% (19/22) underwent tracheotomy, 50% (11/22) had a VTE, and 50% (11/22) died. Seventy-five per cent (53/71) of all patients with IMV and all (22/22) patients on ECMO received proning therapy. Details of the subgroup of patients receiving proning therapy have been reported elsewhere [25].

Haemodialysis was initiated in 30.4% (51/168) of patients, and in 66.2% (47/71) of patients with IMV. Haemodialysis was initiated after a median of 8 days (IQR 4.5–14 days) following hospital admission and 5 days (IQR 2–8.8 days) after intubation. Thirty-eight per cent (18/47) of IMV patients with haemodialysis died. For details on tracheotomy, ECMO and haemodialysis see Supplementary Table 2.

As no evidence of efficacy of antiviral and anti-inflammatory treatments was available at the time, these were not used systematically and only in a small subgroup of patients of this cohort. Seventeen per cent (29/168) of all patients received corticosteroids in ≥ 40 mg prednisolone equivalent for ≥ 1 day. For details see Supplementary Table 3.

Virological and routine laboratory data

Viral concentration data were available for 166/168 patients. On average, each patient had seven RT-PCR tests (SD: 5.3, min = 1, max = 29, including positive and negative result) from the day of symptom onset (or 10 days from first admission, if the date of symptom onset was not available) to the end of hospitalisation, with tests performed every 8.4 days on average (SD: 8.8). Eighty-six patients had two final negative RT-PCR tests at the end of the disease course. Median first-measured viral concentration differed by 0.68 \log_{10} viral copies between IMV and non-IMV patients (5.9, IQR 4.68–7.28 vs 5.22 \log_{10} viral copies, IQR 4.49–7.28, respectively; $p=0.12$, Fig. 2a), and median highest viral concentration by 1.19 \log_{10} viral copies (6.7, IQR 5.35–7.62 vs 5.51 \log_{10} viral copies, IQR 4.7–7.62, respectively; $p=0.02$, Fig. 2b). Decline of viral concentration (Supplementary Fig. 1) was significantly slower in IMV versus non-IMV patients (-0.13 , IQR -0.19 to -0.08 vs -0.22 \log_{10} viral concentration decrease / day, IQR -0.3 to -0.08 , respectively; $p < 0.01$) (Fig. 2c, Supplementary Fig. 2a–d). The duration of shedding was significantly longer in IMV patients than in non-IMV patients (median 33, IQR 26–46.75 vs 18 days, IQR 16–46.75, $p < 0.01$) (Fig. 2d). We found no association between viral concentration and the duration from symptom onset to admission and no difference in first or in highest viral concentrations in patients requiring long versus short IMV (Supplementary Fig. 3a–d, Supplementary Table 1).

A statistically significant difference between non-IMV and IMV patients was observed in the levels of C-reactive protein (CRP), procalcitonin (PCT), Interleukin-6 (IL-6), lactate dehydrogenase, ferritin, leukocyte count, lymphocyte count, neutrophil-to-lymphocyte ratio, creatinine, urea, aspartate aminotransferase, creatine kinase, N-terminal pro-hormone of brain natriuretic peptide, and troponin (Supplementary Table 4). The course of 12 routine laboratory parameters over time in non-IMV and IMV patients is shown in Fig. 3.

Complications during treatment

Eighteen per cent (31/168) of patients developed sepsis. Occurrence of sepsis was associated with organ replacement therapies, but not with patient-related risk factors (Supplementary Table 5). The first sepsis episode occurred after a median of 16 days (IQR 8–21) from hospital admission and 11.5 days (IQR 3–18.3 days) from intubation. In 15/31 (48.4%) of patients with sepsis, ECMO was initiated during or soon after occurrence of sepsis (median time from occurrence of sepsis and initiation of ECMO, 0 days, IQR 0–6.25 days).

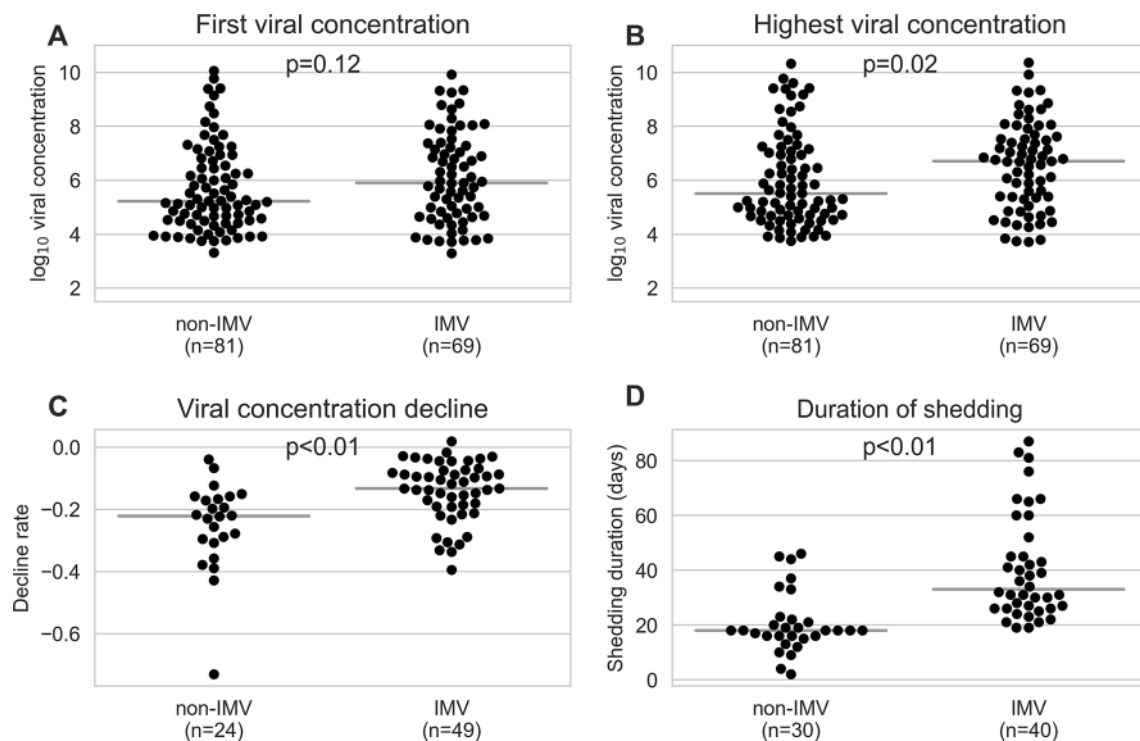


Fig. 2 Comparison of viral concentration between patients with invasive mechanical ventilation (IMV) and those without IMV (non-IMV). **a** First-measured viral concentration: Median \log_{10} viral concentration and (IQR) are 5.9 (4.68–7.28) for IMV patients and 5.22 (4.49–7.28) for non-IMV patients. **b** Highest viral concentration: Median \log_{10} viral concentrations and (IQR) are 6.7 (5.35–7.62) for IMV patients and 5.51 (4.7–7.62) for non-IMV patients. **c** Differences in the slopes of \log_{10} viral concentration decline rates were estimated using a linear regression of viral concentration from the full disease

course of a patient and days since symptom onset ($n=63$) or admission ($n=10$) for patients with and without IMV. Only patients with at least four viral concentration measurements were included. **d** Duration from symptom onset to the first of at least two final negative RT-PCR results for ventilated and non-ventilated patients. Median 33 days (IQR: 26–46.75) for IMV vs 18 days (IQR: 16–46.75) for non-IMV patients, $p<0.01$. Pairwise comparisons were performed using a Mann–Whitney U test. Grey horizontal lines indicate the median

Nineteen per cent (32/168) of patients were diagnosed with at least one VTE. Due to evidence for increased risk of thromboembolic events in COVID-19 (36), therapeutic or semitherapeutic anticoagulation was introduced in all critically ill patients from April 2020. A quarter of VTEs (8/32) occurred without anticoagulatory treatment, 18.8% (6/32) under prophylactic anticoagulation, and 46% (15/32) under therapeutic anticoagulation. In 9.3% (3/32) of patients, VTE was diagnosed at autopsy and anticoagulation status at onset was unclear.

Twenty-four per cent of patients (41/168) had at least one neurologic event during hospitalisation, including haemorrhagic stroke (9/41, 22%), ischaemic stroke (3/41, 7.3%), delirium (17/41, 41.5%), ICUAW (17/41, 41.5%), and epileptic seizure (3/41, 7.3%). Details of sepsis episodes, VTE and neurologic events are shown in Supplementary table 5.

Outcome

Median time of hospital stay was 14 days (IQR 7–35) for all, 9 days (IQR 6–15.5) for non-IMV, and 49.5 days (IQR 36.8–82.5) for IMV patients.

Seventeen per cent (29/168) of all patients died. Of all patients without therapy limitations (DNR/DNI), 13.6% (22/161) died, 8.7% (14/161) were transferred to other centres, and 77.6% (125/161) were discharged. Median time from first hospitalisation until death was 33 days (IQR 16–98).

In univariate analyses, $\text{CCI} \geq 3$ (uOR 4.35, 95% CI 1.52–12.45, $p<0.01$), short duration of symptoms (uOR 6.08, 95% CI 1.88–19.68, $p<0.01$), occurrence of sepsis (uOR 16.47, 95% CI 5.85–46.5, $p<0.01$), occurrence of VTE (uOR 7.58, 95% CI 2.88–19.97, $p<0.01$) and higher SOFA score during 1st and 2nd week after intubation were associated with death. There was a difference in the median first and highest viral concentration between survivors and non-survivors (6.84, IQR 4.99–7.91 vs 5.38, IQR 4.54–7.91, $p=0.05$; and 7.14, IQR 5.39–7.91 vs 5.86,

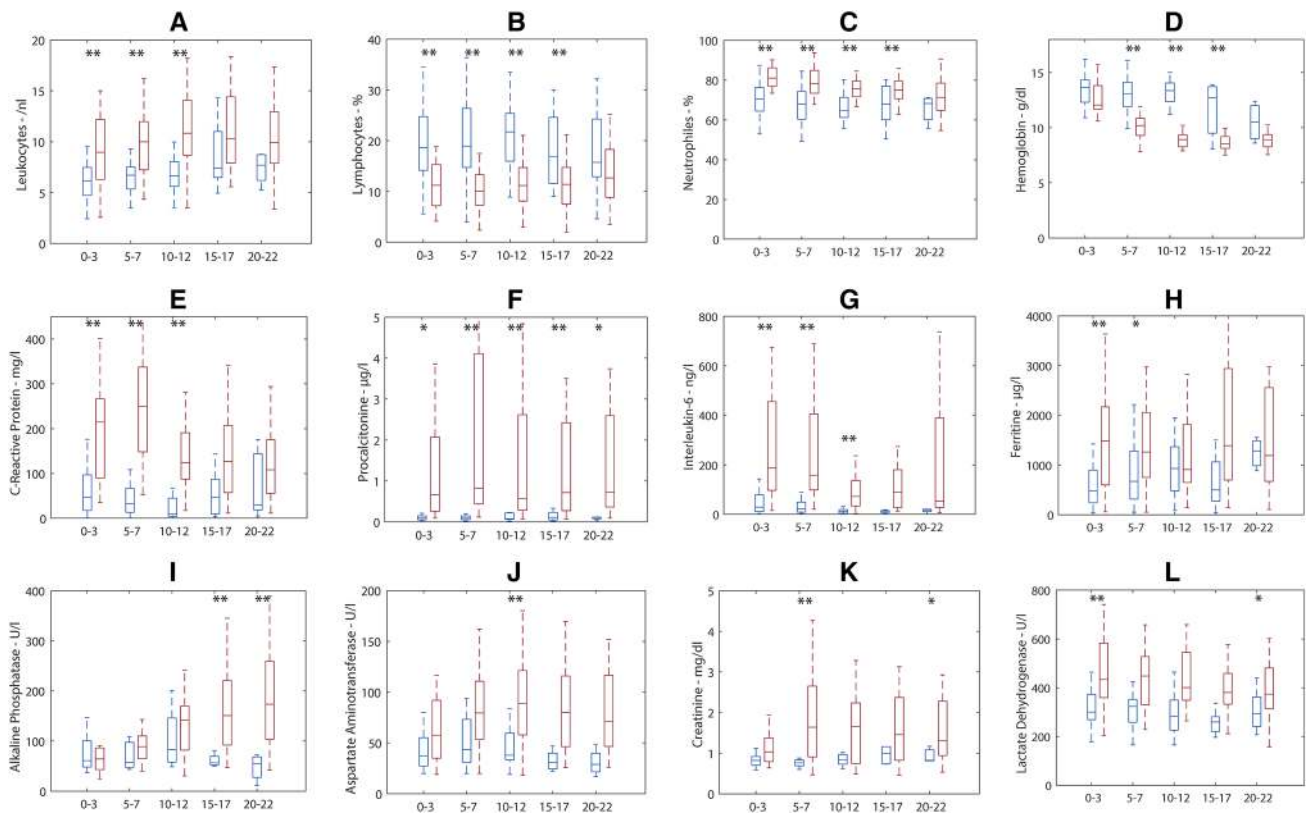


Fig. 3 a–l Comparison of laboratory parameters during the course of disease in IMV (red) versus non-IMV patients (blue). X-axis: days post-admission. The boxes and lines are median 25th and 75th per-

centiles, Whiskers indicate the 1st and 99th percentile. A Welch's *t* test was used: * $p < 0.05$, ** $p < 0.01$

IQR 4.77–7.91, $p = 0.04$, respectively) (Supplementary Table 6).

Of all discharged or transferred patients, 6.5% (9/139) still required IMV, 2.9% (4/139) LTOT, and 1.4% (2/139) new haemodialysis.

Discussion

We analysed a detailed clinical and virological dataset from a prospective observational cohort of COVID-19 patients hospitalised in a tertiary, ECMO/ARDS referral and weaning centre in Germany during the first wave of the SARS-CoV-2 pandemic, before dexamethasone became standard of care.

We report a short duration of symptoms before clinical deterioration as a risk factor for severe COVID-19. Second, our results indicate that severely ill patients have higher maximal viral concentrations and a slower decline of viral concentration compared to mildly affected patients. Third, we describe a comparatively long duration of inpatient treatment for patients with IMV, largely exceeding that described for non-COVID-19 ARDS patients.

Rapid clinical deterioration—as reflected by short duration of symptoms before hospital admission—is a highly relevant risk factor for both need of IMV in a multivariable risk model and death in univariate analyses in our cohort. A shorter duration of symptoms was not associated with higher initial viral concentration. There was also no difference in initial viral concentration in more severely ill patients, i.e., those requiring IMV, compared to mildly ill patients. Yet, we found a significant increase of inflammatory markers such as CRP, PCT, and IL-6 at presentation and over time in IMV compared to non-IMV patients. Moreover, IMV patients had higher maximal concentrations, a slower decline as well as longer duration of shedding of SARS-CoV-2 compared to non-IMV patients. Higher maximal viral concentrations were also found in patients who died, compared to survivors.

These findings underline that the early inflammatory host response to SARS-CoV-2 determines the course of disease more than pathogen factors such as initial SARS-CoV-2 RNA concentration [2, 28, 29]. A short duration of symptoms before admission possibly reflects a rapid increase of the level of inflammation and might serve as an easy to assess prognostic factor for clinical deterioration, a finding that merits further exploration [30]. During the

further course of COVID-19, severe disease is characterised by the inability to rapidly reduce viral particles. A possible explanation for this phenotype—rapid deterioration after symptom onset, high inflammatory markers, and lack of efficient clearing of viral particles—might be the various kinds of immune dysregulation, as reported by our group and others [15, 31]. Conflicting results have been published regarding the association between clinical severity and viral concentration for SARS-CoV-2 so far [32–36]. This could possibly be explained by a rather unbalanced proportion of mildly and severely affected patients in the respective studies as compared to our cohort [35]. However, it is undetermined whether higher maximal viral concentration and longer duration of shedding are a possible cause or an indicator of more severe organ damage and disease.

Although a remarkable proportion (29.8%) of patients was transferred to our center due to severe ARDS, and overall 44.1% needed IMV, we report a comparatively low in-hospital mortality of 13.6% in patients without limitations of therapy. In comparison, Karagiannadis et al. reported in-hospital mortality of 22.2% [1] and Rieg et al. of 23.9% [37] in cohorts from Germany with 17.2% [1] and 32.9% [37] ventilated patients, respectively. Of note, our data show a high median length of hospital stay of 49.5 days for patients requiring IMV. By comparison, the median length of hospital stay for non-COVID ARDS patients was 17 days in a recent global multi-centre prospective study [38]. There is growing evidence that the length of IMV-, ICU-, and inpatient treatment of patients with COVID-19 ARDS exceeds that of patients with ARDS unrelated to COVID-19 [30, 37]. Despite the long median duration of hospital stay, a considerable percentage of patients could not successfully be weaned off the ventilator (18%), and 6% required ongoing oxygen therapy following discharge. The mere number of deceased patients therefore depicts the burden of disease of COVID-19 only very incompletely, particularly with respect to long-term morbidity. The prospective approach of our study will allow us to evaluate long-term complications in the aftermath of COVID-19.

Prospective observational studies are often hampered by selection of patients with relatively mild disease courses due to need for informed consent. The high proportion of severely affected patients in this study cohort indicates that this specific selection bias does not apply to our data. On the contrary, it is rather the selection of severely ill patients referred for ARDS management that might have led to a bias. On the other hand, one-fifth of patients was only mildly affected and did not require oxygen therapy, representing a sub-cohort admitted for clinical observation or due to lacking the possibility of self-isolation. Other major limitations of our work are its monocentricity and small sample size.

Our data give a comprehensive description of the clinical course, virological characteristics, organ support treatment, complications, and outcome of a representative cohort of patients in an unrestricted tertiary care healthcare setting with comparatively low mortality. The reported findings will be of value for comparison of clinical courses in the dexamethasone era and for sample size calculation for interventional studies in similar settings.

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Declarations

Conflict of interest statement Charlotte Thibeault, Barbara Mühlemann, Elisa T. Helbig, Mirja Mittermaier, Tilman Lingscheid, Pinkus Tober-Lau, Lil A. Meyer-Arndt, Leonie Meiners, Sascha S. Haenel, Laure Bosquillon de Jarcy, Lena Lippert, Moritz Pfeiffer, Miriam S. Stegemann, Robert Roehle, Janine Wiebach, Stefan Hippenstiel, Thomas Zoller, Holger Müller-Redetzky, Alexander Uhrig, Christof von Kalle, Norbert Suttorp, Terry C. Jones, Christian Drosten, Leif E. Sander, Victor M. Corman und Florian Kurth have no conflicts of interest to declare. CT reports grants within the frame of the academic program “clinical studies in infectiology” funded by the German Research Foundation (DFG), outside of the submitted work. MM reports grants from the BIH-Charité Digital Clinician Scientist Program funded by the Charité – Universitätsmedizin Berlin, the Berlin Institute of Health (BIH), and the German Research Foundation (DFG), outside the submitted work. FB reports grants from Einstein Foundation, personal fees from Axon Publishing, grants from Vifor Pharma, personal fees from Elsevier Publishing, grants from Federal Ministry of Health, grants from Berlin Institute of Health, grants from Federal Ministry of Education and Research, outside the submitted work. TCJ is in part funded through NIAID-NIH CEIRS contract HHSN272201400008C. MW reports grants from Deutsche Forschungsgemeinschaft, grants from Bundesministerium für Bildung und Forschung, grants from Deutsche Gesellschaft für Pneumologie, grants from European Respiratory Society, grants from Marie Curie Foundation, grants from Else Kröner Fresenius Stiftung, grants from Capnetz Stiftung, International Max Planck Research School, grants and personal fees from Actelion, grants and personal fees from Bayer Health Care, grants and personal fees from Biotest, grants and personal fees from Boehringer Ingelheim, grants and personal fees from Noxxon, grants and personal fees from Panthera, grants from Quark Pharma, grants and personal fees from Silence Therapeutics, grants from Takeda Pharma, grants and personal fees from Vaxxilon, personal fees from Aptarion, personal fees from Astra Zeneca, personal fees from Berlin Chemie, personal fees from Chiesi, personal fees from Glaxo Smith Kline, personal fees from Novartis, personal fees from Sinoxa, personal fees from Teva, outside the submitted work.

Ethics approval Approval was obtained from the ethics committee of Charité Universitätsmedizin Berlin. The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

Consent to participate Informed consent was obtained from all individual participants or legal representatives included in the study.


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