Rapid clinical evolution for COVID-19 translates into early hospital admission and unfavourable outcome: a preliminary report

Markus Heim,1 Tobias Lahmer,2 Sebastian Rasch,2 Silja Kriescher,1 Wiebke Berg-Johnson,1 Kristina Fuest,1 Barbara Kapfer,1 Gerhard Schneider,1 Christoph D. Spinner,2,3 Fabian Geisler,2 Johannes R. Wiedner,2 Kathrin Rothe,4 Susanne Feihl,1 Andreas Ranft1

1Department of Anaesthesiology and Intensive Care Medicine, University hospital rechts der Isar, Technical University of Munich, School of Medicine, Munich
2Department of Internal Medicine II, University hospital rechts der Isar, Technical University of Munich, School of Medicine, Munich
3German Centre for Infection Research (DZIF), Partner Site Munich, Munich
4Institute for Medical Microbiology, Immunology and Hygiene, Technical University of Munich, School of Medicine, Munich, Germany

Background: A wide range of mortality rates has been reported in COVID-19 patients on the intensive care unit. We wanted to describe the clinical course and determine the mortality rate in our institution’s intensive care units.

Methods: To this end, we performed a retrospective cohort study of 50 COVID-19 patients admitted to the ICU at a large German tertiary university hospital. Clinical features are reported with a focus on ICU interventions, such as mechanical ventilation, prone positioning and extracorporeal organ support. Outcome is presented using a 7-point ordinal scale on day 28 and following ICU admission.

Results: The median age was 64 years, 78% were male. LDH and D-Dimers were elevated, and patients were low on Vitamin D. ARDS incidence was 75%, and 43/50 patients needed invasive ventilation. 22/50 patients intermittently needed prone positioning, and 7/50 required ECMO. The interval from onset of the first symptoms to admission to the hospital and to the ICU was shorter in non-survivors than in survivors. By day 60 after ICU admission, 52% of the patients had been discharged. 60-day mortality rate was 32%; 37% for ventilated patients, and 42% for those requiring both: ventilation and renal replacement therapy.

Conclusions: Early deterioration might be seen as a warning signal for unfavourable outcome. Lung-protective ventilation including prone positioning remain the mainstay of the treatment.

Key words: COVID-19; SARS-CoV-2; critical care; mortality; acute respiratory distress syndrome; prone position; invasive ventilation; retrospective cohort study.
Introduction

The coronavirus disease 2019 (COVID-19) outbreak, with its beginning in Wuhan in December 2019, led into a pandemic. While most patients develop mild or uncomplicated illness, other require hospitalisation, and of these about 15% need treatment on an intensive care unit (ICU) [1]. Complications such as acute respiratory distress syndrome (ARDS), sepsis, and multiorgan failure can occur [1-3]. With continuously growing knowledge about the pathogen, its transmission and the manifestations of this new disease, widely varying mortality rates have been reported. Reported clinical data are heterogeneous with respect to the number of patients treated and also the censoring day to determine outcome. For instance, in a cohort of 42 patients on a single ICU in Wuhan, the 28-day mortality rate was 62%, and up to 74% if ARDS was present [4]. Early reports from smaller cohorts in Seattle (WA, USA) showed ICU mortality rates between 50% (12 of 24 patients) and 67% (14 of 21 patients) rising up to 75% in patients on invasive ventilation [5,6]. These mortality rates for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) induced ARDS are significantly higher than those in the ‘LUNG SAFE’ study from the pre COVID-19 era, which presented hospital mortality rates between 35% and 46% depending on the severity of ARDS [7]. In contrast, an in-hospital mortality of 36% (59 of 165 patients) was reported from Atlanta (GA, USA) [8]. It is widely acknowledged that mortality in critically ill patients is associated with the severity of illness on arrival to the ICU and the need for interventions such as mechanical ventilation, renal replacement therapy and vasopressor support [9,10]. Likewise, older age and the presence of comorbidities worsen outcome [4,11,12]. In COVID-19 patients, the presence of chronic lung diseases like asthma or chronic obstructive pulmonary disease (COPD), as well as obesity and persisting elevation of infection parameters are associated with an increased likelihood to develop ARDS [3].

The aim of our study was to characterise the COVID-19 ICU patients treated in our university hospital, to describe the interventions and the outcomes, and to identify differences between patients that had survived and those who had died day 60 after ICU admission.

Methods

We performed a retrospective single-centre cohort study of 50 adult patients with confirmed COVID-19 during the first pandemic wave, admitted to the ICU between 11 March and 24 April 2020. Patients were treated on two different intensive care units in a university hospital with 1,163 beds, one affiliated to the department of internal medicine II and one to the department of anaesthesiology and intensive care medicine.

The Ethics Committee of the Technical University of Munich approved this retrospective study (approval no. 723/20 S-SR).

Medical records including clinical charts and nursing records were reviewed. Data collection included patient biometrics, comorbidities, clinical parameters, laboratory findings, information on inpatient management, ICU interventions, as well as ICU and hospital stay. On day 28 and day 60 from ICU admission, outcome was measured with a 7-point ordinal scale from category 1 (not hospitalized with no limitations on activities) to category 7 (dead) as used before [13].

Laboratory confirmation of SARS-CoV-2 was achieved by polymerase chain reaction (PCR) of respiratory swabs or combination of IgG/IgM-seropositivity and COVID-19 symptoms. Details to the PCR and serological testing methods are published elsewhere [14]. Additionally, a chest computed tomography (CT) scan was performed for nearly all patients (48/50) to identify typical CT findings for COVID-19 [15,16]. Patients with positive PCR or positive IgM/IgG serology results were defined as definite COVID-19 cases. Patients with suspected disease in whom diagnosis could not be confirmed were excluded from the analysis.

Continuous data are described by median (interquartile range from quartile 25% to quartile 75%), and categorical data by absolute and relative frequencies. Data were analysed using a chi-square or Wilcoxon rank-sum test for categorical and continuous variables, respectively, with a two-sided p-value of less than 0.05 considered statistically significant. Due to the exploratory nature of the study, uncorrected p-values are reported. Statistical analyses were performed using Microsoft Excel 2013 and IBM SPSS Statistics ver. 25.0 (IBM Corp, Armonk, NY). The complete anonymised set of individual patient data is available from the authors upon request.

Medical records

In March and April 2020, 50 adult patients with a confirmed diagnosis of COVID-19 were admitted to ICU in our university hospital. Comprehensive datasets containing clinical and laboratory parameters were compiled from these cases. Thirty-three patients (66%) had initially been treated on the normal ward before transfer to the ICU, 17 patients (34%) were assigned directly to the ICU via the emergency department. At the time of symptom onset, 6 patients (12%) were in hospital for a diagnosis other than COVID-19. Oxygen therapy was started when SpO2 dropped below 94%. All COVID-19 patients received respiratory therapy by a physiotherapist at least once daily. According to our standard operating procedure for COVID-19 patients, the need for intensive care was discussed when the respiratory rate rose above 30 per min and SpO2 fell below 90% at an oxygen flow rate of 8 L/min by face mask. An overview of the variables not presented in Tables 1 and 2 can be found the Tables S1 to S4 in the Supplementary Material. Presence of SARS CoV-2 was proven by PCR in 47 cases. In 42 out of 44 cases, serologic testing (IgG and IgM) indicated SARS-CoV-2 infection, including all three cases with negative PCR. Imaging findings were consistent with COVID-19 in all patients receiving a chest-CT scan (n=48).

Patient characteristics

The median age in the whole cohort was 64 (range, 26-96) years. Seventy-eight percent (39/50) of patients were male. In ten patients (20%), no prior comorbidity was documented. At least one underlying comorbidity was present in 38/50 patients (76%), with arterial hypertension being the most frequent (in 56%). Three or more comorbidities were present in 36% of all patients (supplementary Table S1). The distribution of blood groups in the ABO system was similar between survivors and non-survivors, with comparable proportions of group O.

After a median of four days (1-7) after onset of symptoms, patients were admitted to hospital, and one day (0-3) later, transferred to ICU. On admission to the ICU, sepsis-related organ failure assessment score (SOFA) score was six (3-10) and acute physiology and chronic health evaluation score (APACHE) was 18 (14-26). The majority of patients (92%) was lymphopenic, and all showed elevated LDH and D-dimers. Median concentration of vitamin D (25-OH-vitamin D3) was 14 ng/mL; more than three quarters of our patients were low on vitamin D (30 ng/mL), and 43% presented a manifest deficiency (threshold, 12 ng/mL). Hypalbuminaemia (33 g/dL) was found in 70%, with a median of 3.0 g/dL. Leucocytes, PCT and interleukin-6 did not show a
In our hospital, lopinavir/ritonavir, chloroquine or hydroxychloroquine (other glucocorticoid) were not administered routinely, as no generation of remdesivir within clinical studies or early access programs, and six patients died in this period. The SOFA score was 10 (10-11). Nine days (6-11) on invasive ventilation, seven patients underwent treatment (high flow nasal oxygen, HFNO) was used in four cases but could not obviate the need for subsequent endotracheal intubation. 43 (86%) of the patients received invasive ventilation. In prone position, oxygenation improved significantly (prone -1 to -2, n=20), and in prone position (prone, n=20, median, lower/upper quartile, and 1.5 times interquartile range. In prone position, oxygenation improved significantly (prone -1 to -2, n=20), and in prone position (prone, n=20, median, lower/upper quartile, and 1.5 times interquartile range. During hospital stay, nine patients of our ICU cohort received remdesivir within clinical studies or early access programs, and six patients received convalescent plasma. Dexamethasone (or any other glucocorticoid) were not administered routinely, as no general recommendation was available at the time of the study period. In our hospital, lopinavir/ritonavir, chloroquine or hydroxychloroquine (other glucocorticoid) were not administered routinely, as no general recommendation was available at the time of the study period. In our hospital, lopinavir/ritonavir, chloroquine or hydroxychloroquine (other glucocorticoid) were not administered routinely, as no general recommendation was available at the time of the study period. In our hospital, lopinavir/ritonavir, chloroquine or hydroxychloroquine (other glucocorticoid) were not administered routinely, as no general recommendation was available at the time of the study period. 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quine were used for potential treatment of COVID-19. 84% of all patients needed vasopressor support. 20 patients (40%) underwent renal replacement therapy (Supplementary Table S4). As described recently, severe bacterial and fungal co-infections were rare in our cohort [14]. During their hospital stay, 48 patients (96%) were treated with antibiotics. Bloodstream infections on the day of admission were rare and could be detected in a total of 14 patients (28%) during the course of intensive care therapy. For prevention of thromboembolism, all patients received low-molecular-weight heparins in double prophylactic dosage, with the exception of patients for whom therapeutic anticoagulation was indicated (e.g., due to ECMO therapy).

Results

Median length of stay on the ICU was 17 days (9-38). Ventilated patients spent 19 days (11-42) on the ICU with an average time on the ventilator of 18 days (6-11). Among the 31 patients that could be discharged from the ICU, 22 were transferred to a regular ward, 4 were transferred to another ICU or a weaning facility, 4 to rehabilitation centre, and 1 patient could return home. On day 60, 52% of our patients (n=26) had been discharged home, and 38% of them (n=10, a fifth of the whole cohort) reported no limitations on activities. Four (8%) patients were still on ICU on day 60, one of them still being on ECMO. Sixty-day mortality rate was 32% for all patients, 37% for the patients on ventilator and 42% for patients requiring both mechanical ventilation and renal replacement therapy. Four of seven patients treated with ECMO died, three of them due to fatal intracerebral haemorrhage. One patient was still on ECMO on day 60 (Table 2).

Factors associated with adverse outcome in COVID-19 have repeatedly been described, among them, age, obesity and comorbidities [18,19]. For further exploratory analysis, we divided our cohort into two subgroups: Patients who survived (n=34) or died (n=16) up to day 60 after ICU admission. Between these groups, age, body mass index and number of comorbidities did not differ significantly. A large proportion of survivors (76%) and all (100%) non-survivors needed vasopressor support (p=0.04). Patients not surviving to day 60 after ICU admission received dialysis more frequently (50% vs 35%), although this was not statistically significant. Counted from the first onset of symptoms, non-survivors were admitted earlier than survivors – both to hospital and to ICU (Figure 2 A,B and Supplementary Table S3), and this difference was statistically significant (hospital admission: 1.5 vs 4.5 days, p<0.01, ICU admission: 4 vs 8 days, p<0.01). The in-house interval ‘from door to ICU’ however, did not differ. None of the laboratory results on day of admission to the ICU was associated with survival (Table 1) and also disease severity scores (APACHE and SOFA, Figure 2 C,D) were similar between groups. Taken together, early disease progression (expressed as time interval from symptom onset to hospital admission) was found to be more rapid in patients who did not survive 60 days. *Vice versa,* a lower prob-

**Figure 2.** Delay of admission (days after onset of symptoms) and severity of illness on first day in ICU. Patients who died until day 60 were admitted earlier (A) to Hospital (p=0.0018), and (B) to ICU (p=0.0037, both Mann Whitney U test) compared to those who survived day 60. Days are counted from ICU admission. (C) APACHE and (D) SOFA scores did not differ significantly (Mann Whitney U test). Box and whiskers as explained in Figure 1.
ability of survival was also shown when the total cohort was divided into patients admitted to hospital within 2 days of symptom onset or later (Figure 3).

Discussion

In our first 50 COVID-19 patients treated on the ICU, we initially focused on the extent of lung damage in comparison with other cohorts. In a retrospective study on 10,021 hospitalized COVID-19 patients in 920 German hospitals, 17% received mechanical ventilation [20]. Although this proportion of 17% not necessarily equals the prevalence of ARDS (which was not reported), it is far below ARDS prevalence of about 33% in 2,486 hospitalized COVID-19 patients in five countries. In this cohort, 63% of patients needed mechanical ventilation, and ARDS prevalence was 75% [21]. In our ICU patients, a proportion of 78% fulfilled the diagnostic criteria for ARDS. Among those who were mechanically ventilated, ARDS prevalence exceeded 90% and remained on this level in a second assessment the subsequent day. Although being profoundly hypoxaemic, our patients showed comparatively well-preserved lung mechanics, which is rarely seen in patients with ‘typical’ ARDS. The combination of a large shunt fraction and a rather good lung compliance suggests a novel pathophysiology, thus leading to the hypothesis of gasless tissue being hyperperfused. Accordingly, an increase in oxygenation achieved by PEEP or prone positioning might not primarily result from recruitment but rather from gravity and/or pressure forces [22]. Proning or prone positioning might not primarily result from recruitment but rather from gravity and/or pressure forces [22]. Proning

"Figure 3. Kaplan Meier estimates of survival (A) in the whole cohort and (B) in the subgroups of patients admitted to hospital within 2 days or later after onset of symptoms. The two survival curves differ significantly (Log-rank test, p=0.0003)."
Against the backdrop of the German retrospective mega study which offered data on the course of the disease [20], our group of patients showed a comparatively good outcome. Clearly, the time from onset of symptoms to admission to the hospital or to the ICU was significantly lower in the group of non-survivors. It might therefore be concluded that early deterioration of symptoms predicts an unfavourable course of the disease.

Vitamin D values were generally low in our patient cohort. It is still not known whether this is a relevant prognostic factor. It is also unknown whether a substitution (of calcifediol or cholecalciferol) can play a role in treatment of COVID-19 or whether a prophylactic substitution might be warranted. Inverse correlations between vitamin D status and COVID-19 incidence and mortality have been reported in Europe [30,31]. Higher levels of circulating vitamin D have been associated with lower SARS-CoV-2 positivity rates [32]. As vitamin D has pleiotropic actions on the immune system, the supplementation might help to protect against an infection with SARS-CoV-2. In a pilot study, administration of a high-dose calcifediol reduced the need for ICU treatment in patients with COVID-19 [33].

The limitations of our study are the retrospective design, the single centre character and the small sample size. The lack of standardised pharmacological treatment also may be an important parameter influencing the outcome.Ordinal scoring of outcome on a 7-point scale might be seen as an improperly simplistic assessment of patients with COVID-19. However, we captured data from all of our first 50 patients, including the outcome score for each of them on day 60 after ICU admission. We feel our data can illustrate the potential harm for COVID-19 patients at any age group, as well as the potential for recovery even for the most severely affected patient group with the need for ventilator and renal replacement therapy.

Conclusions

Rapid deterioration after onset of symptoms can be seen as an early warning signal for a further unfavourable course of disease and, ultimately, a poor outcome in COVID-19. The consistently low vitamin D concentration gives reason to take a closer look at the role of vitamin D in COVID-19 patients. As long as there is no specific drug that mitigates the course of COVID-19, lung-protective ventilator therapy including prone positioning remain mainstay of the treatment.

Abbreviations

COVID-19, coronavirus disease 2019; ICU, intensive care unit; ARDS, acute respiratory distress syndrome; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COPD, chronic obstructive pulmonary disease; PCR, polymerase chain reaction; CT, chest computed tomography; SOFA, sepsis-related organ failure assessment score; APACHE, acute physiology and chronic health evaluation score; ECMO, extracorporeal membrane oxygenation; NIV, non-invasive ventilation; HFNO, high flow nasal oxygen; HI, Horovitz index; PEEP, positive end expiratory pressure.

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