

## Peer Review File

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### Reviewer A

**Comment 1:** The authors conducted a retrospective study on ICU patients with COVID-19 and analyzed the prognostic values for COVID-19 death. The study is sound and design is clear. However, several points need to be clarified or corrected here.

1. Lines 17-18, COVID-19 patients differed clinically from those with SARS-CoV-2..., the statement is not understood.

**Reply 1:** We thank the reviewer for the opportunity to clarify this distinction:

For a detailed reply, we refer to our response to question 4-2 below. This specific comment pertains only to the abstract. Here we have added the following:

**Changes in the text:** We added the following in the abstract text: “COVID-19 patients differed clinically from those with SARS-CoV-2 as comorbidity (such as severe heart or renal failure or sepsis as the leading cause of ICU admission) despite similar mortality rates (44.0% vs. 45.5%,  $p>0.5$ ).” (page 2, line 47f.)

**Comment 2:** Introduction part is too simply written. Authors have not stated why they initiated such a study as prognosis study on COVID-19 mortality is quite a lot. They need to point out clearly their rationale and novelty in the study.

**Reply 2:** We thank the reviewer for the opportunity to extend the introduction to better explain the rationale and novelty of our study. In brief, from the first days of the pandemic, our hospital used a different approach to treat patients with COVID-19 compared to most other hospitals in Germany. The main difference was, that many severely hypoxemic COVID-19 patients at our clinic were initially treated on a COVID-19 intermediate care ward (“COVID-IMC”) and NIV was used to treat almost all stages of hypoxemia. In fact, invasive mechanical ventilation (IMV) was considered only the last option of respiratory support. As a result, patients were transferred to ICU comparatively late when they were initially cared for on the COVID-IMC. The strategy at our hospital outside ICU was accompanied by a lively debate in Germany (and elsewhere), if and when these patients should be escalated to invasive mechanical ventilation (IMV). We have referenced the national guidelines (ref. 1,12,13) and the

approach chosen at our clinic (ref. 10,11). As the pandemic continued, many patients died on our ICU. It was therefore our aim to systematically review and analyze the clinical course of our patients. We sought to identify parameters that predict the prognosis and learn lessons, in order to improve treatment of patients in the future, at our clinic and elsewhere. We obtained approval from the local ethics committee to study all patients that were admitted during the first year (i.e. “all-comers study”). In this manuscript, we present the result of this exploratory analysis. We sincerely hope and believe that our experience is relevant also to other colleagues on ICUs worldwide, for COVID-19 and other future pandemics.

We have modified the introduction to better explain the rationale of our work.

**Changes in the text** (page 3, lines 73ff., changes here in bold): “Therefore, many patients admitted to our hospital were initially referred to a “COVID-19 intermediate care unit” with high rates of NIV (10,11), unless they had concomitant diseases other than COVID-19 that necessitated ICU therapy. This led to identification of two distinct groups of patients, i.e. those with COVID-19 and those with SARS-CoV-2 infection as comorbidity, e.g. with sepsis, severe heart or renal failure, etc., as the leading cause for ICU admission. In some patients, respiratory function deteriorated and they were escalated to invasive mechanical ventilation (IMV) according to guidelines (1,12,13). Despite all efforts, mortality rates appeared to be high. It is therefore the aim of this exploratory study to examine the clinical course of patients admitted to our ICU in this setting and to identify predictors of intubation and mortality.”

**Comment 3:** Inclusion and exclusion criteria of patient participants are better presented in a flow chart.

**Reply 3:** We thank the reviewer for the opportunity to clarify inclusion and exclusion criteria. As suggested, we developed a flow chart, which we added to the appendix. As this is an all-comers study, we extended the flow chart to a figure that includes the path of patients just before and just after ICU. If this is deemed important enough, we would be happy to include this flow-chart in the main manuscript.

**Changes in the text:** We added the following to the text: “All patients transferred to our ICU entered the database (Appendix Fig. 1).” (page 4, line 105). We included the flow chart in the appendix (page 36).

**Comment 4:** Tables 1-2 are not the major point of interest for study, but the baseline characteristics of COVID-19 patients. What do you mean by " with SARS-CoV-2 as a comorbidity". This statement has been quite not misunderstood in the text.

**Reply 4.1** ("table 1-2 not major point of interest"): We thank the reviewer for pointing this out. This question also relates to comment 1 and comment 4.2 (see above and below).

We have placed these table first in the manuscript because it is an all-comers study per protocol. We followed the protocol and hence wanted to report data for all patients first. We agree, though, that we had given the manuscript a slightly different main focus. This may have been confusing. We therefore now included tables 3 and 4, i.e. comparison of COVID-19-patients versus those with SARS-CoV-2 as comorbidity, into the main manuscript.

**Changes in the text:** we included tables 3 and 4 into the main manuscript and made according changes in referencing the tables correctly.

**Reply 4.2** ("What do you mean by " with SARS-CoV-2 as a comorbidity" ..."):

We thank the reviewer for the opportunity to better explain this distinction: early on in the pandemic the question was asked, if patients died of or with COVID-19. For example, it was claimed that many patients who were documented as COVID-19 deaths would have died shortly after anyways, i.e. that they were at very old age, or had fatal diseases such as cancer, severe heart failure, etc. On our ICU we also saw these two groups of patients. We treated many patients with COVID-19, i.e. patients who were admitted to our ICU because they mainly suffered from the disease caused by the SARS-CoV-2 virus with all its pulmonary, vascular and other end-organ sequelae. These patients were labeled "COVID-19 patients". Other patients were admitted to ICU for reasons other than COVID-19, e.g. with heart or renal failure. Some of them were also infected with SARS-CoV-2. They were treated with the same precautions installed to protect staff and to avoid transmission to other patients. Yet, these patients did not develop the full picture of pulmonary and vascular disease. They were not admitted to ICU because of their viral infection, but because of other diseases. These patients were labeled "patients with SARS-CoV-2 as comorbidity".

In the manuscript, we had stated: "We distinguished patients admitted due to COVID-19, from those admitted with SARS-CoV-2 infection as comorbidity, ...". We found that these two patient groups differed significantly with regard to clinical (and the

accompanying laboratory) characteristics. However, their mortality rates were similar, as shown in tables 3 and 4.

Even though numbers are low, we believe that this is an important and under-reported finding. Therefore, we have now included these tables in the main manuscript and modified the text as indicated below.

We would agree, though, and leave it to the discretion of the reviewers and the editors, to finally keep these tables in the appendix, if this is preferred.

**Changes in the text:** we added the following sentence to the manuscript: “This led to identification of two distinct groups of patients, i.e. those with COVID-19 and those with SARS-CoV-2 infection as comorbidity, e.g. with sepsis, severe heart or renal failure, etc., as the leading cause for ICU admission.” (Page 3, line 76ff).

**Comment 5:** Authors collected all patient cases through one year from 2020-2021. Amid the pandemic, the treatment strategies have been evolving, especially different between early wave of COVID-19 and COVID-19 in 2021. This would affect the prognosis of the disease. How about authors should discuss this point related to their results?

**Reply 5:** We thank the reviewer for this highly relevant comment and the opportunity to extend the discussion. Indeed, as pointed out by the reviewer, treatment recommendations have changed throughout the pandemic. We have quoted the scientific statements that pertain to and are relevant for Germany (1,12,13). Changes in recommendations were indicated in the scientific statement texts and mainly comprise ventilation support, anticoagulation, and corticosteroids. We have added a section in the discussion:

**Changes in the text** (page 14f., lines 358ff.): “During the pandemic, treatment recommendations have been modified (1,12,13). For the period of this study, the modifications mainly pertained to ventilation support strategies, corticoid therapy and anticoagulation. Throughout the study period, we were restrictive with invasive mechanical ventilation, and used NIV below the pO<sub>2</sub>/FiO<sub>2</sub>-thresholds suggested in guidelines. Early on, we used i.v. corticosteroids in COVID-19 patients with ARDS, as suggested by Surviving Sepsis Campaign guidelines (41). Even though anticoagulation was not mentioned in the initial guidelines (12), all patients were individually treated with prophylactic, half-therapeutic or full-dose unfractionated or low molecular weight

heparin depending on risk factors such as overweight or elevated d-dimers (1,7,13). The degree to which such variation in therapy over time may have affected outcome is difficult to estimate. Interestingly, a decrease of early invasive mechanical ventilation from 75% in the first period to 37% in the second period of the pandemic did not reduce overall mortality (8).”

**Comment 6:** Conclusion in this study is not stated with a clarity. Intubation or NIV could worsen the acute lung injury already insulted by COVID-19 infection. What is the exact point the authors may suggest to improve the survival rate of ICU patients with COVID-19, especially those on ventilators?

**Reply 6:** We thank the reviewer for this important question and the opportunity to clarify this issue. Indeed, either intubation / invasive mechanical ventilation (IMV) or NIV may support ventilation and ameliorate dyspnea, while both strategies may also contribute to lung injury (“VILI” or “P-SILI”). At our institution, NIV was used to treat hypoxemia beyond what was recommended in the guidelines (see comment 1-2 and 1-5). We observed that patients who had been on NIV for more than 5 days, and who then did not improve with NIV and had to be transferred to ICU, had a poor prognosis. This is in line with observational data from a national registry. However, our data extend these findings in that others had not reported underlying pO<sub>2</sub>/FiO<sub>2</sub>-categories in relation to intubation and mortality rates (see Fig. 2). We found that prognosis worsens with worsening degree of lung damage in initially spontaneously breathing patients. As recommendations towards liberal intubation, especially at the beginning of the pandemic, were widely used, these data are so far not available for COVID-19 patients. We aimed at clarifying this issue in the text.

We do not present a prospective randomized controlled trial, though. Therefore, we cannot make comparative statements with respect to IMV versus NIV. This issue is still unresolved and prospective trials are still missing. We therefore believe and hope that our data contribute to patient treatment, to justify prospective trails and design treatment protocols with respect to timing of IMV related to underlying disease severity and accompanying inflammation. A lesson from our data is that intubation should be strongly considered in patients with deteriorating disease especially when they had been on NIV for more than 5 days.

**Changes in the text** (page 14f., lines 366ff, here changes in bold): “Especially patients  $\geq 5$  days on NIV appear to have a very poor prognosis. Our data indicate that patients with severe COVID-19 hypoxemia that do not improve on NIV during the first days, should be considered candidates for invasive ventilation to reduce work of breathing and maybe P-SILI. Yet, it is currently unclear if long duration on NIV aggravates the disease process or if it indicates lack of recovery, or both.”

## **Reviewer B**

In this retrospective single center study, the Authors assessed potential predictors of unfavorable outcome in a group of 61 patients admitted to the ICU and affected by COVID-19. Severe ARDS, NIV-duration > 5 days on ICU admission remained independently predictive of mortality. This is a clear and very well-structured text. However, I have some major concerns about it:

**Comment 1:** The sample size is limited, I don't believe this small single center study could modify or confirm literature on this topic, especially on NIV therapy.

**Reply 1:** We agree with the reviewer that the sample size is limited. However, until today, there is very limited data on the prognosis of initially spontaneously breathing patients with severe COVID-19-induced ARDS.

We have acknowledged in the limitations section that the sample size is limited. However, despite the small patient cohort, we were able to detect characteristics that are associated with patients' outcome, indicating that statistical power was sufficient to address the research hypothesis.

**Changes in the text:** No changes necessary.

**Comment 2:** Criteria on ICU admission should be clarified.

**Reply 2:** We thank the reviewer for the opportunity to clarify ICU admission criteria. In fact, patients were usually admitted to the COVID-19 IMC unit first as long as they were hemodynamically stable and experienced no major complication. The decision to transfer patients to ICU were made on an individual basis by the treating physician. Frequent criteria were increases in cardiac troponin values, in NT-pro-BNP, or d-Dimers, worsening renal failure, etc., all indicating a threat of complications and/or hemodynamic instability. Other indications included reduced vigilance and/or

confusion, mediastinal or cutaneous emphysema, or any etiology of shock. We have made changes to the text as follows:

**Changes in the text:** We have modified a subtitle in the methods section to “Inclusion and Exclusion Criteria and Admission Criteria to ICU” (page 4, line 111ff.)

In this section, we added the following: “Patients were admitted to ICU using established criteria such as hemodynamic or metabolic instability, including elevated troponin-, NTpro-BNP-, and/or D-dimer-values, renal failure, sepsis, reduced Glasgow coma scale (GCS), etc. Hypoxemic awake COVID-19 patients were transferred to ICU in case of respiratory failure with CO<sub>2</sub>-elevation despite NIV-therapy, or complications such as subcutaneous or mediastinal emphysema.”