J Crit Care 85 (2025) 154942

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

Long-term characteristics and outcomes of septic critically ill patients with and without COVID-19

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ARTICLE INFO

Keywords:
Sepsis
COVID-19
EQ-5D
Health-related quality of life
Long-term survival

ABSTRACT

Background: In-hospital mortality of septic critically ill patients with COVID-19 is significantly higher than in those without COVID-19. The knowledge on long-term outcomes remains scarce. In this retrospective analysis, we compare clinical characteristics, long-term functional outcomes, and survival in septic critically ill patients with and without COVID-19.

Methods: Data of septic critically ill patients without COVID-19 were collected as part of the Comprehensive Sepsis Center Dresden-Kreischa registry from 2020 to 2023. The data of septic critically ill patients with COVID-19 were collected as part of the local ARDS/COVID-19 registry over the same period. Diagnosis of sepsis was based on the Sepsis-3 definition. Variables collected for analyses were obtained from electronic health records. Long-term follow-up was performed 6–12 months after sepsis diagnosis. Survival was depicted using Kaplan-Meier curves. Associations between long-term mortality and risk factors were modeled by Cox Regression.

Results: 372 septic patients without COVID-19 and 301 with COVID-19 were enrolled. Septic patients with COVID-19 were significantly younger, had a significantly lower Charlson Comorbidity Index, and had a significantly higher SOFA score at ICU admission. Long-term follow-up showed a significantly higher mortality in septic patients with COVID-19 (73.4 % vs. 30.1 %; HR 3.4 (95 % CI 2.73–4.27; $p < 0.05$)). COVID-19 infection was associated with significant increased mortality (adjusted HR 3.27; 95 % CI 2.48–4.33; $p < 0.05$) and reduced health-related quality of life, measured by the EQ-5D-3 L Index, (0.56 (0.16–0.79) vs. 0.79 (0.69–0.99); $p < 0.05$).

Conclusions: In our cohort of septic critically ill patients, health-related quality of life and long-term survival were considerably reduced in patients with concomitant COVID-19. Furthermore, COVID-19 could be identified as an independent risk factor for higher long-term mortality in these patients.

Abbreviations: ARDS, Acute respiratory distress syndrome; BMI, Body mass index; CCI, Charlson Comorbidity Index; CRP, C-reactive protein; CSC, Comprehensive Sepsis Center; CI, Confidence interval; COVID-19, Coronavirus disease 2019; ECMO, Extracorporeal membrane oxygenation; EQ-5D, EuroQol-5 Dimensions; 3 L, 3 Level; 5 L, 5 Level; HR, Hazard Ratio; ICM, Integrated Care Manager; ICU, Intensive care unit; PCT, Procalcitonin; RKI, Robert Koch Institut; SOFA, Sepsis-related Organ Failure; SARS-CoV-2, Severe acute respiratory syndrome coronavirus type 2; SOP, Standard operating procedure; Subdistribution hazard ratio, SHR; Visual Analogue Scale, VAS.

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https://doi.org/10.1016/j.jcrc.2024.154942

Available online 31 October 2024
0883-9441/

1. Introduction

Coronavirus disease 2019 (COVID-19), caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is known as a life-threatening disease [1] and might aggravate high mortality in septic critically ill patients. The COVID-19 pandemic has been one of the greatest threats to public health, with over seven million deaths reported worldwide [2]. Although mortality associated with sepsis or septic shock is already high [3], we could recently demonstrate, that intensive care unit (ICU) mortality is significantly increased in patients with concomitant COVID-19 [4]. Based on these results, we aimed to analyse long-term outcomes of these patients. It is well known that long-term mortality in infectious diseases increases by over 10 % if patients meet Sepsis-3 criteria [5]. However, knowledge regarding long-term mortality and functional outcomes in septic patients with COVID-19 remains uncertain. The Comprehensive Sepsis Center (CSC) Dresden-Kreischa was founded in 2019 with the aim of improving survival and long-term functional outcomes of septic patients by improving intersectoral care and clinical pathways [6]. In this retrospective analysis, we compared clinical characteristics, long-term functional outcomes, and long-term mortality in septic patients with and without COVID-19.

2. Methods

2.1. Study design

This retrospective study was conducted at the University Hospital Dresden, Germany, in accordance with the Declaration of Helsinki. Standardised follow-up was conducted by the cooperation site at Klinik Bavaria Kreischa, Germany. The retrospective study received approval from the Dresden University Ethics Committee (BO-EK-374072021).

2.2. Study protocol

Data of septic critically ill patients without COVID-19 were collected as part of the prospective CSC registry from February 2020 to May 2023. Similarly, data of septic critically ill patients with COVID-19 were gathered over the same period as part of the local acute respiratory distress syndrome (ARDS)/COVID-19 registry. Study size was reached by convenience sampling. Patients were screened for sepsis and COVID-19 in three ICUs at the University Hospital of Dresden. Diagnosis of sepsis was based on the Sepsis-3 definition [7]. Patients were at least 18 years old at the time of diagnosis. Informed consent was obtained from either the patient or a legal representative. All patients were treated in accordance with the Surviving Sepsis Campaign Guidelines [8]. Additionally, COVID-19 patients were treated following the German guidelines for COVID-19 [9] and the regularly updated recommendations of the COVRIIN expert group of the Robert Koch Institut (RKI) [10]. All septic patients without COVID-19 received treatment according to the multidisciplinary and multisectoral pathway of the CSC, including standard operating procedures (SOP) for diagnostic measurements, antibiotic administration, and surgical treatment of sepsis origin. Long-term follow-up, typically conducted 6–12 months after sepsis diagnosis, involved a telephone survey assessing survival, presence of ongoing organ replacement therapies and EuroQol-5 Dimensions Score (EQ5D) scores. Two versions of the EQ-5D were utilised due to the use of two different registries. Patients from the CSC registry were assessed with EQ-5D-3 Level (3 L), while patients from the COVID-19 registry were assessed with the EQ-5D-5 Level (5 L). The EQ-5D-3 L and EQ-5D-5 L are both versions of the EQ-5D questionnaire, developed by the EuroQol Group to assess health-related quality of life. The EQ-5D-3 L features three levels of severity (no problems, some problems, and extreme problems) across five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D-5 L expands this to five levels, allowing for a more detailed assessment by adding two categories between the original three. Both versions include a Visual Analogue Scale (VAS) for measuring overall health [11,12]. For comparison, EQ5D-5 L scores were mapped to EQ-5D-3 L using the Stata eq5dmap command from the University of Sheffield [16]. Patients survived the initial hospital stay were transferred to various rehabilitation centers and hospitals for further care.

2.3. Data collection

Variables collected for analysis were obtained from the clinical information system (ORBIS, Dedalus, Bonn, Germany) as well as the patient data management system (Integrated Care Manager (ICM), Dräger Medical, Lübeck, Germany) and respective sub-systems (ixserv, ixmid Software Technologie GmbH, Köln, Germany). In addition to basic demographic and anamnestic data (age, sex, height, weight, chronic diseases), we assessed the Charlson Comorbidity Index (CCI) [13,14] at ICU admission. Further patient characteristics, such as sepsis origin, Sepsis-related Organ Failure Assessment (SOFA) score [15] at ICU admission, and the need for invasive ventilation, dialysis, and extracorporeal membrane oxygenation (ECMO) during ICU stay, were also evaluated.

2.4. Laboratory analysis

Laboratory analyses were conducted daily as part of routine procedures. These included a complete blood cell count to measure leukocytes using EDTA tubes, as well as measuring additional inflammatory parameters such as C-reactive protein (CRP) and procalcitonin (PCT) using serum or lithium heparin tubes. All laboratory tests, except bedside blood gas analysis using ABL Flex90 systems (Radiometer, Brønshøj, Denmark), were performed at the Institute for Laboratory Medicine at the University Hospital Dresden, following standard procedures.

2.5. Statistical analysis

Statistical analyses were conducted using SPSS Statistics 29 (IBM, Inc., Armonk, NY, USA) and GraphPad PRISM version 10.1.2 (San Diego, CA, USA). A two-tailed p-value <0.05 was considered statistically significant. All tests should be understood as constituting exploratory analysis, meaning no adjustments for multiple testing were made. Categorical variables are presented as absolute and relative frequencies. Group comparisons were assessed using Fisher's exact test. Continuous variables are expressed as medians with interquartile ranges (IQR; 25th and 75th percentiles). Group comparisons for continuous variables were assessed using the Mann-Whitney U test. Long-term mortality was defined as the primary outcome. Survival was illustrated using Kaplan-Meier curves and assessed using the log-rank test. Long-term mortality and independent risk factors were analysed using Cox Regression. To address the increased mortality rate during ICU stay of septic critically ill patients with COVID-19 compared to those without COVID-19, the event of death was considered as a competing event for length of ICU stay in a Fine and Gray test and is given as a subdistribution hazard. The precision of hazard ratio (HR) estimates was quantified using 95 % confidence intervals (CIs). For assessment of long-term functional outcomes of septic patients with and without COVID-19 we examined the established EQ-5D [11,12]. EQ5D-5 L scores were mapped to EQ-5D-3 L using the Stata eq5dmap command from the University of Sheffield [16].

3. Results

3.1. Patient characteristics

In total, 673 patients were enrolled in this study. Including 372 septic critically ill patients without COVID-19 and 301 septic critically ill patients with COVID-19. Septic patients with COVID-19 were significantly younger than those without COVID-19 (63 [56–69] vs. 65 [57–74] years; $p < 0.05$). The CCI at ICU admission was significantly higher in septic patients without COVID-19 (4.0 [3-6] vs. 2.5 [1-4] points; $p < 0.05$). All septic patients with COVID-19 had a pulmonary sepsis origin. In septic patients without COVID-19, abdominal (32.3 %) and pulmonary (22.0 %) origins of sepsis predominated. Urosepsis and skin or soft tissue-related sepsis were found in one-quarter of these patients, with the remaining quarter caused by other sources of infection. High mortality was particularly associated with sepsis of pulmonary (39.0 %), abdominal (30.8 %), device-associated (36.3 %), and central nervous system (40.0 %) origin. Septic patients with COVID-19 had a significantly higher SOFA score at ICU admission compared to those without COVID-19 (12 [10-14] vs. 9 [6-13]; $p < 0.05$). A total of 35.2 % of all patients were classified with septic shock at ICU admission, with significantly more cases in septic patients without COVID-19 (144 [38.7 %] vs. 93 [30.9 %]; $p < 0.05$). Further characteristics of the study population are provided in Table 1.

Table 1
Patient characteristics.

n	372 (55.27 %)	301 (44.73 %)	
Basic characteristics			
Age in years	65 (57–74)	63 (56–69)	**0.012**
Male Sex (n)	269 (72.7 %)	219 (72.8 %)	0.99
BMI [kg/m^2]	26.3 (23.9–30.9)	30.4 (26.2–34.6)	**<0.0001**
Height [cm]	175 (170–180)	175 (170–180)	0.19
Weight [kg]	80 (70–93)	90 (80–105)	**<0.0001**
CCI	4 (3–6)	3 (1–4)	**<0.0001**
Excerpt from pre-existing conditions			
Diabetes Type I or II (n)	149 (40.1 %)	110 (36.5 %)	0.35
CKD (n)	72 (19.4 %)	33 (11.0 %)	**0.0024**
COPD (n)	37 (9.9 %)	31 (10.3 %)	0.91
Laboratory parameters			
CRP maximum value [mg/L]	289 (213.7–349.9)	298.5 (223.7–376.2)	0.17
PCT maximum value [ng/ml]	14.8 (4.1–54.3)	4.7 (1.5–12.1)	**<0.0001**
Leucocytes maximum value [Gpt/L]	22.6 (15.4–30.7)	21.8 (17.0–28.7)	0.82
Sepsis origin			
Pulmonary (n)	82 (22 %)	301 (100 %)	**<0.0001**
Abdominal (n)	120 (32.3 %)		
Urogenital (n)	44 (11.8 %)		
Skin or soft tissue related (n)	51 (13.7 %)		
Device associated (n)	22 (5.9 %)		
Central Nervous System (n)	5 (1.3 %)		
Bone/Joint related (n)	10 (2.7 %)		
Unknown (n)	38 (10.3 %)		
ICU characteristics			
SOFA score at ICU admission	9 (6–13)	12 (10–14)	**0.0013**
Septic shock at ICU admission (n)	144 (38.7 %)	93 (30.9 %)	**<0.0001**
Vasopressor at ICU admission (n)	224 (60.2 %)	298 (99.0 %)	**<0.0001**
P/F ratio (Horovitz) at ICU admission	249.6 (152.1–343.2)	105 (82.5–150)	**<0.0001**
ECMO (n)	27 (7.3 %)	140 (46.5 %)	**<0.0001**
ECMO [hours]	181 (115–380)	346 (211–598)	**0.0006**
Ventilation (n)	247 (66.4 %)	301 (100 %)	**<0.0001**
Ventilation [hours]	333 (120–693)	360 (216–552)	0.12
Dialysis (n)	129 (34.7 %)	142 (47.2 %)	**0.0012**
Dialysis [hours]	378 (102–644)	154 (59–275)	**<0.0001**
ICU length of stay [days]	29 (15–48)	14 (9–21)	**0.46**
ICU mortality (n)	98 (26.3 %)	204 (67.8 %)	**<0.0001**

Discrete variables are presented as absolute and relative frequencies. Comparison between groups were assessed using Fisher's exact test. Continuous variables are given as medians with 25; 75 percentiles. Comparison between groups were assessed using Mann-Whitney *U* test, ICU length of stay was assessed using Fine and Gray test.
BMI = body mass index, CCI = Charlson Comorbidity Index, CKD = chronic kidney disease, COPD = chronic obstructive pulmonal disease, CRP = C-reactive protein, P/F ratio = Partial pressure of oxygen in arterial blood/ Fraction of inspired oxygen; ECMO = extracorporeal membrane oxygenation, ICU = Intensive Care Unit, PCT = Procalcitonin, Sepsis-related Organ Failure = SOFA.

3.2. ICU treatment

The rate of invasive mechanical ventilation was significantly higher in septic patients with COVID-19 compared to those without COVID-19 (100 % vs. 66.4 %, $p < 0.05$). Correspondingly, the need for ECMO therapy was significantly higher in septic patients with COVID-19 (46.5 % vs. 7.3 %, $p < 0.05$). 47.2 % of septic patients with COVID-19 received dialysis during ICU stay compared to 34.7 % of septic patients without COVID-19 ($p < 0.05$), even though they had significantly less pre-existing presence of chronic kidney disease (11.0 % vs. 19.4 %, $p < 0.05$). ICU length of stay was shorter for septic patients with COVID-19 (14 [9-21] vs. 29 [15–48] days). According to the competing risk analysis, COVID-19 did not significantly alter the length of stay in the intensive care unit in our cohort (subdistribution hazard ratio (SHR) 0.916; CI 97.5 % 0.729–1.15; $p = 0.46$).

3.3. Survival and regression of long-term mortality

Long-term follow-up showed significantly higher mortality in septic patients with COVID-19 compared to those without COVID-19 (73.4 % vs. 30.1 %; HR 3.4, 95 % CI 2.73–4.27; $p < 0.05$) (Fig. 1A). Most deceased patients died during the hospital stay. However, once patients had survived the initial hospital stay, long-term mortality did not differ significantly between septic patients with COVID-19 and those without COVID-19 (10.1 % vs. 5.1 %; HR 1.76, 95 % CI 0.67–4.64; $p > 0.05$) (Fig. 1B).

For subgroup analysis, different origins of sepsis were identified and clustered into eight groups (Table 1). Long-term mortality of all patients with pulmonary origin of sepsis was analysed, including 82 septic patients without COVID-19 and all 301 septic patients with COVID-19. In the comparison of pulmonary sepsis, long-term follow-up showed significantly higher mortality in septic patients with COVID-19 (73.4 % vs. 39.0 %; HR 2.34, 95 % CI 1.77–3.11; $p < 0.05$) (Fig. 2A). However, in this subgroup analysis of patients with a pulmonary sepsis origin, once the hospital stay was survived, long-term mortality was not significantly different between the groups of patients with and without COVID-19 (10.1 % vs. 5.7 %; HR 1.59, 95 % CI 0.47–5.41; $p > 0.05$) (Fig. 2B).

Adjusted group comparison between septic patients with and without COVID-19 was performed using Cox regression. Eight variables were included: basic patient characteristics such as sex, body mass index (BMI), as well as conditions noted at ICU admission, including CCI, SOFA score, presence of septic shock, vasopressor requirements and P/F ratio (Horovitz index). The adjusted HR for long-term data showed an increased rate of death in septic patients with COVID-19 compared to other septic patients (HR 3.27; 95 % CI 2.48–4.33; $p < 0.05$). In addition to COVID-19, other risk factors such as CCI (HR 1.10; 95 % CI 1.05–1.15; $p < 0.05$), SOFA score at ICU admission (HR 1.08; 95 % CI 1.04–1.12; $p < 0.05$) and the presence of septic shock at ICU admission (HR 1.67; 95 % CI 1.31–2.13; $p < 0.05$) were also significantly related to an increased rate of death in the long-term (Table 2).

3.4. Health-related quality of life

Data from 71 septic patients without COVID-19 and 79 septic patients with COVID-19 were available. Long-term health-related quality of life, measured by the EQ-5D-3 L Index, was significantly lower in septic patients with COVID-19 (0.56 [0.16–0.79] vs. 0.79 [0.69–0.99]; $p < 0.05$) (Fig. 3). Interviewed septic patients with and without COVID-19 reported most often the highest impairment level with 'extreme problems' in 'self-care' (12.5 %) and 'usual activities' (15.2 %) compared to 'mobility' (6.6 %), 'pain/discomfort' (5.3 %), and 'anxiety/depression' (3.3 %).

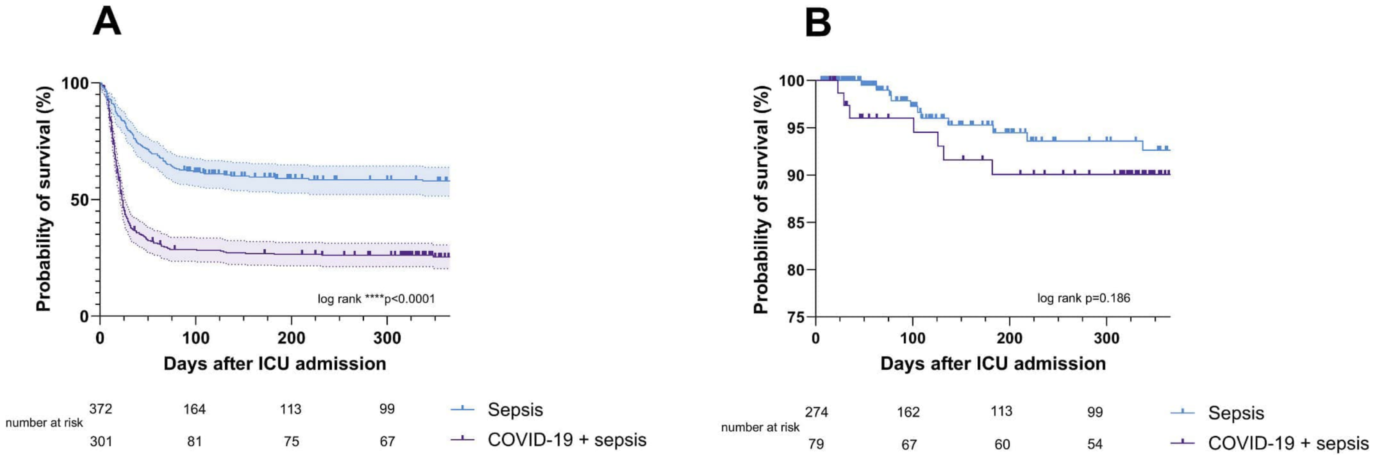

Fig. 1. A: Long-term survival.
Probability of survival depicted as Kaplan-Meier curves in septic patients without COVID-19 and septic patients with COVID-19, long-term follow-up. Number at risk as indicated; Log rank test, p < 0.0001.
Fig. 1B: Long-term survival of hospital survivors.
Probability of survival depicted as Kaplan-Meier curves in septic patients without COVID-19 and septic patients with COVID-19, which survived hospital stay with long-term follow-up. Number at risk as indicated; Log rank test, p = 0.1862.

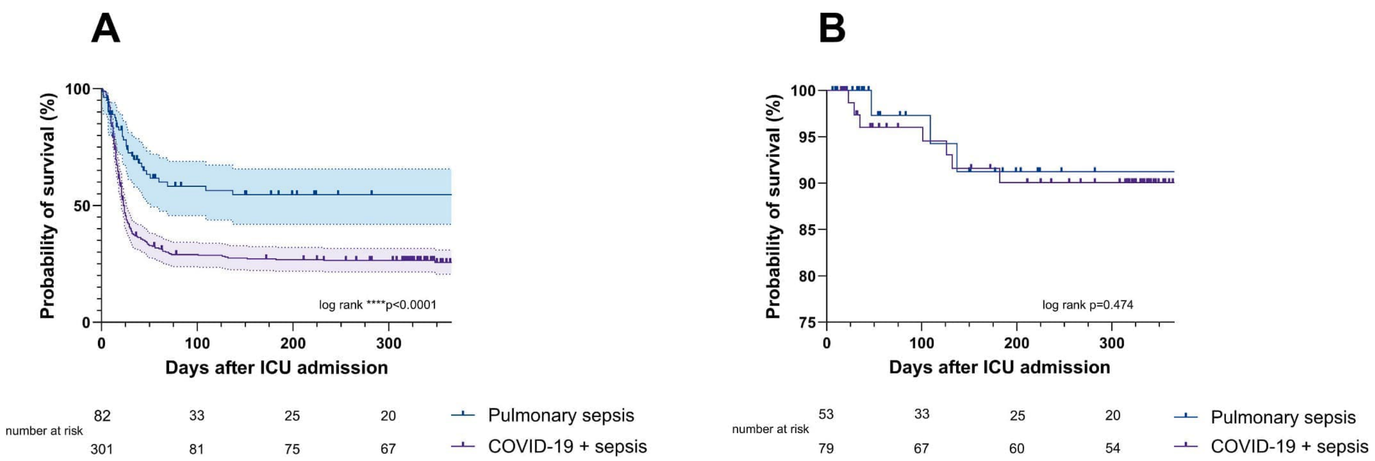

Fig. 2. A: Long-term survival for pulmonary sepsis.
Probability of survival depicted as Kaplan-Meier curves in septic patients with pulmonary origin of sepsis and septic patients with COVID-19, long-term follow-up. Number at risk as indicated; Log rank test, p < 0.0001.
Fig. 2B: Long-term survival for pulmonary sepsis of hospital survivors.
Probability of survival depicted as Kaplan-Meier curves in septic patients with pulmonary origin of sepsis and septic patients with COVID-19, which survived hospital stay with long-term follow-up. Number at risk as indicated; Log rank test, p = 0474.

Table 2
Cox regression with HR and 95 % CI.

	p-value	HR	95 %-CI	
			Lower	Upper
COVID-19 (ref: no)	**<0.001**	**3.27**	2.48	4.33
CCI	**<0.001**	1.10	1.05	1.15
SOFA-Score at ICU admission	**<0.001**	**1.08**	1.04	1.12
Septic shock at ICU admission (ref: no)	**<0.001**	**1.67**	1.31	2.13

Hazard Ratio's (HR) from Cox Regression for long-term mortality with 95 % confidence intervals (CI's).
Parameters considered in the Cox Regression were Coronavirus disease 19 (COVID-19) reference (ref): no; body mass index (BMI), Sex; Charlson Comorbidity Index (CCI); Sepsis-related organ failure assessment (SOFA); Septic shock at intensive care unit (ICU) admission ref.: no; Vasopressor requirement at ICU admission; P/F ratio at ICU admission.

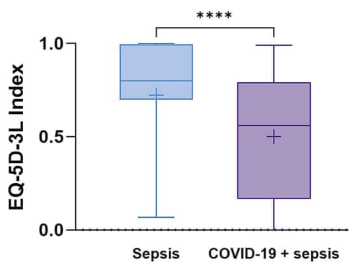

Fig. 3. Health-related quality of life.
Health-related quality of life in septic patients with and without COVID- 19, long-term follow-up. EQ-5D- 3 L = EuroQol 5 Dimensions 3 Level Version. Data from n = 71 in sepsis and n = 79 COVID-19 + sepsis group were available, Mann-Whitney U test, p < 0.0001.

4. Discussion

4.1. Survival

In 2022, our group published new findings based on data from the ongoing CSC registry, focusing on patient care and risk stratification of septic patients with and without COVID-19. Septic patients without COVID-19 showed an ICU mortality rate of 21 %, compared to 53 % in septic patients with COVID-19. COVID-19 was identified as an independent risk factor for in-hospital mortality [4]. Due to the larger number of patients (673 vs. 368), ICU mortality rates were slightly different in the recent analysis, showing an ICU mortality rate of 26.3 % for septic patients without COVID-19 and 67.8 % for septic patients with COVID-19. ICU stay in days was shorter in septic critically ill patients with COVID-19 compared to those without COVID-19. In further analysis with the Fine and Gray subdistribution hazard model we were able to show that differences in ICU stay were not significantly influenced by COVID-19 when death during ICU stay was considered as a competing event.

Follow-up showed a significantly higher long-term mortality of 73.4 % in septic patients with COVID-19 compared to 30.1 % in septic patients without COVID-19 (Fig. 1A). These finding is particularly noteworthy as it cannot be explained by patient characteristics, since septic patients with COVID-19 were younger and had a lower CCI at ICU admission. Furthermore, Cox Regression showed COVID-19 as an independent risk factor for long-term mortality. A secondary analysis of all patients surviving the acute care hospital showed that the survival rate after discharge from the acute care hospital was high and was not influenced by COVID-19 (Fig. 1B). As expected, a higher SOFA score and the presence of septic shock at ICU admission were associated with higher mortality rates based on the Cox Regression analysis. SOFA score and elevated lactate levels, as seen in septic shock, are already known as independent risk factors for mortality in septic patients [17,18].

The source of infection may have an impact on survival and long-term outcomes, such as health-related quality of life, and may differ among treatment options [19]. Pulmonary sepsis appears to be associated with particularly impaired long-term outcomes [20]. Our data confirmed that pulmonary sepsis is one of the most challenging infections, with a long-term mortality rate of almost 40 %, compared to abdominal sepsis with 30.8 % and urosepsis with 13.6 % mortality. Based on that, we compared septic patients with COVID-19, to septic patients without COVID-19 suffering from pulmonary sepsis (22 %). This sub-analysis showed that long-term mortality differed considerably (Fig. 2A). This implies that not only pulmonary sepsis is associated with higher mortality, but COVID-19 as a pulmonary sepsis trigger may lead to even higher mortality rates. However, the extremely high mortality in this study might also be influenced by a certain selection bias, as COVID-19 patients were specifically transferred to the University Hospital Dresden as a tertiary referral center for specialized lung support and ECMO therapy.

The difference in long-term mortality seems to be primarily attributable to the increased deathrate of septic patients with COVID-19 during the acute phase of hospitalization compared to septic patients without COVID-19. Once the septic patients survived the initial hospital stay and were discharged from hospital, their mortality was not significantly different between patients with or without COVID-19, regardless of whether patients had a pulmonary origin of sepsis or not (Fig. 1B and Fig. 2B). This suggests that the acute phase of illness, which requires intensive interventions and critical care, plays a crucial role in the elevated mortality observed in patients with COVID-19. Surviving this critical period appears to equalize the long-term survival rates between the two groups.

4.2. Health-related quality of life

Long-term health-related quality of life, measured by the EQ-5D-3 L Index, was significantly impaired in septic patients with COVID-19 compared to those without COVID-19 (Fig. 3). Current studies have shown better health-related long-term outcomes in younger and healthier patients, regardless of the underlying disease [20,21]. Despite being significantly younger and having a lower CCI at ICU admission, septic patients with COVID-19 had significantly impaired long-term health-related quality of life compared to those without COVID-19. This is particularly notable given the ongoing investigations into post-COVID conditions, suggesting COVID-19 might have a more substantial negative effect on neurological status and quality of life than other infectious diseases [22]. Our data underscore the significant impact of COVID-19 on long-term quality of life, beyond that of other infectious diseases. The EQ-5D measures five dimensions: 'self-care', 'usual activities', 'mobility', 'pain/discomfort', and 'anxiety/depression' [11]. Predominantly, the dimensions 'usual activities'and 'self-care'were impaired in all investigated groups and subgroups. This points towards the role and impact of sepsis in exacerbating functional limitations in survivors of critical illness, highlighting the need for further research to understand and address these challenges.

4.3. Study limitations

This study faces all typical limitations of retrospective, observational studies, including the lack of control over potential confounders. Demographic differences such as age, body weight, and pre-existing conditions are likely to influence our results. There are discrepancies in long-term follow-up from the use of two different registries. In the CSC registry (which includes septic critically ill patients without COVID-19), long-term follow-up was conducted after 12 months, whereas in the COVID-19 registry, it was performed between 6 and 12 months. This might influence the endpoint of long-term mortality. To address this issue Cox regression was utilised to minimise the effect of varying time endpoints.

COVID-19 is a disease that can affect multiple organ systems, yet it is primarily associated with pulmonary dysfunction during the acute phase. Therefore, in a sub-analysis, only patients with a pulmonary origin of their sepsis were compared. For more detailed insights, a comparison of ARDS diagnoses and severity levels, along with ventilation modalities, would be of interest; however, these data are unfortunately not available. Nevertheless, the P/F ratio (Horovitz index) was available and was analysed as a surrogate of pulmonary function and was incorporated into the Cox regression. Most data from COVID-19 patients were recorded during the early stages of the pandemic when there was no vaccine available. At the end of the pandemic, 76 % of the German population got vaccinated [23]. Furthermore, most of the unvaccinated individuals have acquired natural immunity through prior contact or infection with SARS-CoV-2 before hospital admission. Furthermore, COVID-19 as a disease has varied between SARS-CoV-2 variants, with changes in mortality over time [24,25]. Despite overlaps between COVID-19 and sepsis therapy there are certain differences in treatment. Standardised glucocorticoid therapy with dexamethasone in COVID-19 patients could be a confounder. While some studies suggest a better outcome for COVID-19 patients with glucocorticoid therapy, recent research also indicates potential benefits for septic patients [26,27].

Long-term health-related quality of life was assessed using the EQ-5D, with different versions utilised in this study: EQ-5D-5 L for COVID-19 patients and EQ-5D-3 L for CSC registry patients. While EQ5D-5 L was mapped to EQ-5D-3 L using a standardised approach, comparing the same EQ-5D versions would enhance reliability. Furthermore, varying time endpoints of 6 to 12 months could introduce bias into the results concerning long-term health-related quality of life. However, we want to emphasize that the median long-term follow-up in septic, critically ill patients with COVID-19 was conducted approximately nine months after discharge. Despite efforts to mitigate biases, this study is subject to selection bias.

5. Conclusions

Survival and quality of life are significantly impaired in septic critically ill patients with concomitant COVID-19, despite their younger age and fewer comorbidities compared to those without COVID-19. While COVID-19 impacts survival mainly during hospitalization and ICU stay, mortality rates become comparable during post-acute phase. However, long-term quality of life remains persistently impaired by COVID-19.

Funding

This study was funded by the Kurt Goldstein Institute, Germany (KGI-KochT-1–052019).

Availability of data and materials

The datasets are not publicly available due to data sharing protocols but are available from the corresponding author on reasonable request.

Declaration of Generative AI and AI-assisted technologies in the writing process'

Not applicable.

Consent for publication

Not applicable.

CRediT authorship contribution statement

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Declaration of competing interest

None of the authors has a conflict of interest to declare.

Acknowledgement

The authors thank Stephanie May, Ines Roessler and the staffs of the ICUs of the University Hospital Dresden and the Klinik Bavaria Kreischa.

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