



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Original article

Characteristics and outcomes of sepsis patients with and without COVID-19

Lars Heubner^a, Sara Hattenhauer^a, Andreas Güldner^a, Paul Leon Petrick^a, Martin Rößler^b, Jochen Schmitt^b, Ralph Schneider^c, Hanns Christoph Held^d, Jan Mehrholz^e, Ulf Bodechtel^f, Maximilian Ragaller^a, Thea Koch^a, Peter Markus Spieth^{a,*}

^a Department of Anesthesiology and Critical Care Medicine, University Hospital Carl Gustav Carus and Carl Gustav Carus Faculty of Medicine, TU Dresden, Dresden, Germany

^b Center for Evidence-Based Healthcare (ZEGV), University Hospital Carl Gustav Carus and Carl Gustav Carus Faculty of Medicine, TU Dresden, Dresden, Germany

^c Department of General, Thoracic and Vascular Surgery, University Hospital Carl Gustav Carus and Carl Gustav Carus Faculty of Medicine, TU Dresden, Dresden, Germany

^d Department of Medicine I, University Hospital Carl Gustav Carus, University Hospital Carl Gustav Carus and Carl Gustav Carus Faculty of Medicine, TU Dresden, Dresden, Germany

^e Wissenschaftliches Institut, Klinik Bavaria Kreischa, Germany

^f Department of Interdisciplinary Intensive Care Medicine and Intensive Rehabilitation, Klinik Bavaria Kreischa, Germany

ARTICLE INFO

Article history:

Received 25 January 2022

Received in revised form 10 May 2022

Accepted 12 May 2022

Keywords:

COVID-19

ARDS

Sepsis

Septic Shock

ABSTRACT

Background: The aim of this study was to describe and compare clinical characteristics and outcomes in critically ill septic patients with and without COVID-19.

Methods: From February 2020 to March 2021, patients from surgical and medical ICUs at the University Hospital Dresden were screened for sepsis. Patient characteristics and outcomes were assessed descriptively. Patient survival was analyzed using the Kaplan-Meier estimator. Associations between in-hospital mortality and risk factors were modeled using robust Poisson regression, which facilitates derivation of adjusted relative risks.

Results: In 177 ICU patients treated for sepsis, COVID-19 was diagnosed and compared to 191 septic ICU patients without COVID-19. Age and sex did not differ significantly between sepsis patients with and without COVID-19, but SOFA score at ICU admission was significantly higher in septic COVID-19 patients. In-hospital mortality was significantly higher in COVID-19 patients with 59% compared to 29% in Non-COVID patients. Statistical analysis resulted in an adjusted relative risk for in-hospital mortality of 1.74 (95%-CI=1.35–2.24) in the presence of COVID-19 compared to other septic patients. Age, procalcitonin maximum value over 2 ng/ml, need for renal replacement therapy, need for invasive ventilation and septic shock were identified as additional risk factors for in-hospital mortality.

Conclusion: COVID-19 was identified as independent risk factor for higher in-hospital mortality in sepsis patients. The need for invasive ventilation and renal replacement therapy as well as the presence of septic shock and higher PCT should be considered to identify high-risk patients.

© 2022 Published by Elsevier Ltd on behalf of King Saud Bin Abdulaziz University for Health Sciences. CC_BY_NC_ND_4.0

Abbreviations: AKI, Acute Kidney Injury; ARDS, Acute Respiratory Distress Syndrome; BMI, Body mass index; CI, Confidence interval; CRP, C-reactive protein; CRS, Cytokine release syndrome; COVID-19, Coronavirus disease 2019; ECMO, Extracorporeal membrane oxygenation; HAI, Hospital acquired infection; ICU, Intensive care unit; IL-6, Interleukin 6; iNO, Inhaled nitric oxide; LDH, Lactate dehydrogenase; PCT, Procalcitonin; RR, Relative risk; RRT, Renal replacement therapy; SOFA score, Sequential organ failure assessment score; WHO, World Health Organization

* Correspondence to: Department of Anesthesiology and Critical Care Medicine University Hospital Carl Gustav Carus, Dresden Fetscherstraße 74, 01307 Dresden, Germany.

E-mail address: peter.spieth@uniklinikum-dresden.de (P.M. Spieth).

<https://doi.org/10.1016/j.jiph.2022.05.008>

1876-0341/© 2022 Published by Elsevier Ltd on behalf of King Saud Bin Abdulaziz University for Health Sciences. CC_BY_NC_ND_4.0

1. Introduction

Sepsis is a life threatening organ dysfunction caused by a dys-regulated host response to infection [1]. It is one of the most common diseases and causes of death worldwide. A study by the Institute for Health Metrics and Evaluation estimated 49 million sepsis cases and 11 million sepsis-associated deaths per year [2]. In 2020, the Jena Sepsis Registry reported an in-hospital mortality rate of 35.3% and 52% for sepsis and septic shock, respectively [3]. Furthermore, studies showed that more than 20% of patients who survived sepsis died within the following two years, not explained by

the health status before sepsis [4]. In this context, the World Health Organization declared sepsis as a global health priority [1].

The COVID-19 pandemic represents currently another challenge and affected the healthcare systems world-wide. Karagiannidis et al. (2020) reported mortality rates between 22% (non-ventilated patients), 53% (invasively ventilated patients) and 73% (patients on dialysis) in a large German wide cohort study with 10,021 patients [5]. Increased disease severity in COVID-19 was found to be associated with demographic factors (higher age, male gender) and comorbidities such as, obesity, diabetes, hypertension and coronary heart disease [6]. The development of acute kidney injury (AKI) and increased SOFA score on admission are considered negative prognostic factors for clinical outcomes [7–10]. Moreover, increased white blood cell count, elevated level of C-reactive protein (CRP), Procalcitonin (PCT), Interleukin 6 (IL-6), tumor necrosis factor alpha (TNF- α), lactate dehydrogenase (LDH) and signs of hypercoagulopathy (low platelet count and increased D-dimers, Fibrinogen and Prothrombin Time) were associated with higher severity and increased mortality of COVID-19 [11–14]. Biochemical parameters of liver injury (high levels of ALT, AST and γ GT) were observed in severe and fatal cases (49.1% of all patients at hospital admission) [11]. Furthermore, severe COVID-19 infection is characterized by cytokine release syndrome (CRS) which can also be observed in sepsis [15]. In fact, Sepsis and Covid-19 manifestations present so similar that management guidelines for COVID-19 have been directly developed from similar sepsis guidelines [16].

The aim of this study was to describe and compare clinical characteristics and outcomes in critically ill septic patients with and without COVID-19. The hypothesis of this study is, that the combination of sepsis and COVID-19 negatively affects clinical outcomes in critical ill patients.

2. Methods

2.1. Study design

This was a single-center, retrospective study performed at three surgical and medical intensive care units (ICU) at the University Hospital Dresden, Germany. This study was approved by the responsible Ethics Committee (BO-EK-374072021) and performed in accordance with the Declaration of Helsinki.

2.2. Study protocol

From February 2020 to March 2021, all ICU patients were screened for Sepsis and Septic Shock as defined by the International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) [1]. After informed consent, sepsis patients were enrolled in the Comprehensive Sepsis Center Dresden Kreischa registry. During the COVID pandemic, all ICU patients were additionally screened for SARS-CoV2 infection. COVID-19 patients were treated according to hospital guidelines for COVID-19, which was regularly updated based on the German guideline for COVID-19 [17] as well as the recommendations of the COVRIIN expert group of the Robert Koch Institute (RKI) [18]. Therefore, treatment of septic COVID-19 was not fully equal to treatment of patients with sepsis from other causes, other than COVID-19, being the main difference of administration of dexamethasone in all COVID-19 patients according to the results of the RECOVERY trial in July 2020 [19].

From sepsis diagnosis until hospital discharge, all sepsis patients were treated according to a standardized clinical pathway based on the German guideline for sepsis and septic shock. These guidelines are congruent with the Survival sepsis Campaign 2021 guidelines [16]. All adult ICU patients treated in the medical and surgical ICUs at the University Hospital Dresden were screened daily for eligibility. Patients were eligible if they were age \geq 18 years and diagnosed with

sepsis or septic shock according to Sepsis 3 definition [1]. Informed consent was obtained by the patient or a legal representative.

2.3. Data acquisition

All patients' data were recorded during the entire ICU stay during standard patient care using an electronic patient data management system (ORBIS, Dedalus, Bonn, Germany) as well as respective sub-systems (PDMS, ICM, Dräger Medical, Lübeck, Germany and ixserv, ixmid Software Technologie GmbH, Köln, Germany). SOFA score [20] and Charlson Comorbidity Index [21,22] were calculated using standardized protocols at day of ICU admission.

2.4. Laboratory analysis

Standard laboratory analyses were performed daily. Conventional analyses were performed using EDTA-tubes for complete blood cell count as well as citrate tubes for conventional coagulation tests. A serum collecting tube was used for measurements of inflammatory parameters, e.g. CRP and PCT. All standard laboratory tests were performed in the Institute for Laboratory Medicine at the University Hospital Dresden, according to standard procedures. Blood gas analysis was performed at the bedside using ABL Flex90 systems (Radiometer, Brønshøj, Denmark).

2.5. Statistical analyses

Statistical analyses were performed using SPSS Statistics 27 (IBM, Inc, Armonk, NY, U.S.) and R version 3.2.4. All categorical variables were described as absolute and relative frequencies; comparison between groups was done using Fisher's exact test. Continuous variables were presented as median and 1st / 3rd quartile; group comparison was based on the Mann-Whitney *U* test. Patient survival times after admission and on ICU, respectively, were analyzed using the Kaplan-Meier estimator. Associations between in-hospital mortality and risk factors were modeled using robust Poisson regression [23], which facilitates derivation of adjusted relative risks. In a first model specification adjustment for the patients' individual characteristics, i.e. age, sex, obesity, Charlson Comorbidity Index and SOFA score at ICU admission was performed. Primary outcome was defined as mortality during hospital stay. The precision of relative risk (RR) estimates was quantified using 95%-confidence intervals (CIs). Significance level was set at 0.05.

3. Results

3.1. Characteristics of the cohort

From February 2020 to March 2021, 191 patients with sepsis and 177 patients with sepsis and COVID-19 were enrolled in this study. These 177 sepsis patients with COVID-19 represented 94% of the total number of 188 COVID-19 treated in the ICUs of the University Hospital Dresden. Groups did not differ significantly regarding demographic data. COVID-19 patients had higher BMI (29 vs 27, $p < 0.05$) and Non-COVID sepsis patients had higher Charlson Comorbidity Index (4 vs 3 points, $p < 0.05$, Table 1).

In Non-COVID patients, different causes of sepsis were observed. Abdominal (35%), pulmonary (20%) and urogenital (12%) foci were most frequently diagnosed. In COVID-19 patients, sepsis was primarily related to a pulmonary focus in all cases. Blood stream infection was frequent in both groups (48% in COVID-19 septic patients, 53% in Non-COVID septic patients), while coagulase negative staphylococcus was the most frequently isolated pathogen. Only enterococcus was significantly more frequent in Non-COVID patients (14% vs 6%, $p < 0.05$), all other pathogens were comparable in both groups. Septic shock at ICU admission was present in 29% of all

Table 1
Patients ICU characteristics.

	Non-COVID	COVID-19	<i>p</i>
Demographics			
n	191	177	
Male [n]	138 (72%)	128 (72%)	<i>n.s.</i>
Age [years]	65 (55; 75)	67 (61; 73)	<i>n.s.</i>
Charlson Comorbidity Index	4 (2; 7)	3 (2; 5)	< 0.05
BMI [kg/m ²]	27 (24; 31)	29 (26; 33)	< 0.05
WHO Adipositas Scale			
Underweight [n]	3 (2%)	0	<i>n.s.</i>
Normal Weight [n]	65 (34%)	34 (19%)	<i>n.s.</i>
Overweight [n]	68 (36%)	67 (38%)	<i>n.s.</i>
Adipositas Grade I [n]	31 (16%)	39 (22%)	<i>n.s.</i>
Adipositas Grade II [n]	16 (8%)	24 (14%)	<i>n.s.</i>
Adipositas Grade III [n]	8 (4%)	13 (7%)	<i>n.s.</i>
Focus [n]			
Pulmonary	38 (20%)	177 (100%)	< 0.05
Abdominal	66 (35%)		<i>n.s.</i>
Urogenital	22 (12%)		<i>n.s.</i>
Device associated	17 (9%)		<i>n.s.</i>
Central Nervous System	3 (2%)		<i>n.s.</i>
Bone/Joint related	4 (2%)		<i>n.s.</i>
Skin or soft tissue related	20 (10%)		<i>n.s.</i>
Unknown	21 (10%)		<i>n.s.</i>
Blood Stream infection [n]			
β-Streptococcus	102 (53%)	85 (48%)	<i>n.s.</i>
Coagulase negative Staphylococcus	4 (2%)	0	<i>n.s.</i>
Enterococcus	43 (23%)	46 (26%)	<i>n.s.</i>
Klebsiella	26 (14%)	10 (6%)	< 0.05
Non-ferment microbes	14 (7%)	11 (6%)	<i>n.s.</i>
Serratia marescens	5 (3%)	11 (6%)	<i>n.s.</i>
Gram-negative microbes	2 (1%)	3 (2%)	<i>n.s.</i>
Proteus	22 (12%)	14 (8%)	<i>n.s.</i>
Yeast-like fungi	3 (2%)	0	<i>n.s.</i>
Yeast-like fungi	7 (4%)	7 (4%)	<i>n.s.</i>
Ventilation before ICU-admission			
non-invasive [d]	0 (0; 0)	2 (1; 3)	< 0.05
invasive [d]	0 (0; 0)	1 (0; 5)	< 0.05
ICU characteristics			
SOFA Score at ICU admission	9 (6; 13)	12 (10; 13)	< 0.05
Septic shock at ICU admission	82 (43%)	25 (14%)	< 0.05
Tracheostomy performed [n]	64 (34%)	80 (45%)	< 0.05
inhaled nitric oxide [n]	4 (2%)	61 (35%)	< 0.05
RRT [n]	56 (29%)	67 (38%)	<i>n.s.</i>
Duration RRT, only for patients under RRT [hours]	399 (107; 647)	155 (32; 311)	< 0.05
ECMO support [n]	9 (5%)	49 (28%)	< 0.05
Duration ECMO support, only for patients under ECMO therapy [hours]	165 (54, 245)	275 (179, 353)	<i>n.s.</i>
Non-invasive ventilation [n]	28 (15%)	39 (22%)	<i>n.s.</i>
Duration non-invasive ventilation, only for patients with non-invasive ventilation [days]	3 (2; 8)	3 (2; 5)	<i>n.s.</i>
Invasive ventilation [n]	107 (56%)	177 (100%)	< 0.05
Duration invasive ventilation, only for patients with invasive ventilation [days]	18 (7; 30)	12 (8; 17)	< 0.05
ICU stay [days]	12 (5; 28)	15 (10; 22)	<i>n.s.</i>
Hospital stay [days]	28 (13; 49)	17 (12; 25)	< 0.05
Laboratory parameters			
CRP maximum value [mg/L]	279 (190; 345)	267 (203; 345)	<i>n.s.</i>
PCT maximum value [ng/ml]	13 (3; 48)	3 (1; 11)	< 0.05
Leucocytes maximum value [Gpt/L]	23 (15; 30)	19 (15; 26)	< 0.05
Leucocytes minimum value [Gpt/L]	6 (4; 8)	7 (4; 9)	< 0.05
Lactate maximum value [mmol/ml]	3.3 (2.0; 7.4)	3.2 (2.2; 9.5)	<i>n.s.</i>

Table 1 (continued)

	Non-COVID	COVID-19	<i>p</i>
Demographics			
Platelets maximum value [Gpt/L]	358 (228; 484)	321 (258; 418)	<i>n.s.</i>
Platelets minimum value [Gpt/L]	88 (45; 167)	124 (64; 195)	< 0.05
Complications during ICU stay [n]			
Deep vein thrombosis	13 (7%)	56 (32%)	< 0.05
Pulmonary Embolism	5 (3%)	56 (32%)	< 0.05
Discharge from ICU [n]			
Deceased	40 (21%)	93 (53%)	< 0.05
Other ICU/IMC	25 (13%)	35 (19%)	<i>n.s.</i>
Rehab Hospital	38 (20%)	31 (18%)	<i>n.s.</i>
Other Hospital	4 (2%)	8 (5%)	<i>n.s.</i>
Standard Care Ward	82 (43%)	10 (5%)	< 0.05
At Home	2 (1%)	0	<i>n.s.</i>
Discharge from hospital [n]			
Deceased	56 (29%)	105 (59%)	< 0.05
Withdraw of care by patients will	42 (22%)	82 (46%)	< 0.05
Nursing home	7 (3%)	0	<i>n.s.</i>
Rehab Hospital	51 (27%)	54 (31%)	<i>n.s.</i>
Other Hospital	15 (8%)	9 (6%)	<i>n.s.</i>
At Home	65 (33%)	7 (4%)	< 0.05

Categorical variables were described as absolute and relative frequencies; comparison between groups was done using Fisher's exact test. Continuous variables were presented as median and 1st / 3rd quartile (Q1; Q3); group comparison was based on the Mann-Whitney *U* test.

CRP = C-Reactive Protein, ECMO = Extracorporeal Membrane Oxygenation, ICU = Intensive Care Unit, IMC = Intermediate Care Unit, PCT = Procalcitonin, RRT = Renal Replacement Therapy.

patients and occurred more frequently in Non-COVID septic patients (43% vs 14%, *p* < 0.05).

3.2. Survival and complications

Median in-hospital stay was 17 days in COVID-19 septic patients and 28 days in Non-COVID patients (*p* < 0.05). Overall in-hospital mortality for septic patients was 44% and was significantly higher in COVID-19 patients with 59% compared to 29% in Non-COVID patients (unadjusted RR=2.02, 95%-CI=1.57–2.60, *p* < 0.05, Fig. 1). Furthermore, COVID-19 septic patients suffered more from thromboembolic complications. Pulmonary Embolism was observed in 32% of COVID-19 patients and in 3% of Non-COVID septic patients (*p* < 0.05).

3.3. Characteristics of ICU treatment

All patients received antibiotic treatment as well as fluid administration and catecholaminergic support, to maintain mean blood pressure \geq 65 mmHg. 56% of Non-COVID patients received mechanical ventilation, while all COVID-19 patients were treated with invasive mechanical ventilation. Since September 2020, all COVID-19 patients were treated with dexamethasone (6 mg) for 10 days, while Non-COVID patients did not receive standardized corticosteroids. Dexamethasone was used in 90% of all septic COVID-19 patients (*n* = 160) and in no case of Non-COVID septic patients.

Progressive ARDS was more frequent in COVID-19 compared to Non-COVID patients with the need of inhaled nitric oxide (iNO) therapy (35% vs 2%, *p* < 0.05) and extracorporeal membrane oxygenation (28% vs 5%, *p* < 0.05) to obtain sufficient gas exchange. SOFA scores at ICU admission were increased in COVID-19 compared to Non-COVID patients (12 vs 9, *p* < 0.05), mainly due to higher rate of respiratory failure in COVID-19 septic patients. Renal replacement therapy (RRT) was frequently used in both groups (38% in COVID-19% and 29% in Non-COVID patients), but Non-COVID patients needed longer RRT support (*p* < 0.05). Furthermore, COVID-19 septic patients needed prolonged invasive mechanical ventilation (12 vs 3

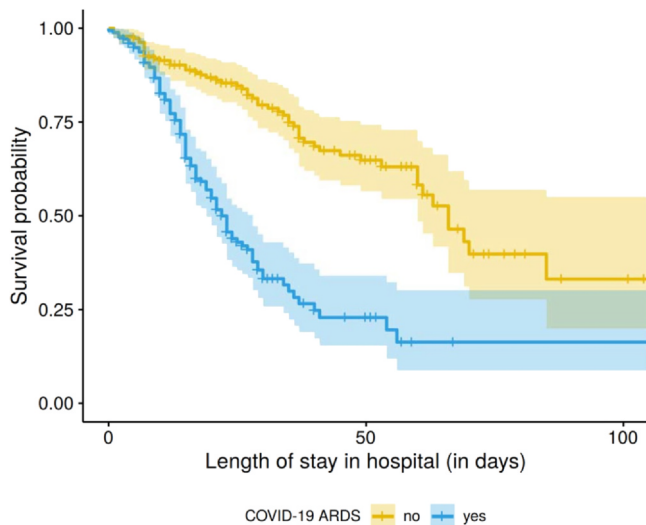


Fig. 1. Kaplan-Meier survival estimates with 95%-confidence intervals for septic patients with and without COVID-19 ARDS during hospital stay.

days, $p < 0.05$). Tracheostomy was more frequently performed in COVID-19 patients (45% vs 34%, $p < 0.05$) compared to patients with sepsis of other causes. Patients with sepsis without COVID-19 presented higher systemic inflammation according to maximum values of Leucocytes (23 vs 19 Gpt/L, $p < 0.05$) and PCT (13 vs 3 ng/ml, $p < 0.05$) compared to COVID-19 septic patients. ICU-stay did not differ significantly with 15 days in COVID-19 patients and 12 days in Non-COVID patients ($p = 0.060$). Only 47% of COVID-19 patients were discharged alive from ICU compared to 79% of Non-COVID septic patients (Fig. 2, $p < 0.05$).

3.4. Modeling of in-hospital mortality

Adjusted group comparisons were performed using a robust Poisson regression model (Table 2). Adjusting for the patients' individual characteristics resulted in a RR for in-hospital mortality of 1.74 (95%-CI=1.35–2.24) in the presence of COVID-19 compared to other septic patients. In a second model specification, ICU process characteristics, i.e. need of RRT / ECMO, invasive ventilation and occurrence of pulmonary embolism / deep vein thrombosis and maximum values of laboratory parameters, e.g. CRP, PCT and maximum value of leucocytes were included. Estimation of this model specification also indicated a significantly higher relative risk of in-hospital mortality for septic COVID-19 patients (RR=1.61, 95%-CI=1.23–2.12).

In addition to COVID-19 infection, the following risk factors were significantly related to in-hospital mortality: Age (RR per year of age=1.02, 95%-CI=1.00–1.03), PCT maximum value over 2 ng/ml (RR=1.64, 95%-CI=1.15–2.33), need or RRT (RR=1.49, 95%-CI=1.18–1.89), need for invasive mechanical ventilation (RR=2.38, 95%-CI=1.32–4.27) and septic shock present at ICU admission (RR=1.43, 95%-CI=1.12–1.82).

4. Discussion

4.1. Critical discussion of the findings

This study presents several important new findings that are highly relevant for patient care and risk stratification of patients with sepsis with and without COVID-19. First of all, it clearly indicates that COVID-19 is an independent risk factor for mortality in sepsis. Second, elderly patients with the need for invasive mechanical ventilation and RRT are at high risk for in-hospital mortality and

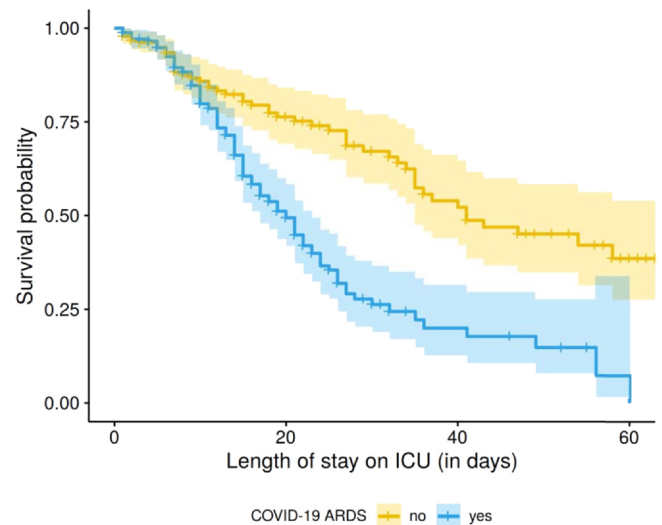


Fig. 2. Kaplan-Meier survival estimates with 95%-confidence intervals for septic patients with and without COVID-19 ARDS during ICU stay.

the maximum values of PCT during ICU and the presence of septic shock at ICU admission should be considered carefully for patients particularly at risk.

In the present study an overall in-hospital mortality of 44% in septic patients has been reported, which is comparable to previous results of large cohort studies [24]. Non-COVID septic patients showed favorable outcome with in-hospital mortality rate of 29% compared to septic COVID-19 patients (59%).

A standardized treatment pathway has been established for septic patients within the framework of the Comprehensive Sepsis Center Dresden Kreischa Registry. Considering the high complexity, morbidity and mortality of sepsis, early diagnosis and immediately treatment is the main goal in the acute phase (“frapper forte et frapper vite”) [25]. Septic patients in this study were treated according to a multidisciplinary and multisectoral pathway. This pathway includes standard operation procedures (SOP) for diagnostic measurements, antibiotic treatment and focus control (e.g. surgical intervention), as well as regular interdisciplinary specialist consulting to discuss microbiology and pharmacology issues. The pathway defines mandatory treatments, e.g. differentiated fluid and catecholamine therapy in case of septic shock in accordance with national and international sepsis guidelines [26]. Nonetheless, treatment of septic COVID-19 patients differs from treatment of Non-COVID patients in some points. Since the RECOVERY trial was published in July 2020 – showing lower 28-day mortality in hospitalized COVID-19 patients with administration of dexamethasone [19] – institutional guidelines changed including glucocorticoid administration in all COVID-19 ARDS patients. For Non-COVID patients there is no general recommendation for the use of glucocorticoids in septic patients in national guidelines [26], but some recent published large meta-analysis suggest also a benefit for adult patients with sepsis [27]. Since there is a lack of evidence further research is needed to investigate on this effect. This study is not powered on the effect of glucocorticoids in septic patients and therefore, the authors would not recommend to extrapolate any suggestion on the benefit of glucocorticoids in these patients.

Mortality in septic patients remains high with up to 40% in Germany wide studies [28], ranging from 26.7% for hospitalized to 41.9% for ICU patients [24]. However, a recent published multicenter trial from Australia and New Zealand reported quite lower in-hospital mortality up to 6.2% for septic patients, treated with a comprehensive pathway [29]. Assumable, mortality in septic patients depends on more other variables, e.g. occurrence of septic shock and

Table 2
Relative risk estimates from robust Poisson regressions with 95%-confidence intervals.

Risk factor	RR	95%-CI	RR	95%-CI	RR	95%-CI
COVID-19 ARDS (ref: no)						
yes	2.02 *	(1.57–2.60)	1.74 *	(1.35–2.24)	1.80 *	(1.12–2.90)
Age (in years)			1.02 *	(1.00–1.03)	1.02 *	(1.00–1.03)
Sex (ref: female)						
male			0.92	(0.72–1.19)	0.87	(0.69–1.11)
BMI (in kg/m ² ref: <35)						
35- < 40			0.81	(0.55–1.21)	0.86	(0.60–1.22)
40 +			1.10	(0.71–1.71)	1.06	(0.74–1.53)
Charlson Comorbidity Index			1.01	(0.96–1.06)	1.01	(0.96–1.06)
SOFA score			1.08 *	(1.04–1.12)	1.02	(0.99–1.05)
RRT (ref: no)						
yes					1.49 *	(1.18–1.88)
ECMO (ref: no)						
yes					1.18	(0.91–1.53)
Invasive ventilation (ref: no)						
yes					2.45 *	(1.36–4.41)
PE (ref: no)						
yes					1.09	(0.84–1.41)
DVT (ref: no)						
yes					1.02	(0.79–1.31)
CRP maximum value (in mg/L ref: <200)						
200–400					1.34	(0.98–1.84)
> 400					1.03	(0.69–1.53)
PCTmax (in ng/mlref: <2)						
> =2					1.62 *	(1.14–2.31)
Leucocytes minimum value_cat (in GPt/L ref: <=3.8)						
> 3.8					1.03	(0.77–1.39)
Leucocytes maximum value_cat (in GPt/L ref: <20)						
> =20					0.98	(0.78–1.24)
Septic schock (ref: no)						
yes					1.43 *	(1.12–1.81)
Other focus than pulmonary (ref: no)					1.17	(0.70–1.96)
yes						
Constant	0.29 *	(0.24–0.37)	0.05 *	(0.02–0.12)	0.02 *	(0.01–0.04)
n	368		368		368	

ARDS = Acute Respiratory Distress Syndrome, BMI = Body Mass Index, CRP = C - reactive protein, DVT = Deep Vein Thrombosis, ECMO = Extracorporeal Membrane Oxygenation, LAE = Intensive Care Unit, PE = Pulmonary Embolism, PCT = Procalcitonin, RRT = Renal Replacement Therapy.

RR = relative risk; CI = confidence interval; significance levels: * <5%.

significance of organ damage. This study reports about a severely ill patient cohort with mean SOFA score of 9 points for Non-COVID septic patients and occurrence of septic shock at ICU at admission of 43% resulting in an observed in-hospital mortality of 29%. Nine points in SOFA score predicts a mortality of > 33%, validated in large multicenter studies [30,31]. On the other hand, hospital mortality for septic shock is unlike higher approaching 40–60% [32]. Results from the current study reported Non-COVID septic patients are well comparable to current data in terms of mortality rate. The authors observed a slightly better than expected in-hospital mortality and hypothesize that increased survival in our patients might be due to the established multidisciplinary and multisectoral pathway. Severity of COVID-19 infection and a higher SOFA seem to be strongly associated [8]. In this context, it should be noted that platelet count and parameter of liver injury (bilirubin) and kidney disease (serum creatinine) are part of the SOFA score, which furthermore comprises ventilation (oxygenation index) and circulation-support parameters (use of vasoactive medication), as well as Glasgow Coma Score value which is decreased in critically ill patients due to sedation.

In the current study, in-hospital mortality was significantly higher in COVID-19 patients (59%) than in non-COVID sepsis patients (29%). This study reported median SOFA-score at ICU admission of 12 points for septic COVID-19 patients, predicting hospital mortality of 50% [30,31], which was significantly higher than in Non-COVID patients. COVID-19 cause severe lung injury making lung supportive therapy as invasive ventilation ($p < 0.05$), iNO ($p < 0.05$) and ECMO therapy ($p < 0.05$) more frequently necessary than in non-COVID septic patients. Therefore, multiple regression analysis to adjust for clinically relevant patient-individual and ICU characteristics,

including SOFA score were performed. In these analyses, COVID-19 has been identified as independent risk factor for higher in-hospital mortality (RR=1.61, 95%-CI=1.23–2.12) after risk adjustment. This result indicates that COVID-19 infection leading to ARDS and septic syndrome is more fatal than septic syndrome of other etiology. This is in line with the high number of reported deaths leading to ICU mortality up to 84.6%[33] and approximately 49% [5] and 53.4% [34] reported in larger cohort studies - even if sepsis was not present or not diagnosed. Mortality in COVID-19 caused ARDS patients seems to be higher than in seasonal influenza caused ARDS patients [35]. Besides, deep vein thrombosis and pulmonary embolism were significantly more frequent in septic COVID-19 patients. Other studies identified the occurrence of pulmonary embolism as a single risk factor for mortality in COVID-19 patients [36]. These findings reflect the clinical rational, that PE is associated with a higher risk of death up to 30% if untreated and up to 10–15% under treatment [37]. However, statistical analysis for this cohort did not result in a significantly higher risk of in-hospital mortality if PE or DVT was diagnosed. The authors might hypothesize, that the increased anticoagulation therapy in COVID-19 patients might not prevent from DVT/PE, but might protect patients from early death. According to current clinical standards, all COVID-19 ICU patients received sub-therapeutic dose of heparin compared to only prophylactic dose in Non-COVID patients. If PE or DVT was diagnosed, all patients were treated with therapeutic anticoagulation, if no contraindications existed. Miró et al. showed in a recent published study, that PE in COVID-19 patients was associated with less severity than in Non-COVID patients [38]. This could also be an explanation for the missing relevance of PE for mortality in our cohort.

In septic patients, bacterial or fungal blood stream infection could be detected in 53%, but also co-infection or superinfection was present in 48% of COVID-19 septic patients in this study. Compared to recent studies, this is higher than expected. Da Silva Ramos et al. reported in their review an incidence ranging from 5.9% in hospitalized to 8.1% in critical ill patients up to a pooled incidence of 17% in ICU patients [39]. Despite this fact, over 70% received antibiotic therapy, speculating non-accurate detection of bacterial infection or overuse [39]. However, early results from Wuhan in January 2020 suggested that non-survivors presented significant higher rates of co-infections up to 50% [7]. Therefore, co-infections should be carefully monitored and immediately addressed. Grasselli et al. reported in 2020 a high incidence of hospital acquired infections (HAI) in COVID-19 patients with 46% and multidrug-resistant bacteremia in already 35% [40]. COVID-19 patients with septic shock following HAI were prone to decrease by double, which is comparable to our findings. Furthermore, patients with the need of RRT and mechanical ventilation showed worse outcome in this study. Karagiannidis et al. reported in 2020 an in-hospital mortality in COVID-19 patients with the need of RRT and invasive ventilation of 73% [5] and recent data from Brazilian nationwide surveillance database reported mortality up 80% in mechanical ventilated patients [41]. However, structural differences between Brazilian and German health care organization and capacities during the pandemic should be considered. The finding from the current study suggests that PCT values over the cut-off of 2 ng/ml correlate with worse outcome. In accordance, Tang et al. highlighted in a study in 2020 the importance for IL-6 and PCT measurement as predictive biomarkers for COVID-19 severity [42]. Furthermore, a recently published multicenter COVID-19 cohort study identified higher PCT, CRP and interleukin-6 values as three out of ten most important predictive values for ICU mortality by machine learning model in 1039 patients [43].

4.2. Study limitations

As this is an observational study, it faces all the limitations associated with this type of analyses. Mainly considering the observational study design, the results of this analysis are prone to be misinterpreted as confounders were not measured in a controlled way compared to prospective trials. The authors observed different variations in patient characteristics and quantities that are likely to influence the prognosis. This study may observe a selection bias, since COVID-19 patients were specifically transferred to the University Hospital Dresden as tertiary referral center for differentiated lung support and ECMO therapy.

5. Conclusion

In-hospital mortality was significantly increased in septic COVID-19 patients compared to septic Non-COVID patients while pre-hospital patients' characteristics were comparable between both groups. ICU characteristics differed related to the various causes of sepsis in Non-COVID patients. However, regression-based adjustment indicates that COVID-19 infection can be considered as an independent risk factor for higher mortality in septic patients. The need of invasive ventilation and renal replacement therapy as well as the presence of septic shock and PCT values over 2 ng/ml should be considered to identify patients at risk for in-hospital mortality in septic patients.

Ethics approval and consent to participate

All procedures were performed in accordance with the ethical standards of the institution and the Helsinki Declaration. The

Dresden University Ethics Committee approved this retrospective study (BO-EK-374072021).

Funding

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

CRediT authorship contribution statement

LH – study design, conducting research, drafting the paper including critical revisions. SH – conducting research, collection of clinical data. AG - study design, conducting research, revising the paper, PP – collection of clinical data. MR – conducting research, revising the paper. JS – critical contributions. RS – clinical management, critical contributions. HCH – clinical management, critical contributions. JM – critical contributions. UB – revising the draft, critical contributions. MR – clinical management, critical contributions. TK – revising the draft, critical contributions. PMS – supervision, drafting and revising the paper. All authors read and approved the final manuscript.

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 Competing Interest

None of the authors has a conflict of interest to declare. Unrelated to this study, JS received institutional funding for IITs from Sanofi, Novartis, ALK, and Pfizer, and acted as a consultant for Sanofi, Lilly, Novartis and ALK.

Acknowledgement

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

Consent for publication

Not applicable.

References

- [1] Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *Jama* 2016;315(8):801–10.
- [2] Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, et al. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. *Lancet* 2020;395(10219):200–11.
- [3] Schmidt K, Gensichen J, Fleischmann-Struzek C, Bahr V, Pausch C, Sakr Y, et al. Long-term survival following sepsis. *Dtsch Arztebl Int* 2020;117(46):775–82.
- [4] Prescott HC, Osterholzer JJ, Langa KM, Angus DC, Iwashyna TJ. Late mortality after sepsis: propensity matched cohort study. *Bmj* 2016;353:i2375.
- [5] Karagiannidis C, Mostert C, Hentschker C, Voshaar T, Malzahn J, Schillinger G, et al. Case characteristics, resource use, and outcomes of 10 021 patients with COVID-19 admitted to 920 German hospitals: an observational study. *Lancet Respir Med* 2020;8(9):853–62.
- [6] Wolff D, Nee S, Hickey NS, Marschollek M. Risk factors for Covid-19 severity and fatality: a structured literature review. *Infection* 2021;49(1):15–28.
- [7] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054–62.
- [8] Yang Z, Hu Q, Huang F, Xiong S, Sun Y. The prognostic value of the SOFA score in patients with COVID-19: A retrospective, observational study. *Medicine (Baltimore)* 2021;100(32):e26900.

- [9] Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. *Kidney Int* 2020;97(5):829–38.
- [10] Shao M, Li X, Liu F, Tian T, Luo J, Yang Y. Acute kidney injury is associated with severe infection and fatality in patients with COVID-19: A systematic review and meta-analysis of 40 studies and 24,527 patients. *Pharmacol Res* 2020;161:105107.
- [11] Li X, Xu S, Yu M, Wang K, Tao Y, Zhou Y, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. *J Allergy Clin Immunol* 2020;146(1):110–8.
- [12] Danwang C, Endomba FT, Nkeck JR, Wouna DLA, Robert A, Noubiap JJ. A meta-analysis of potential biomarkers associated with severity of coronavirus disease 2019 (COVID-19). *Biomark Res* 2020;8:37.
- [13] Lippi G, Plebani M. Procalcitonin in patients with severe coronavirus disease 2019 (COVID-19): a meta-analysis. *Clin Chim Acta* 2020;505:190–1.
- [14] Zeng Z, Yu H, Chen H, Qi W, Chen L, Chen G, et al. Longitudinal changes of inflammatory parameters and their correlation with disease severity and outcomes in patients with COVID-19 from Wuhan, China. *Crit Care* 2020;24(1):525.
- [15] Sokolowska M, Lukasik ZM, Agache I, Akdis CA, Akdis D, Akdis M, et al. Immunology of COVID-19: Mechanisms, clinical outcome, diagnostics, and perspectives—A report of the European Academy of Allergy and Clinical Immunology (EAACI). *Allergy* 2020;75(10):2445–76.
- [16] Alhazzani W, Evans L, Alshamsi F, Möller MH, Ostermann M, Prescott HC, et al. Surviving sepsis campaign guidelines on the management of adults with coronavirus disease 2019 (COVID-19) in the ICU: first update. *Critical Care Medicine* 2021;49(3):e219–34.
- [17] Kluge S, Janssens U, Welte T, Weber-Carstens S, Schälte G, Salzberger B, et al. Recommendations for treatment of critically ill patients with COVID-19: Version 3 S1 guideline. *Der Anaesthetist* 2020:1–11.
- [18] Koch-Institut SAdK-uBfKdHEaR. Hinweise zu Erkennung, Diagnostik und Therapie von Patienten mit COVID-19. Online Ressource, 13082021: (https://www.rki.de/DE/Content/Kommissionen/Stakob/Stellungnahmen/Stellungnahme-Covid-19_Therapie_Diagnose.html), 2021.
- [19] Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, et al. Dexamethasone in Hospitalized Patients with Covid-19. *The New England journal of medicine* 2021;384(8):693–704.
- [20] Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 1996;22(7):707–10.
- [21] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40(5):373–83.
- [22] Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, et al. Updating and validating the charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol* 2011;173(6):676–82.
- [23] Zou G. A Modified Poisson Regression Approach to Prospective Studies with Binary Data. *Am J Epidemiol* 2004;159(7):702–6.
- [24] Fleischmann-Struzek C, Mellhammar L, Rose N, Cassini A, Rudd KE, Schlattmann P, et al. Incidence and mortality of hospital- and ICU-treated sepsis: results from an updated and expanded systematic review and meta-analysis. *Intensive Care Med* 2020;46(8):1552–62.
- [25] Ehrlich P. Address in Pathology, ON CHEMOTHERAPY: delivered before the Seventeenth International Congress of Medicine. *Br Med J* 1913;2(2746):353–9.
- [26] Leitlinie. AdWMFA-SK. S3-Leitlinie Sepsis - Prävention, Diagnose, Therapie und Nachsorge. Online Ressource Verfügbar: (https://www.wmf.org/uploads/tx_szeitlinien/079-001k_S3_Sepsis-Prävention-Diagnose-Therapie-Nachsorge_2020-02.pdf) (Zugriff am 150621). 2018.
- [27] Fang F, Zhang Y, Tang J, Lunsford LD, Li T, Tang R, et al. Association of corticosteroid treatment with outcomes in adult patients with sepsis: a systematic review and meta-analysis. *JAMA internal medicine* 2019;179(2):213–23.
- [28] Fleischmann-Struzek C, Mikolajetz A, Schwarzkopf D, Cohen J, Hartog CS, Pletz M, et al. Challenges in assessing the burden of sepsis and understanding the inequalities of sepsis outcomes between National Health Systems: secular trends in sepsis and infection incidence and mortality in Germany. *Intensive Care Med* 2018;44(11):1826–35.
- [29] Keijzers G, Macdonald SP, Udy AA, Arendts G, Bailey M, Bellomo R, et al. The Australasian Resuscitation In Sepsis Evaluation: Fluids or vasopressors in emergency department sepsis (ARISE FLUIDS), a multi-centre observational study describing current practice in Australia and New Zealand. *Emerg Med Australas* 2020;32(4):586–98.
- [30] Cárdenas-Turanzas M, Ensor J, Wakefield C, Zhang K, Wallace SK, Price KJ, et al. Cross-validation of a Sequential Organ Failure Assessment score-based model to predict mortality in patients with cancer admitted to the intensive care unit. *J Crit Care* 2012;27(6):673–80.
- [31] Ferreira FL, Bota DP, Bross A, Mélot C, Vincent JL. Serial evaluation of the SOFA score to predict outcome in critically ill patients. *Jama*. 2001;286(14):1754–8.
- [32] Cecconi M, Evans L, Levy M, Rhodes A. Sepsis and septic shock. *The Lancet* 2018;392(10141):75–87.
- [33] Armstrong RA, Kane AD, Cook TM. Outcomes from intensive care in patients with COVID-19: a systematic review and meta-analysis of observational studies. *Anaesthesia*. 2020;75(10):1340–9.
- [34] Grasselli G, Greco M, Zanella A, Albano G, Antonelli M, Bellani G, et al. Risk factors associated with mortality among patients with COVID-19 in intensive care units in Lombardy, Italy. *JAMA Intern Med* 2020;180(10):1345–55.
- [35] Piroth L, Cottenet J, Mariet AS, Bonniaud P, Blot M, Tubert-Bitter P, et al. Comparison of the characteristics, morbidity, and mortality of COVID-19 and seasonal influenza: a nationwide, population-based retrospective cohort study. *Lancet Respir Med* 2021;9(3):251–9.
- [36] Scudiero F, Silverio A, Di Maio M, Russo V, Citro R, Personeni D, et al. Pulmonary embolism in COVID-19 patients: prevalence, predictors and clinical outcome. *Thrombosis research* 2021;198:34–9.
- [37] Maestre Peiró A, González Gasch A, Monreal, Bosch M. Update on the risk stratification of acute symptomatic pulmonary thromboembolism. *Rev Clin Esp (Barc)* 2017;217(6):342–50.
- [38] Miró Ò, Jiménez S, Llorens P, Roussel M, Gorlicki J, García-Lamberechts EJ, et al. Pulmonary embolism severity and in-hospital mortality: An international comparative study between COVID-19 and non-COVID patients. *Eur J Intern Med* 2022.
- [39] da Silva Ramos FJ, de Freitas FGR, Machado FR. Sepsis in patients hospitalized with coronavirus disease 2019: how often and how severe? *Current Opinion in Critical Care* 2021;27(5):474–9.
- [40] Grasselli G, Scaravilli V, Mangioni D, Scudeller L, Alagna L, Bartoletti M, et al. Hospital-acquired infections in critically ill patients with COVID-19. *Chest*. 2021.
- [41] Ranzani OT, Bastos LSL, Gelli JGM, Marchesi JF, Baião F, Hamacher S, et al. Characterisation of the first 250,000 hospital admissions for COVID-19 in Brazil: a retrospective analysis of nationwide data. *Lancet Respir Med* 2021;9(4):407–18.
- [42] Tang J, Lin J, Zhang E, Zhong M, Luo Y, Fu Y, et al. Serum IL-6 and procalcitonin are two promising novel biomarkers for evaluating the severity of COVID-19 patients. *Medicine* 2021;100(22). e26131-e.
- [43] Magunia H, Lederer S, Verbuecheln R, Gilot BJ, Koeppen M, Haeberle HA, et al. Machine learning identifies ICU outcome predictors in a multicenter COVID-19 cohort. *Crit Care* 2021;25(1):295.