

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

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ABSTRACT

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 60 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.

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

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 52 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 until 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 in 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 42% presented a manifest deficiency (threshold, 12 ng/mL). Hypalbuminaemia (€3.5 g/dL) was found in 70%, with a median of 3.0 g/dL. Leukocytes, PCT and interleukin-6 did not show a

Table 1. Demographic characteristics and laboratory findings on ICU admission.

Characteristics, median (IQR)	All (n=50)	Survivors* (n=34)	Non-survivors* (n=16)	p°
Age 64 (53–77)	59.5 (53–75)	71 (54–81)	0.174	
Male sex, n (%)	39 (78)	26 (76)	13 (81)	1.0
SOFA	6 (3–10)	6 (3–10)	7 (4.5–10.5)	0.5552
Apache II	18 (14–25.5)	17 (14–23)	21 (14.5–34.5)	0.215
Comorbidities				
None, n (%)	10 (20)	8 (23.5)	2 (12.5)	0.4684
Any, n (%)	38 (76)	25 (73.5)	13 (81.3)	0.7278
≥3, n (%)	18 (36)	13 (38.2)	5 (31.3)	0.7568
Laboratory findings on ICU admission				
Leucocytes (G/L)	7.93 (5.9–10.9)	7.92 (6.02–10.77)	8.79 (4.97–11.61)	0.6527
Lymphocytes (% of Leucs)	9 (5–13)	9 (7–12)	8 (4–14.5)	0.984
CRP (mg/dL)	13.65 (8.6–20.6)	15.1 (10.4–21)	10.3 (7.3–17.8)	0.7114
Il6 (pg/mL)	135 (89–195)	135 (85–193)	133 (118–193)	0.3125
PCT (ng/mL)	0.3 (0.1–0.9)	0.3 (0.2–1.4)	0.3 (0.1–0.8)	0.5093
D-Dimer (µg/L FEU)	1983 (982–6614)	2023.5 (983–6578)	1983 (1093–6640)	0.9442
LDH (U/L)	468 (340–592)	468 (355–573)	471 (319–713.75)	0.8026
Albumin (g/dL)	3 (2.6–3.5)	3 (2.7–3.5)	3.1 (2.6–3.8)	0.5029
25-OH-Vitamin D ₃ (ng/mL)	14 (8.5–26.5)	14 (8–27)	13 (10.25–19.5)	0.7642

*Until outcome day 60 from ICU admission; °Chi Square or Wilcoxon rank-sum test comparing those who survived vs died up to day 60 from ICU admission.

notable elevation. For four selected timepoints during the ICU stay (on day of admission, intubation, first proning and extracorporeal membrane oxygenation (ECMO) initiation), no significant changes in the laboratory parameters (leukocytes, CRP, Il6, PCT, LDH and D-dimer) could be detected. Median time to first negative PCR was 16 days (10–22). Patient characteristics and initial laboratory data are shown in Table 1 and supplementary Table S1, course of laboratory data are shown in Supplementary Table S2.

Treatment and course of disease

Non-invasive ventilation (NIV) or high flow nasal oxygen therapy (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 more than 90%, the Berlin criteria for diagnosis of ARDS were met on day of intubation, with 65% (n=28) categorized as moderate or severe with a median Horovitz index (HI) of 160 mmHg (113–216) [17]. On the day after intubation, there was no relevant change in severity of ARDS. After intubation, the median peak airway pressure was 25 mbar, with a median positive endexpiratory pressure (PEEP) of 10 mbar which was largely maintained on this level until the next day. Half of the ventilated patients (n=22) needed prone positioning at a median HI of 87 mmHg (72–107). During the first proning period (approximately 16 hours) the achieved average HI was 135 mmHg (115–155), a clinically relevant and statistically significant increase (p<0.01) (Figure 1). After a median of nine days (6–11) on invasive ventilation, seven patients underwent veno-venous ECMO. On day of ECMO initiation, the median SOFA score was 10 (10–11).

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 hydroxychloro-

Table 2. Outcome on day 28 and 60 after ICU admission.

Scale value	Description	Day 28 n (%)	Day 60 n (%)
1	Not hospitalized, no limitation on activities	6 (12)	10 (20)
2	Not hospitalized, limitation on activities	11 (22)	16 (32)
3	Hospitalized, not requiring supplemental oxygen	3 (6)	1 (2)
4	Hospitalized, requiring supplemental oxygen	3 (6)	3 (6)
5	Hospitalized, on non-invasive ventilation or high flow	2 (4)	0 (0)
6	Hospitalized, on invasive ventilation or ECMO	14 (28)	4 (8)
7	Dead	11 (22)	16 (32)

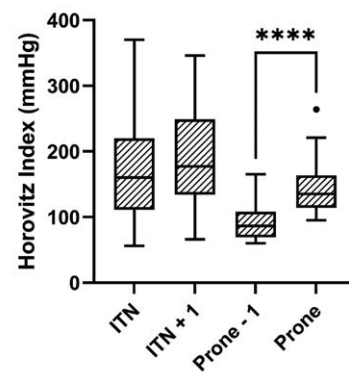


Figure 1. Oxygenation (expressed as Horovitz Index) on day of intubation ('ITN', n=43), one day later ('ITN +1', n=39), before proning (prone -1, n=20), and in prone position (prone, n=20, average of repeated measurements). In prone position, oxygenation improved significantly (prone -1 vs prone, p<0.0001, Wilcoxon matched-pairs signed rank test). Box and whiskers are median, lower/upper quartile, and 1.5 times interquartile range.

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-

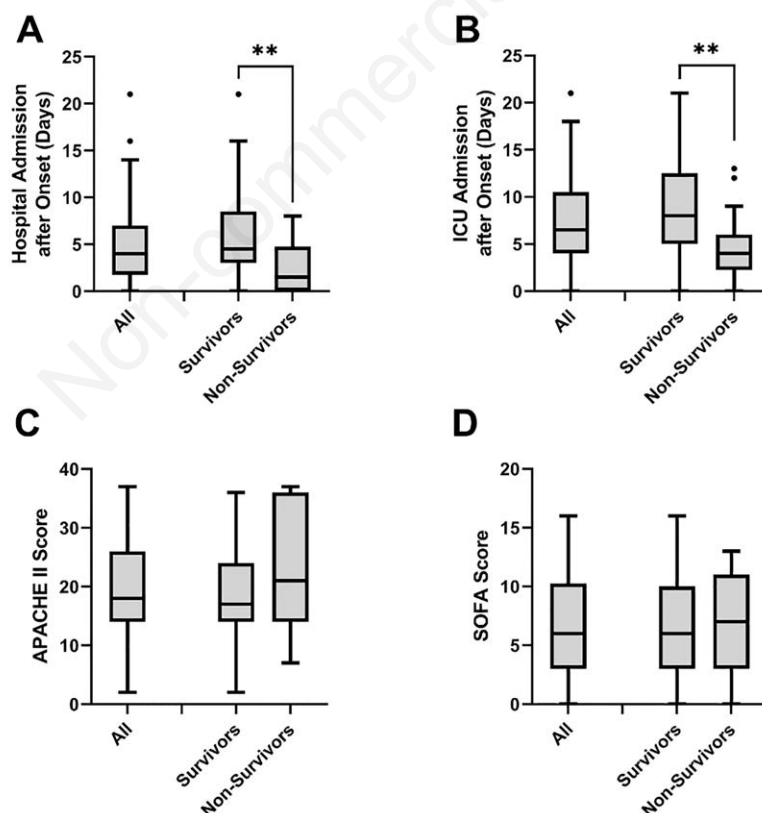


Figure 2. Delay of admission (days after onset of symptoms) and severity of illness on first day in ICU. Patients who died until day 60 were admitted earlier (A) to Hospital ($p=0.0018$), and (B) to ICU ($p=0.0037$, both Mann Whitney U test) compared to those who survived day 60. Days are counted from ICU admission. (C) APACHE and (D) SOFA scores did not differ significantly (Mann Whitney U test). Box and whiskers as explained in Figure 1.

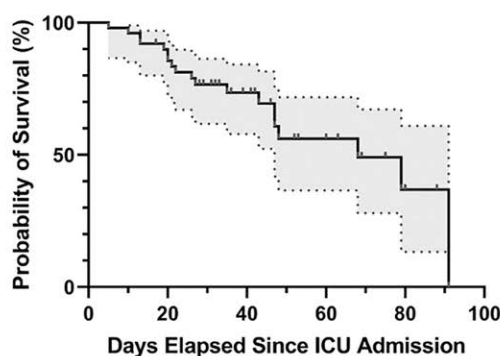
ability of survival was also shown when the total cohort was divided into patients admitted to hospital within 2 days of symptom onset or later (Figure 3).

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]. Prone patients with relatively high compliance therefore might not hold much promise. Nevertheless, half of our ventilated patients (n=22) were put in the prone position, and during the first proning period, pO_2 rose considerably (Figure 1). Survivors underwent three periods in prone position in median. It has been put forward that autopsy findings of deceased patients with COVID-19 pneumonia matched the original description of ARDS, as diffuse alveolar damage was seen in most cases, notably also in patients who had never been invasively ventilated [23]. Clinically, patients who underwent ECMO therapy presented the 'typical' ARDS findings at this stage of disease: the initially well-preserved lung compliance had finally been lost. This might not only be due to the natural course of the viral pneumonia, but also due to mechanical chal-

lenge caused by the great and sustained respiratory efforts of COVID-19 patients before receiving ventilator support. Last but not least, the worsening of lung compliance might also result from positive pressure ventilation itself [24]. In our cohort, NIV or HFNO was rarely used due to the concern of spreading viral aerosols. Furthermore, the distressed patients arriving at our ICUs needed immediate relief from their pronounced shortness of breath – and this included sedation to an extent that precluded an initial non-invasive support. All our patients requiring invasive ventilation were intubated at the latest one day after ICU admission. Since our hospital (like the German health-care system in general) was not overrun by the pandemic at any time during the last months, all patients in need for intensified therapy and mechanical ventilation could be admitted to ICU. In our hospital, all physicians on the wards could call an intensivist 24/7 to discuss the treatment including the possible need to transfer the patient to the ICU. Also, ECMO indication was discussed in an interdisciplinary approach between anaesthesiological and medical ICU specialists. This invasive strategy could be put into action in every case the board had agreed on the indication. Although their number is low, the high in-hospital mortality of our ECMO patients (86%) compares with the one in the large German retrospective study (71%) [20]. This exceeds by far the numbers from the ELSO registry, with an in-hospital mortality of 39% in COVID-19 patients [25]. Although a possible bias cannot be ruled out for these numbers from centres which voluntarily decided to report to the registry, the difference remains remarkable. We did not administer dexamethasone (or any other corticosteroid routinely) to our COVID-19 patients, but, regarding the data available until present, this could be a helpful jigsaw piece in the treatment – although it might be desirable to administer this medication before ICU admission [26]. Remdesivir, as an antiviral agent, does not seem promising for patients needing invasive ventilation [27-29]. As long as a specific antiviral or disease modifying drug is not at hand, the established treatment options against non-COVID-19 ARDS remain our cornerstones taking care of our critical ill COVID-19 patients. About half of our patients could return home until day 60, and less than half of them reported no limitation on activities on this day (20% of the whole cohort). This underlines the medium- and long-term consequences of the disease for patients who needed critical care. The worst outcome ensued for the intubated patients with a parallel need for renal replacement therapy (60-day mortality, 42.1%).

A Whole Cohort



B Early and Late Hospitalization

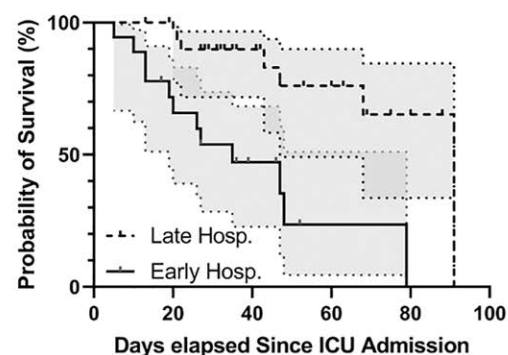


Figure 3. Kaplan Meier estimates of survival (A) in the whole cohort and (B) in the subgroups of patients admitted to hospital within 2 days or later after onset of symptoms. The two survival curves differ significantly (Log-rank test, $p=0.0003$).

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 endexpiratory pressure.

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