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ORIGINAL

COVID-19 increased the risk of ICU-acquired bloodstream infections: a case–cohort study from the multicentric OUTCOMEREA network

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Abstract

Purpose: The primary objective of this study was to investigate the risk of ICU bloodstream infection (BSI) in critically ill COVID-19 patients compared to non-COVID-19 patients. Subsequently, we performed secondary analyses in order to explain the observed results.

Methods: We conducted a matched case-cohort study, based on prospectively collected data from a large ICU cohort in France. Critically ill COVID-19 patients were matched with similar non-COVID-19 patients. ICU-BSI was defined by an infection onset occurring > 48 h after ICU admission. We estimated the effect of COVID-19 on the probability to develop an ICU-BSI using proportional subdistribution hazards models.

Results: We identified 321 COVID-19 patients and 1029 eligible controls in 6 ICUs. Finally, 235 COVID-19 patients were matched with 235 non-COVID-19 patients. We observed 43 ICU-BSIs, 35 (14.9%) in the COVID-19 group and 8 (3.4%) in the non-COVID-19 group ($p \leq 0.0001$), respectively. ICU-BSIs of COVID-19 patients were more frequently of unknown source (47.4%). COVID-19 patients had an increased probability to develop ICU-BSI, especially after 7 days of ICU admission. Using proportional subdistribution hazards models, COVID-19 increased the daily risk to develop ICU-BSI (sHR 4.50, 95% CI 1.82–11.16, $p = 0.0012$). Among COVID-19 patients ($n = 235$), a significantly increased risk for ICU-BSI was detected in patients who received tocilizumab or anakinra (sHR 3.20, 95% CI 1.31–7.81, $p = 0.011$) but not corticosteroids.

Conclusions: Using prospectively collected multicentric data, we showed that the ICU-BSI risk was higher for COVID-19 than non-COVID-19 critically ill patients after seven days of ICU stay. Clinicians should be particularly careful on late ICU-BSIs in COVID-19 patients. Tocilizumab or anakinra may increase the ICU-BSI risk.

Keywords: COVID-19, SARS-CoV-2, ICU, Bloodstream infection, Hospital-acquired

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Introduction

The rapid spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the world led to more than one million deaths at the end of September 2020 [1]. Admission in intensive care unit (ICU) is required for 20% of patients with coronavirus disease 2019 (COVID-19) due to acute respiratory distress syndrome (ARDS) [2]. ICU patients are susceptible to hospital-acquired infections and, more specifically, ICU-acquired bloodstream infections (ICU-BSI) [3] are associated with an increased morbidity and mortality [4]. Although bacterial co-infections at hospital admission are infrequently observed [5], ICU patients with COVID-19 seem more prone to develop bacterial co-infections [6]. However, whether this attributable risk is due to the viral infection or to the critical illness is, to date, not fully elucidated [7]. Indeed, data on ICU-BSI in critically ill COVID-19 patients are scant [8, 9]. We supposed that COVID-19 may impact the risk of ICU-BSI. The primary objective of this study was to investigate the risk of ICU-BSI matching COVID-19 and non-COVID-19 critically ill patients using a large cohort of ICU in France. Subsequently, we performed secondary analyses in order to explain the observed results.

Take-home message

ICU-BSI risk is higher for COVID-19 than non-COVID-19 critically ill patients after 7 days of ICU-stay.

Clinicians should be particularly careful on late ICU-BSIs in COVID-19 patients.

Material and methods

Study design and data sources

We conducted a matched case-cohort study, based on the OutcomeRea™ database, a large French ICU cohort. We prospectively collected data on admission features and diagnosis, daily disease severity, iatrogenic events, nosocomial infections, and vital status. Moreover, during the COVID-19 pandemic, several specific clinical and biological data for the COVID-19 patients were prospectively recorded. Results of blood culture, data on microorganism identification and its susceptibility profile, source of infection, and the antimicrobials administered were prospectively collected. Further details on data collection and quality were described elsewhere [10]. The OutcomeRea™ database was declared to the "Commission Nationale de l'Informatique et des Libertés" (#999,262), in accordance with French law, and this study was approved by the institutional review board of Clermont-Ferrand. Informed consent was not required because the study did not modify patients' management and the data were anonymously collected.

Study population

Only ICUs including COVID-19 and non-COVID-19 patients were included for the current analysis. All COVID-19 patients were adult (≥ 18 years) admitted from January 29, 2020, to 3rd October. Non-COVID-19 patients were selected from September 7, 2012, to April 6, 2020. All patients had an acute respiratory distress syndrome (ARDS) requiring mechanical ventilation. We excluded patients with an ICU hospitalization duration lasting < 48 h. Patients transferred with BSI were excluded. The follow-up started at ICU admission until hospital discharge or death.

Definitions

All COVID-19 patients had a laboratory (real time-PCR) microbiologically confirmed SARS-CoV-2 infection. Ankinra (100 mg/L) was usually administered for five days and tocilizumab was prescribed with a maximal dose of 8 mg/kg. Knaus scale definitions were used to record preexisting chronic organ failures (including respiratory, cardiac, hepatic, renal replacement therapy) [11, 12].

ICU-BSI was defined by an infection onset occurring > 48 h after ICU admission. Typical skin contaminants (e.g., coagulase-negative Staphylococcus [CoNS]) bacteremias were included only if ≥ 2 blood cultures showed the same phenotype on separate occasions within a 48-h period, or ≥ 1 blood culture positive for clinical sepsis, no other infectious process, and antibacterial agent treatment initiated by the attending physician [13, 14]. Polymicrobial ICU-BSI was defined by the identification of several species microorganisms from one blood culture, with clinical evidence that all species were from the same primary focus of infection [15]. ICU-BSI source was classified as unknown if no source of infection was identified. Secondary BSI was defined by the identification of the same microorganism in one blood culture and in the suspected source of infection. All ICU-BSIs were critically reviewed by two investigators (NB and JFT). All catheter-related BSI (CRBSI) were documented by quantitative tip culture [16] and followed French and American definitions [17, 18]. Catheter tip cultures were routinely performed in all ICUs. Solely the first ICU-BSI was included in the statistical analysis.

Statistical analyses

Characteristics of patients were described as median (interquartile range) or count (percent) for qualitative and quantitative variables, respectively. Matched groups were compared using McNemar, Bowker and

Wilcoxon signed rank tests, as appropriate. Non-matched groups were compared with Chi-square, Fisher and Wilcoxon tests, as appropriate.

We used a matched-cohort approach to select patients and an optimal matching without replacement was performed. The following matching criteria were selected in order (1) to exclude factors that could influence BSI and (2) to create a similarly population between COVID-19 and non-COVID-19 patients: ICU, admission category (medical versus surgical), age, sex, SOFA score and intubation in the two first ICU days. To assess the quality of matching, we computed standardized mean differences (SMD) for each variable. Thresholds of ≥ 0.20 for SMDs were used to identify potentially important imbalances, with smaller SMDs indicating a better balance between patient groups.

In our matched population, the effect of COVID-19 on the probability to develop a BSI was estimated using proportional subdistribution hazards models (Fine and Gray models) [19]. Time zero (T0) was the ICU admission. Patients who have not experienced ICU-BSI at the end of follow-up were censored. To determine the risk of BSI the fundamental assumption is that censoring is not associated with an altered chance of the event occurring at any given moment. In the current analysis, death and ICU discharge were considered as competing events. The risk of COVID-19 (versus non-COVID-19) was then estimated using Cox proportional subdistribution hazards models stratifying by matched pairs. Proportionality of hazard risk was tested graphically. Risk of ICU-BSI was expressed in subdistribution hazard ratios (sHR): a $sHR > 1$ indicated an increased risk for ICU-BSI.

We conducted several additional/explanatory analyses. First, we performed an additional analysis adjusting for antibiotics received in the first two days after ICU admission. Second, we performed a sensitivity analysis using only controls from 2015 onwards. Third, we performed an additional confirmatory analysis using propensity score matching (Greedy matching, see electronic supplementary material [ESM] for supplementary information on this method). Fourth, we used the endpoint CRBSI instead of ICU-BSI in order to evaluate the impact of COVID-19 on this healthcare associated infections. Third, we performed a sub-analysis of COVID-19 patients (i.e., excluding non-COVID-19 patients) to evaluate the effect of corticosteroids or IL-antagonists (i.e., tocilizumab or anakinra) on ICU-BSI using proportional subdistribution hazards models.

p Values < 0.05 were considered to be significant. Statistical analyses were performed using SAS 9.4 (Cary, North Carolina, USA).

Results

Unmatched and matched patients

In the OutcomeRea™ database, we identified 321 COVID-19 patients from six ICUs from March 2020 to September 18, 2020, and 1029 eligible controls from September 7, 2012, to October 3, 2020. Finally, 235 COVID-19 patients from six ICUs could be matched with 235 controls according to the predefined criteria (Fig. 1). A comparison between unmatched and matched COVID-19 patients is showed in the ESM Table E1. Overall, matched and unmatched COVID-19 patients were similar; however, matched COVID-19 patients were more often male (80% versus 65%, $p = 0.0057$) and had slightly higher median SOFA score (5 versus 4, $p = 0.0092$).

The characteristics of unmatched and matched cohorts are illustrated in Table 1. Overall, matched COVID-19 and non-COVID-19 were well-balanced (graphical illustration of SMD in the ESM, Figure E1). In the matched population overall, the mean age was 59.8 (SD 13.2) and 80% ($n = 376$) of patients were male. Of note, antibiotics at ICU admission were more frequently administered in COVID-19 patients (79% versus 68%, $p = 0.006$).

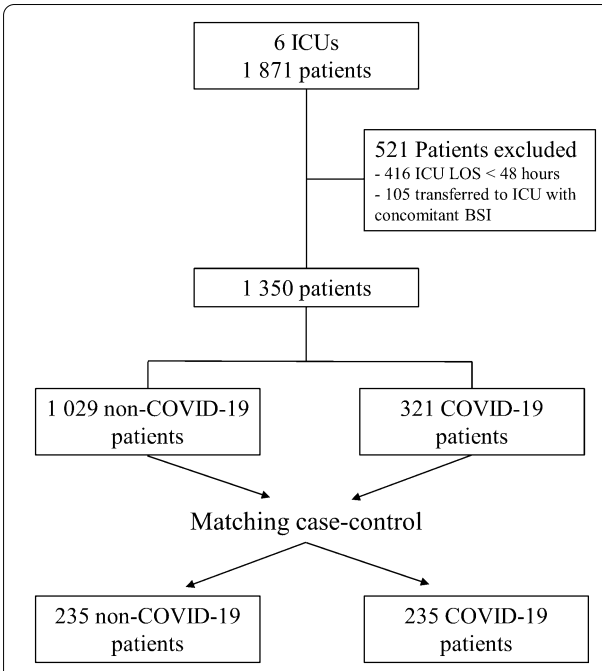

Fig. 1 Flowchart. *ICU* intensive care unit, *LOS* length of stay, *BSI* bloodstream infection

Table 1 Description of unmatched and matched COVID-19 and non-COVID-19 critically ill patients

	Unmatched			Matched		
	Non-COVID-19 $n=1029$	COVID-19 $n=321$	SMD	Non-COVID-19 $n=235$	COVID-19 $n=235$	SMD
Age, mean (std)	62.2 (15.8)	60.2 (13.4)	0.141	59.8 (13.8)	59.8 (12.7)	0.001
Sex, male, %	62.2	76	0.302	80	80	0.000
Admission category, medical admission, %	84.9	99.1	0.539	98.7	98.7	0.000
SOFA score, mean (std)	5.9 (4.6)	5.4 (3.5)	0.129	5.8 (3.6)	5.7 (3.7)	0.042
SAPS II, mean (std)	43 (19.9)	35.8 (17.7)	0.380	38.2 (19.6)	37.4 (18.3)	0.042
Invasive mechanical ventilation ICU days 1–2, %	42.8	42.7	0.002	46.4	46.4	0.000
Antibiotics ICU days 1–2, %	61.7	79.4	0.396	67.7	79.1	0.262
PaO_2/FIO_2, mean (std)	222.8 (137)	252 (293.5)	0.127	260 (142.4)	245.5 (262.4)	0.069
≥ 1 chronic comorbidity, %	49.7	41.4	0.166	49.8	43	0.137
Chronic cardiac comorbidity*, %	23.9	29	0.115	22.6	31.1	0.193
Chronic respiratory failure*, %	17.6	12.1	0.153	19.1	13.2	0.162
Chronic renal failure*, %	11	9.7	0.043	9.8	10.2	0.014
Immunosuppression*, %	18.3	11.8	0.180	16.6	12.3	0.121

SMD standardized mean differences, *SOFA* Sepsis-related Organ Failure Assessment, *SAPS* Simplified Acute Physiology Score

*According to the Knaus' definitions

Table 2 Outcomes in the matched population

	Non-COVID-19 ($n=235$)	COVID-19 ($n=235$)	*p* value
Length of stay ICU, mean days [IQR]	6 [4; 11]	9 [5; 20]	<0.0001
ICU-BSI, *n* (%)	8 (3.4)	35 (14.9)	<0.0001
Time between ICU admission and BSI, median days [IQR]	6.5 [5; 12.5]	12 [9; 16]	0.086[§]
Mortality day-60, *n* (%)	38 (16.2)	84 (35.7)	<0.0001
Mortality day-60 among BSIs, *n* (%)	2 (25.0)	25 (71.4)	0.037[§]

Groups were compared using McNemar, Bowker and Wilcoxon signed rank test, as appropriate

ICU intensive care unit, *BSI* bloodstream infection

[§] Wilcoxon or Fisher tests, as appropriate

Bloodstream infections

We observed 43 ICU-BSIs, eight (3.4%) were in the non-COVID-19 group and 35 (14.9%) in the COVID-19 group ($p \leq 0.0001$, Table 2), respectively. ICU-BSIs among COVID-19 patients occurred in median 12 (IQR 9–16) days after ICU admission (versus 6.5 days [IQR 5–12.5] for non-COVID-19 patients, $p=0.086$). Among COVID-19 patients, the median time between Symptoms' onset and ICU-BSI was 20 days (IQR 17–30). Eighty-four (35.7%) and 38 (16.2%) patients died at 60-day in the COVID-19 and non-COVID-19 groups ($p \leq 0.0001$), respectively. Using graphical description, we observed that COVID-19 patients had an increased probability to develop ICU-BSI, especially from the 7th day after ICU admission (Fig. 2). Using proportional subdistribution hazards models, COVID-19 increased the daily risk to develop ICU-BSI (sHR 4.50, 95% CI [confidence interval] 1.82–11.16, $p=0.0012$). The proportionality of hazard was not respected and the risk of ICU-BSI significantly increased after day 7 from ICU admission. After introducing a time-dependent variable, we estimated a sHR for COVID-19 of 8.74 at Day 7. After adjustment for antibiotics received in the first two days after ICU admission, we observed similar results (sHR 5.03, 95% CI 1.91–13.29, $p=0.001$). A sensitivity analysis excluding controls recruited from 2012 to 2014 showed similar results (sHR 3.00, 95% CI 1.23–7.34, $p=0.016$). Among microorganisms detected in ICU-BSI, CoNS and enterococci tended to be more frequently observed in the COVID-19 group (Table 3). In the COVID-19 group, the source of infection was more frequently unknown (Table 3). Among unknown sources of infection, we observed more bacteria that live in the digestive tract in COVID-19 patients,

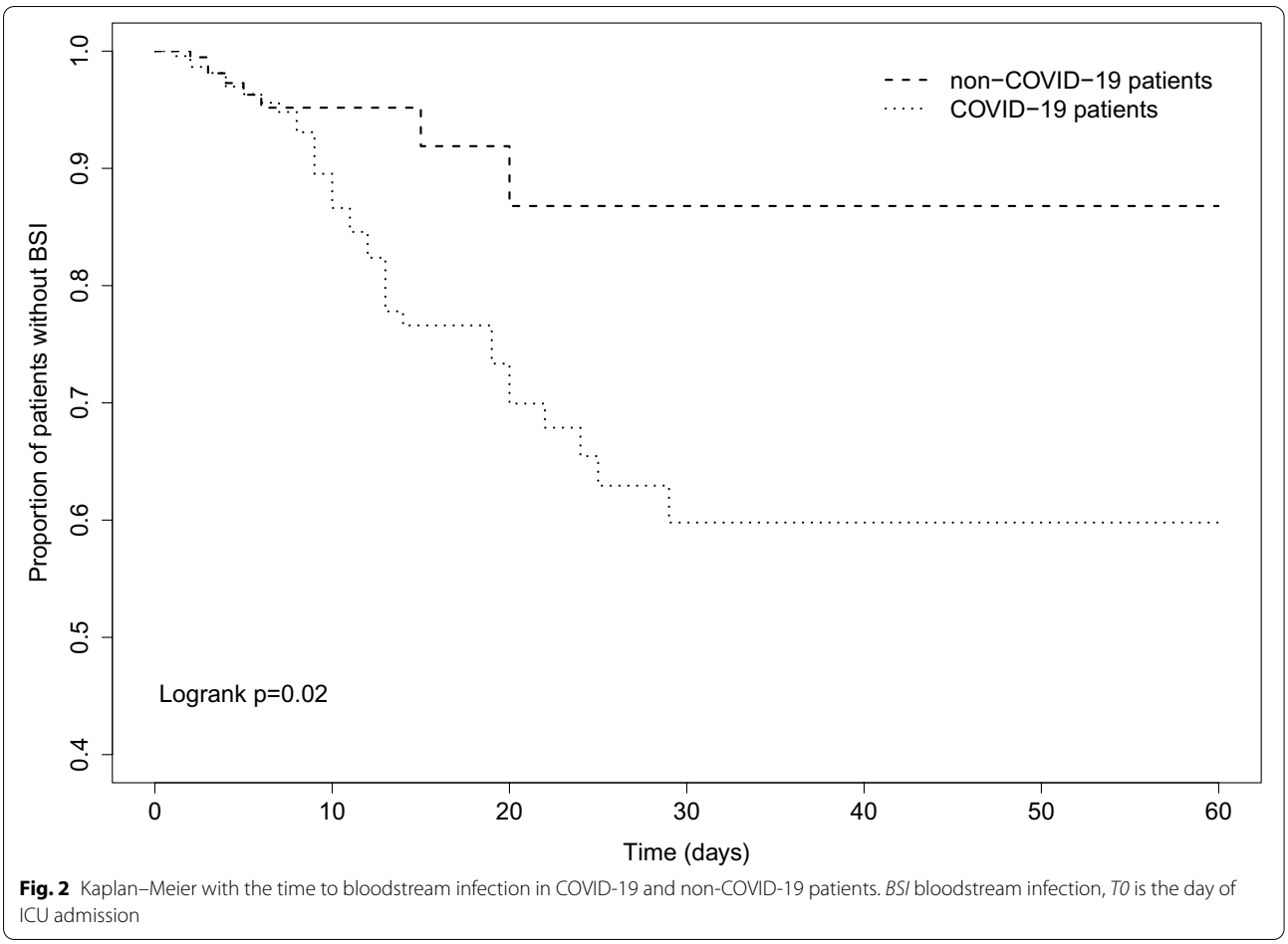

Fig. 2 Kaplan–Meier with the time to bloodstream infection in COVID-19 and non-COVID-19 patients. *BSI* bloodstream infection, *T0* is the day of ICU admission

whereas CoNS were more frequently detected in non-COVID-19 patients (ESM Table E2).

Using a propensity score Greedy matching method, the characteristics of unmatched ($n=1350$) and matched cohorts ($n=554$) are illustrated in Table E3 (ESM). Of note, SOFA score was higher in the non-COVID-19 group. Using proportional subdistribution hazards models, COVID-19 increased the daily risk to develop ICU-BSI (sHR 2.11, 95% CI 1.16–3.83, $p=0.014$).

Explanatory analyses

Overall, we observed 10 CRBSIs, 2 (0.9%) in the non-COVID-19 group and 8 (3.4%) in the COVID-19 group (Table 3). The COVID-19 status was not associated with a statistically significant increase of CRBSI risk in our matched population (sHR 2.50, 95% CI 0.71–8.83, $p=0.15$). However, among all ICU-BSI episodes, the mean CVC duration was 11.6 (standard deviation [std] 6.2) and 8.7 (std 6.6) in the COVID-19 and non-COVID-19 group, respectively.

Among COVID-19 patients ($n=235$), 21 and 9 patients received anakinra and tocilizumab, respectively. We observed a significantly increased risk for ICU-BSI in patients who received tocilizumab or anakinra (sHR 3.20, 95% CI 1.31–7.81, $p=0.011$), whereas corticosteroids administered in the first two ICU days did not show statistically significant ICU-BSI risk (HR 0.85, 95% CI 0.39–1.84, $p=0.67$). Interestingly the risk for BSI was marginally increased for ankinra (sHR 2.54, 95% CI 0.96–6.73, $p=0.061$) and tocilizumab (sHR 2.87, 95% CI 1.06–7.77, $p=0.038$).

Discussion

Using high-quality prospectively collected data from several ICUs, we showed that the daily hazard rate of ICU-BSI in critically ill COVID-19 patients was increased, especially from seven days after ICU admission. This risk was associated with the use of IL-1 or IL-6 receptors antagonists in critically ill COVID-19 patients.

Although data on superinfections in COVID-19 patients are available, BSI data in critically ill COVID-19 patients are scarce. A systematic review and meta-analysis of observational studies showed that COVID-19 critically ill patients had more frequently bacterial co-infections

Table 3 Distribution of microorganisms in ICU bloodstream infections (BSI, *n* = 48) and sources of infection (*n* = 46) among COVID-19 and non-COVID-19 patients

	Non-COVID-19	COVID-19
Microorganisms identified (n = 48)*		
Coagulase-negative Staphylococci	2 (22.2)	14 (35.9)
Staphylococcus aureus	1 (11.1)	3 (7.7)
Enterococcus spp	0 (0)	4 (10.3)
Other Gram-positive	3 (33.3)	3 (7.7)
Enterobacterales	2 (22.2)	5 (12.8)
Pseudomonas aeruginosa	1 (11.1)	5 (12.8)
Anaerobic bacteria	0 (0)	1 (2.6)
Candida albicans	0 (0)	4 (10.3)
Source of infection (n = 46)*		
Intra-abdominal	1 (12.5)	1 (2.6)
Skin/soft tissue	0 (0)	2 (5.3)
CRBSI	2 (25)	8 (21.1)
Pulmonary	3 (37.5)	8 (21.1)
Urinary tract	0 (0)	1 (2.6)
Unknown	2 (25)	18 (47.4)

Values were expressed as number and percentage. The total number of ICU-BSI was 43

Spp species, *CRBSI* catheter-related bloodstream infection

*There were one polymicrobial ICU-BSI in the non-COVID-19 group and three polymicrobial ICU-BSIs in the COVID-19 group

**Three patients had multiple sources of infection

than patients in mixed ward/ICU settings [6]. However, this meta-analysis focused only on COVID-19 patients, included only few ICU studies, did not specifically assessed ICU-BSI, and did not compare critically ill COVID-19 and non-COVID-19 patients. To our knowledge, only few studies specifically focused on BSI in critically ill COVID-19 patients, but without performing a comparison with similar non-COVID-19 patients [9, 20]. After correcting for the duration of ICU-stay and after taking into account case fatality as a competing risk, we illustrated that the COVID-19 had an increased risk for ICU-BSIs compared to similar non-COVID-19 critically ill controls. Our study was not designed to investigate the reasons for this increase. However, in light of the results obtained in our explanatory analysis, it is conceivable that immune-modulatory therapies administered in COVID-19 patients (i.e., tocilizumab or anakinra) may increase the risk of ICU-BSI. This hypothesis may be suggested by several studies, which investigated the role of tocilizumab in COVID-19 patients. A recent systematic review and meta-analysis showed that secondary infections were notably higher for tocilizumab (versus standard of care [SOC]) but not statistically significant [21]. Moreover, a randomized-controlled trial (RCT, tocilizumab versus SOC) showed that tocilizumab group was associated with an increased proportion of patients with superinfections, and a similar trend was observed in the BSI subgroup [22]. However, two other recent RCTs did not show an increased risk for infections in the tocilizumab group [23, 24]. Unfortunately, we could not assess the risk of BSI depending on doses administered. Other explanations for an increased risk of BSI focused on either pathogenetic mechanisms of SARS-CoV-2 or concomitant comorbidities. First, SARS-CoV-2 may impair antigen presentation or trigger an acquired immunosuppression with concomitant lymphopenia, thus probably leading to an increased susceptibility to superinfection [25, 26]. Second, the coagulopathy associated with SARS-CoV-2 may affect the micro- and macrocirculation [27], thus probably increasing the risk of bacterial translocation (e.g., in gastrointestinal tract) [28]. Moreover, endothelial dysfunctions of the digestive tract were frequently observed in COVID-19 and were associated with more mesenteric infarctions [29]. In support of this argument, we found that pathogens from the intestinal microbiota were more frequently observed in ICU-BSI of unknown origin. Of note, COVID-19 patients did not show a statistically significant increased risk of CRBSI; however, among all ICU-BSI episodes, the catheter duration was longer in the COVID-19 group, and therefore, a healthcare associated etiology could not be excluded.

The fact that ICU-BSI were mostly unknown origin deserves further elucidations in the future. To our knowledge, to date, this issue remains under-investigated. A large multi-centric cohort study including only COVID-19 highlighted that the most common presumed source was unknown or not reported [30]. Moreover, the role of bacterial translocation should further be evaluated: a recent monocentric Italian study showed an increased risk for enterococcal BSI among COVID-19 patient, thus suggesting an enteric involvement in patients with severe COVID-19 [31].

Our findings have clinical implications. First, after 7 days in ICU, the risk of BSI started to significantly increase in critically ill COVID-19 patients; therefore, clinicians should particularly be careful on late ICU-BSI. Second, COVID-19 patients treated with IL-antagonists may be more susceptible to ICU-BSI and should be cautiously monitored.

Our study has several limitations. First, matched COVID-19 patients had slightly increased SOFA score compared to non-matched COVID-19 patients. Our analysis may represent the most critically ill COVID-19 patients. Second, we selected threshold of ≥ 0.20 to identify important imbalances which may be criticized. However, as we used two different matching methods showing the same results, we mitigated the risk of imbalance due to cofounding. Third, we illustrated data from six French ICU, thus limiting the generalizability of our results.

Fourth, we focused only on ICU-BSIs; therefore, our results did not reflect other healthcare-associated infections (e.g., ventilator-associated pneumonia). Fifth, we did not investigate mortality associated with ICU-BSI. The impact of ICU-BSI on mortality in COVID-19 patients should be assessed in further studies. Sixth, the first episode only of ICU-BSI was considered and no firm conclusions on subsequent BSIs could be performed. Finally, we generated hypotheses on causality between IL-antagonists and occurrence of ICU-BSI; however, this finding should be interpreted with caution because it was derived from an exploratory analysis. Further studies should explore this association. Moreover, explanatory analyses without significant results (e.g., using CRBSI as outcome) were difficult to interpret due to a lack of power.

Conclusions

Using prospectively collected multicentric data, we showed that the ICU-BSI risk was higher for COVID-19 than non-COVID-19 critically ill patients after seven days of ICU-stay. Clinicians should be particularly careful on late ICU-BSIs in COVID-19 patients.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1007/s00134-021-06346-w.

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Author contributions
NB, SR, and JFT designed the study. JFT, JR, NT, YC, SS, EdM, CD acquired the data. SR, NB and JFT did the statistical analysis. NB, SR, and JFT analyzed and interpreted the data. NB, SR, and JFT drafted the manuscript. All authors critically reviewed the manuscript and approved the final report.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflicts of interest
The authors have disclosed that they do not have conflict of interest. NT reports fees from Pfizer outside the submitted work. JFT reports, outside the submitted work, participations to advisory boards for Pfizer, MSD, Nabriva, Medimune, Gilead, Becton–Dickinson, and lecture fees from MSD, Pfizer, Biomerieux.

Ethics approval
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The studies were approved by the regional ethic committees of Clermont-Ferrand.

Consent to participate
Informed consent was not required because the study did not modify patients' management and the data were anonymously collected.

Consent for publication
Not applicable.

Publisher's Note

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