Bloodstream infections in critically ill patients with COVID-19

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Abstract
Background: Little is known about the incidence and risk of intensive care unit (ICU)-acquired bloodstream infections (BSI) in critically ill patients with coronavirus disease 2019 (COVID-19).

Materials and methods: This retrospective, single-centre study was conducted in Northern Italy. The primary study objectives were as follows: (a) to assess the incidence rate of ICU-acquired BSI and (b) to assess the cumulative risk of developing ICU-acquired BSI.

Results: Overall, 78 critically ill patients with COVID-19 were included in the study. Forty-five episodes of ICU-acquired BSI were registered in 31 patients, with an incidence rate of 47 episodes (95% confidence interval [CI] 35-63) per 1000 patient-days at risk. The estimated cumulative risk of developing at least one BSI episode was of almost 25% after 15 days at risk and possibly surpassing 50% after 30 days at risk. In multivariable analysis, anti-inflammatory treatment was independently associated with the development of BSI (cause-specific hazard ratio [csHR] 1.07 with 95% CI 0.38-3.04 for tocilizumab, csHR 3.95 with 95% CI 1.20-13.03 for methylprednisolone and csHR 10.69 with 95% CI 2.71-42.17 for methylprednisolone plus tocilizumab, with no anti-inflammatory treatment as the reference group; overall P for the dummy variable = 0.003).

Conclusions: The incidence rate of BSI was high, and the cumulative risk of developing BSI increased with ICU stay. Further study will clarify if the increased risk of BSI we detected in COVID-19 patients treated with anti-inflammatory drugs is outweighed by the benefits of reducing any possible pro-inflammatory dysregulation induced by SARS-CoV-2.

Keywords
BSI, coronavirus, COVID-19, SARS-CoV-2, steroid, tocilizumab
1 | BACKGROUND

In a very few months, coronavirus disease 2019 (COVID-19) has become pandemic, and several countries worldwide are currently dealing with unprecedented epidemic foci of severe acute respiratory infection, a possible presentation of COVID-19 that may require intensive care unit (ICU) admission and carries a high case fatality rate.\(^1\)\(^-\)\(^5\)

While the demographics, clinical characteristics and overall survival of patients with COVID-19 admitted to ICU have been already extensively characterized by large reports from several parts of the world, little is still known about nonviral infectious complications such as bacterial or fungal bloodstream infections (BSI) that may participate in adversely influencing the outcome of any ICU-admitted patient.\(^6\)\(^-\)\(^7\)

In the present study, we aimed to retrospectively assess the incidence rate, cumulative risk, predictors and survival of ICU-acquired BSI in patients with COVID-19 admitted to two ICUs in a large teaching hospital in Northern Italy, one of the most affected areas in Europe to date.\(^8\)

2 | METHODS

This retrospective study was conducted in two ICUs (27 and 12 beds, respectively) at Ospedale Policlinico San Martino—IRCCS, a 1200-bed teaching hospital in Northern Italy. From 20 February to 10 April 2020, all patients with COVID-19 admitted to the participating ICUs for >48 hours were included in the study. The predefined primary study objectives were as follows: (a) to assess the incidence rate of ICU-acquired BSI and (b) to assess the cumulative risk of developing ICU-acquired BSI. Predefined secondary objectives were as follows: (a) to describe the clinical characteristics of ICU-acquired BSI; (b) to assess predictors of ICU-acquired BSI; and (c) to describe survival of ICU-acquired BSI. The collection of anonymized data for the present study was approved by the Ethics Committee of the Liguria Region (registry number 163/2020). Specific informed consent was waived due to the retrospective nature of the study. Reporting of the study conforms to broad EQUATOR guidelines.\(^9\)

2.1 | Definitions

COVID-19 was defined in the presence of a positive real-time polymerase chain reaction (RT-PCR) for SARS-CoV-2 on at least one respiratory specimen (nasopharyngeal swab, sputum and/or lower respiratory tract specimens). ICU-acquired BSI was defined in the presence of at least one positive blood culture for bacteria or fungi, drawn at >48 hours after ICU admission. For coagulase-negative staphylococci and other common skin contaminants, at least two consecutive blood cultures positive for the same pathogen were necessary to define BSI.\(^10\) In patients with multiple blood cultures positive for the same organism, novel BSI events were considered as independent if occurring at least 30 days after the last previous positive blood culture. Polymicrobial infections were considered as separate BSI events, one for each causative organism isolated from blood culture.

2.2 | Data collection

The following data were collected from the patients’ electronic medical records as baseline data at the time of ICU admission: age in years, gender, hypertension, diabetes mellitus, respiratory disease (defined as asthma or chronic obstructive pulmonary disease), end-stage renal disease (defined as estimated glomerular filtration rate <15 mL/min/1.73 m\(^2\)), moderate-to-severe liver disease (defined as compensated or decompensated liver cirrhosis), solid cancer, haematological malignancy, human immunodeficiency virus infection, sequential organ failure assessment (SOFA) score at ICU admission\(^11\) and antibiotic therapy (yes/no and type of administered antibiotic/s). Since they were constantly continued/started at ICU admission, possible off-label anti-inflammatory treatments for COVID-19 (steroid treatment with intravenous methylprednisolone at 1 mg/kg once daily and/or intravenous tocilizumab at 8 mg/kg single administration or repeated once) were also recorded as dichotomic baseline variables (steroid: yes/no; tocilizumab: yes/no).

The following data were collected related to the onset of BSI episodes (ie they were collected the day when the first positive blood culture was drawn): presence of fever (defined as temperature >37.3°C), requirement of vasoactive agents, presence of acute kidney injury (defined as at least stage 1 of KDIGO [Kidney Disease: Improving Global Outcomes] classification of acute kidney injury\(^12\)), source of BSI (defined according to CDC/NHSN criteria\(^13\)), blood neutrophil count in cells × 10\(^{-3}\)/mm\(^3\), blood platelet count in cells × 10\(^{-3}\)/mm\(^3\), serum fibrinogen in g/L, serum lactate in mmol/L, serum C-reactive protein in mg/L, serum procalctonin in ng/mL, causative agents of BSI and susceptibility test results (the VITEK-2 automated system, bioMérieux, Marcy l’Etoile, France, was used for isolate identification and antimicrobial susceptibility testing). Finally, the date of the following was collected, whichever came first: death in the ICU and discharge from the ICU.

2.3 | Statistical analysis

No sample size calculations were performed a priori for this exploratory, descriptive study. The incidence rate of ICU-acquired BSI in the study population was calculated as the
number of events per 1000 patient-days at risk (defined as the cumulative days of stay elapsed from 48 hours after ICU admission to death, discharge from ICU or end of the study period, whichever came first). The 95% confidence interval (CI) for the incidence rate estimate was obtained using the mid-P exact test. The cumulative risk of ICU-acquired BSI was calculated using the Aalen-Johansen method, considering the first occurring BSI as the event of interest, death and discharge from the ICU as competing events, and length of ICU stay equal to 30 days or end of the study period (10 Apr 2020) as right-censoring events. The time of origin was set at 48 hours after ICU admission.

With regard to secondary analyses, demographic and clinical characteristics of BSI episodes were summarized with number and percentages for categorical variables and with median and interquartile range (IQR) for continuous variables. The possible association of demographic and clinical variables with the development of BSI (dependent variable: first occurring ICU-acquired BSI) was first tested in univariable comparisons. Variables with the development of BSI (dependent variable: first occurring ICU-acquired BSI) was first tested in univariable comparisons ($P<.10$) were included in a multivariable Cox regression model for calculating the adjusted cause-specific hazard ratio (csHR) for the development of BSI. Finally, survival of patients with ICU-acquired BSI was described with the Kaplan-Meier method, with death as the event of interest and discharge from ICU or the end of the study period (10 Apr 2020) as right-censoring events. The time of origin was the day when the first positive blood culture of the first occurring BSI episode was drawn.

Statistical analyses were performed using R Statistical Software (version 3.6.0, R Foundation for Statistical Computing, Vienna, Austria) and SPSS Statistics version 21.0 (IBM Corp., Armonk, NY, USA).

### RESULTS

During the study period, 78 patients with COVID-19 admitted to ICU for >48 hours were included in the study. Their median age was 66 years (IQR 57-70), and 77% were males (60/78). Their baseline demographic and clinical characteristics are summarized in Table 1. Of them, 26% (20/78) died with the Kaplan-Meier method, with death as the event of interest and discharge from ICU or the end of the study period (10 Apr 2020) as right-censoring events. The time of origin was the day when the first positive blood culture of the first occurring BSI episode was drawn.

Statistical analyses were performed using R Statistical Software (version 3.6.0, R Foundation for Statistical Computing, Vienna, Austria) and SPSS Statistics version 21.0 (IBM Corp., Armonk, NY, USA).

### Table 1 Characteristics of 78 critically ill patients with COVID-19

| Variable                          | Total   |
|----------------------------------|---------|
| Demographics                     |         |
| Age in years, median (IQR)       | 66 (57-70) |
| Male gender                      | 60 (77) |
| Comorbidities                    |         |
| Diabetes mellitus                | 14 (18) |
| Hypertension                     | 35 (45) |
| Respiratory disease              | 10 (13) |
| End-stage renal disease          | 0 (0)   |
| Moderate/severe liver failure    | 3 (4)   |
| Solid cancer                     | 4 (5)   |
| Haematological malignancy        | 1 (1)   |
| HIV infection                    | 0 (0)   |
| Hospital stay before ICU admission in days, median (IQR) | 2 (0-5) |
| SOFA score, median (IQR)         | 4 (3-5) |
| Antibiotic therapyd              | 75 (96) |
| Anti-inflammatory treatment       |         |
| Methylprednisolone               | 24 (31) |
| Tocilizumab                      | 18 (23) |
| Both of them                     | 14 (18) |
| None of them                     | 22 (28) |

Note: Results are reported as number of patients (%) unless otherwise indicated. Abbreviations: COVID-19, coronavirus disease 2019; HIV, human immunodeficiency virus; ICU, intensive care unit; IQR, interquartile range; SOFA, sequential organ failure assessment.

aDefined as asthma or chronic obstructive pulmonary disease
bDefined as estimated glomerular filtration rate <15 mL/min/1.73 m²
cDefined as compensated or decompensated liver cirrhosis

dCeftriaxone (n = 59), levofloxacin (n = 3), ceftobiprole (n = 2), ceftriaxone plus azithromycin (n = 2), linezolid plus meropenem (n = 2), ceftriaxone (n = 1), cefotaxime/tazobactam (n = 1), ceftazidime/tazobactam (n = 1), piperacillin/tazobactam plus azithromycin (n = 1), ceftazidime plus meropenem (n = 1), ceftazidime plus meropenem (n = 1), linezolid plus daptomycin (n = 1), ceftolozane/tazobactam (n = 1), and linezolid plus meropenem plus amikacin (n = 1)

38% was observed in COVID-19 patients treated with tocilizumab, whereas the highest was observed in those receiving neither tocilizumab nor steroid (9/10, 90%). Serum C-reactive protein values were also the lowest among tocilizumab-treated patients (median 20.6 mg/L, IQR 8.4-33.6 mg/L) and the highest among those receiving neither tocilizumab nor steroid (median 169 mg/L, IQR 70.4-194.0 mg/L). The most frequent causative agents of ICU-acquired BSI were coagulase-negative staphylococci (11/45, 24%), followed by Enterococcus faecalis (8/45, 18%) and Staphylococcus aureus (6/45, 13%). As shown in Figure 1, the estimated cumulative risk of developing
| Characteristic                                      | Total no of episodes (n = 45) | Episodes in patients treated with tocilizumab (n = 16) | Episodes in patients treated with steroid (n = 12) | Episodes in patients treated with tocilizumab and steroid (n = 7) | Episodes in patients treated with neither tocilizumab nor steroid (n = 10) |
|---------------------------------------------------|-------------------------------|-------------------------------------------------------|-------------------------------------------------|------------------------------------------------------------------|---------------------------------------------------------------------|
| **Fever (temperature > 37.3°C), n (%)**           | 24 (53)                      | 6 (38)                                                | 5 (42)                                          | 4 (57)                                                           | 9 (90)                                                              |
| **Requirement of vasoactive agents, n (%)**       | 15 (33)                      | 5 (31)                                                | 3 (25)                                          | 1 (14)                                                           | 6 (60)                                                              |
| **Acute kidney injury**a                         | 9 (2)                        | 2 (13)                                                | 5 (42)                                          | 0 (0)                                                            | 2 (20)                                                              |
| **Source of BSI**b                              |                               |                                                       |                                                 |                                                                  |                                                                     |
| Unknown                                           | 29 (64)                      | 6 (38)                                                | 11 (92)                                         | 3 (43)                                                           | 9 (90)                                                              |
| Lower respiratory tract                           | 10 (22)                      | 4 (25)                                                | 1 (8)                                           | 4 (57)                                                           | 1 (10)                                                              |
| Urinary tract                                     | 2 (4)                        | 2 (13)                                                | 0 (0)                                           | 0 (0)                                                            | 0 (0)                                                              |
| CVC-related                                       | 4 (9)                        | 4 (25)                                                | 0 (0)                                           | 0 (0)                                                            | 0 (0)                                                              |
| **Laboratory results**                            |                               |                                                       |                                                 |                                                                  |                                                                     |
| Blood neutrophil count, cell $\times 10^3$/mm$^3$ | 10.8 (8.1-14.8)              | 8.9 (5.5-14.7)                                        | 13.4 (8.6-16.0)                                 | 12.4 (8.7-16.0)                                                  | 10.4 (6.4-14.5)                                                     |
| Blood platelet count, cell $\times 10^3$/mm$^3$   | 247 (192-332)                | 234 (191-355)                                         | 260 (188-445)                                  | 208 (190-300)                                                    | 244 (184-294)                                                       |
| Serum lactate, mmol/L                            | 1.2 (0.8-1.6)                | 1.3 (1.0-2.1)                                         | 1.2 (0.8-1.5)                                  | 1.2 (0.7-1.4)                                                    | 1.1 (0.6-1.3)                                                       |
| Serum fibrinogen, g/L                            | 4.3 (2.7-6.5)                | 2.8 (2.2-3.1)                                         | 5.9 (4.3-8.0)                                  | 4.4 (2.1-5.4)                                                    | 6.5 (4.3-9.2)                                                       |
| Serum C-reactive protein, mg/L                   | 44.6 (11.3-137.0)            | 20.6 (8.4-33.6)                                       | 105.2 (54.0-164.0)                             | 43.7 (2.9-120.0)                                                 | 169.0 (70.4-194.0)                                                  |
| Serum procalcitonin                               | 0.3 (0.1-1.2)                | 0.1 (0.0-0.3)                                         | 0.9 (0.2-2.3)                                  | 0.1 (0.1-0.2)                                                    | 1.2 (0.4-1.9)                                                      |
| **Causative agent, n (%)**                       |                               |                                                       |                                                 |                                                                  |                                                                     |
| Coagulase-negative staphylococci                 | 11 (24)                      | 4 (25)                                                | 4 (33)                                          | 1 (14)                                                           | 2 (20)                                                              |
| *Staphylococcus aureus*c                         | 6 (13)                       | 4 (25)                                                | 1 (8)                                           | 1 (14)                                                           | 0 (0)                                                              |
| *Enterococcus faecalis*d                         | 8 (18)                       | 3 (19)                                                | 2 (17)                                          | 1 (14)                                                           | 2 (20)                                                              |
| *Enterococcus faecium*e                          | 4 (9)                        | 2 (13)                                                | 1 (8)                                           | 1 (14)                                                           | 0 (0)                                                              |
| *Streptococcus pneumoniae*                       | 1 (2)                        | 0 (0)                                                 | 1 (8)                                           | 0 (0)                                                            | 0 (0)                                                              |
| *Viridans group streptococci*                    | 3 (7)                        | 0 (0)                                                 | 1 (8)                                           | 0 (0)                                                            | 2 (20)                                                              |
| *Pseudomonas aeruginosa*                         | 2 (4)                        | 0 (0)                                                 | 0 (0)                                           | 1 (14)                                                           | 1 (10)                                                              |
| *Enterobacter aerogenes*b                        | 4 (9)                        | 0 (0)                                                 | 1 (8)                                           | 1 (14)                                                           | 2 (20)                                                              |
| *Escherichia coli*                               | 1 (2)                        | 1 (6)                                                 | 0 (0)                                           | 0 (0)                                                            | 0 (0)                                                              |
| *Proteus mirabilis*b                             | 1 (2)                        | 0 (0)                                                 | 0 (0)                                           | 1 (14)                                                           | 0 (0)                                                              |
| *Candida* spp.*                                  | 3 (7)                        | 2 (13)                                                | 0 (0)                                           | 0 (0)                                                            | 1 (0)                                                              |
| *Prevotella* spp.*                               | 1 (2)                        | 0 (0)                                                 | 1 (8)                                           | 0 (0)                                                            | 0 (0)                                                              |

Note: Results are reported as median (IQR) unless otherwise indicated.
Abbreviation: IQR, interquartile range.

*aDefined as at least stage 1 of KDIGO (Kidney Disease: Improving Global Outcomes) stages of acute kidney injury.12
bDefined according to CDC/NHSN criteria.13

c0/6 S. aureus were methicillin-resistant (90%).
d0/8 E. faecalis were ampicillin-resistant (0%); none were vancomycin-resistant (0%).
e4/4 E. faecium were ampicillin-resistant (100%); 1/4 were vancomycin-resistant (25%).
f0/1 S. pneumoniae were ceftriaxone-resistant (0%).
g0/2 P. aeruginosa were piperacillin/tazobactam-resistant, ceftazidime-resistant and/or carbapenem-resistant (0%).
h2/6 members of the Enterobacteriaceae were piperacillin/tazobactam-resistant, ceftazidime-resistant and/or carbapenem-resistant (33%)

1C. albicans (n = 1), C. tropicalis (n = 1), C. parapsilosis (n = 1).
FIGURE 1  Cumulative risk of ICU-acquired BSI in critically ill patients with COVID-19. The cumulative risk of ICU-acquired BSI in patients with COVID-19 at different lengths of ICU stay was estimated using the Aalen-Johansen method, with the first occurring ICU-acquired BSI as the event of interest and death and discharge from the ICU as competing events. Right censoring was applied in the following cases: (a) persistent ICU stay at the end of the study period and (b) persistent ICU stay at day + 30 after the time of origin (defined as 48 h after ICU admission, see study methods). BSI, bloodstream infection; COVID-19, coronavirus disease 2019; ICU, intensive care unit

at least one ICU-acquired BSI episode was of almost 25% after 15 days at risk and possibly surpassing 50% after 30 days a risk.

Univariable and multivariable analyses of factors potentially associated with the development of ICU-acquired BSI are shown in Table 3. In univariable comparisons, the following variables were associated with the development of BSI: diabetes mellitus (cSHR 2.76 with 95% CI 1.09-6.98, P = .032) and anti-inflammatory treatment (cSHR 1.21 with 95% CI 0.44-3.30 for tocilizumab, cSHR 4.48 with 95% CI 1.38-14.56 for methylprednisolone and cSHR 10.84 with 95% CI 2.79-42.08 for methylprednisolone plus tocilizumab, with no anti-inflammatory treatment as the reference group; overall p for the dummy variable = 0.002). In multivariable analysis, only anti-inflammatory treatment (cSHR 1.07 with 95% CI 0.38-3.04 for tocilizumab, cSHR 3.95 with 95% CI 1.20-13.03 for methylprednisolone and cSHR 10.69 with 95% CI 2.71-42.17 for methylprednisolone plus tocilizumab; overall p for the dummy variable = 0.003) retained an independent association with the development of BSI.

As shown in Figure 2, the estimated survival of ICU-acquired BSI was of almost 75% after 24 days (no longer follow-up was available) from the first positive blood culture, although with the important limitation that follow-up after day 12 was available for less than one third of patients at the time of this report.

4  DISCUSSION

In the present study, we estimated an incidence rate of 47 episodes of ICU-acquired BSI per 1000 patient-days at risk in critically ill patients with COVID-19, which is higher than that of 5-19 episodes per 1000 patient-days registered in other heterogeneous, non-COVID-19 ICU populations (even if adjusting for the fact that we considered only patient-days after 48 hours from ICU admission, see Methods).6,16-18

It is also of note that our estimation of a cumulative 30-day risk of developing BSI of more than 50% is in contrast with the low prevalence of BSI or other bacterial/fungal infections (1%-12%) reported in other epidemiological reports from China and the United States.2,19,20 In our opinion, this could be explained by different, nonmutually exclusive reasons. The first is that the number of patients under follow-up in the ICU for more than 20 days was limited in our analysis; thus, any generalization of our 30-day cumulative risk estimate should be made with due caution. On the other hand, the cumulative risk of almost 25% we estimated at day 15 (based on a larger portion of patients still under follow-up) is already higher than the overall prevalence of BSI registered in critically ill COVID-19 patients in earlier studies.2,19,20

In this regard, a possible explanation may be the difficulty of diagnosing BSI in patients receiving anti-inflammatory drugs,21 which prompted us to collect blood cultures in any case of worsening general conditions in COVID-19 patients, even in the absence of fever and increases in C-reactive protein serum levels. In support of this approach, in the present study, for example, fever was detected only in 38% of patients with ICU-acquired BSI previously treated with tocilizumab. Furthermore, serum C-reactive protein levels were frequently low and other classical inflammatory markers were usually uncharacteristic, making it rather difficult to clinically recognize a BSI event. Therefore, we feel the total number of BSI in COVID-19 patients may be underestimated wherever anti-inflammatory drugs are administered, but collection of blood cultures remains based on classical clinical and laboratory indicators of BSI. Finally, and perhaps most importantly, we found an independent association between receipt of anti-inflammatory agents and development of BSI. This effect seems to be mainly driven by steroids rather than tocilizumab, although it is worth noting that the highest instantaneous risk in Cox models was registered in patients receiving both steroid and tocilizumab. In general, such an unfavourable effect of anti-inflammatory drugs on the risk of infection is long known.22-24 What remains unknown in patients with COVID-19 is as to whether this risk of infectious complications is balanced (or better, outweighed) by possible favourable effects of anti-inflammatory drugs on relevant clinical outcomes. Indeed, the rational for administering anti-inflammatory drugs in COVID-19 patients is mostly based on the intention of attenuating the cytokine storm syndrome
possibly prompted by SARS-CoV-2, but high-level evidence supporting the efficacy of this practice is still unavailable, although randomized controlled trials are ongoing.25

Another different finding from previous reports is that we found a higher prevalence of Gram-positive than Gram-negative organisms as causative agents of ICU-acquired BSI in COVID-19 patients.19 Again, at least two different explanations may be considered. The first is that our sample of BSI events was larger than in previous reports, possibly depicting a more reliable estimate of the true distribution of the relative prevalence of the different causative agents. The second is that, borrowing from the observed microbiological epidemiology (higher prevalence of Gram-positive organisms) in patients with severe influenza,26 and considering the frequent inability we had in rapidly differentiating between primary viral pneumonia and bacterial pulmonary superinfection in ICU-admitted COVID-19 patients, most COVID-19 patients in our centre were treated with an anti-methicillin-resistant S aureus cephalosporin (most frequently ceftaroline, see Table 1) at ICU admission. However, while on the one hand this may be in line with the unusual high relative prevalence of enterococcal BSI (because of the impaired activity of ceftaroline against Enterococcus spp., although possible in vitro activity against E faecalis has been reported27), on the other hand, it is also true that coagulase-negative staphylococci and S aureus were the other two most prevalent causative agents of BSI in our cohort. From this standpoint, conversely, the true relative prevalence of Gram-positive organisms could be even higher than that registered in our cohort (because of the anti-staphylococcal and anti-pneumococcal activity of ceftaroline that could have reduced the prevalence, absolute and relative, of staphylococci and pneumococci as causative agents of BSI).

Finally, although we apparently observed an improved survival of BSI in comparison with previous large studies conducted in non-COVID-19 ICU patients,7 it should be reminded that our sample size of BSI patients was limited (n = 31) and that follow-up was very short. Consequently, any related conclusion should be drawn cautiously. Other important limitations of our study are its retrospective nature (mainly because of possible information and selection biases), its single-centre nature that may impact generalization of results, and the lack of adequate power for exploring possible predictors of improved survival in COVID-19 patients with ICU-acquired BSI.

| Variable                        | Unadjusted cause-specific HR (95% CI) | P    | Adjusted cause-specific HR (95% CI) | P    |
|--------------------------------|--------------------------------------|------|------------------------------------|------|
| Age in years                   | 1.00 (0.96-1.04)                     | .970 |                                    |      |
| Male gender                    | 1.60 (0.65-3.94)                     | .304 |                                    |      |
| Diabetes mellitus              | 2.76 (1.09-6.98)                     | .032 | 2.22 (0.80-6.20)                   | .127 |
| Hypertension                   | 0.89 (0.43-1.85)                     | .755 |                                    |      |
| Respiratory disease            | 1.87 (0.54-6.43)                     | .323 |                                    |      |
| Moderate/severe liver failure  | 6.71 (0.77-58.29)                    | .084 | 6.36 (0.59-68.39)                  | .127 |
| Solid cancer                   | 2.71 (0.35-20.99)                    | .340 |                                    |      |
| Haematological malignancy      |                                     |      |                                    |      |
| Hospital stay before ICU admission in days | 1.02 (0.98-1.08) | .339 |                                    |      |
| SOFA score                     | 1.00 (0.80-1.25)                     | .996 |                                    |      |
| Antibiotic therapy             |                                      |      |                                    |      |
| Anti-inflammatory treatment     |                                      |      |                                    |      |
| Methylprednisolone             | 4.48 (1.38-14.56)                    | .002 | 3.95 (1.20-13.03)                  | .003 |
| Tocilizumab                    | 1.21 (0.44-3.30)                     |      | 1.07 (0.38-3.04)                   |      |
| Both of them                   | 10.84 (2.79-42.08)                   |      | 10.69 (2.71-42.17)                 |      |
| None of them (ref)             |                                      |      | (ref)                              |      |

Abbreviations: CI, confidence intervals; COVID-19, coronavirus disease 2019; HR, hazard ratio; ICU, intensive care unit; SOFA, sequential organ failure assessment.

The variables end-stage renal disease and human immunodeficiency virus (HIV) infection were not included in the model since they were not detected in the study population.

Univariable Cox regression model not converging in the presence of very small samples (n = 1 for patients with haematological malignancies and n = 3 for patients without antibiotic therapy at ICU admission).
In conclusion, in critically ill patients with COVID-19, the incidence rate of ICU-acquired BSI was high and the cumulative risk of developing BSI increased with ICU stay. Diagnosis of BSI in tocilizumab-treated COVID-19 patients may prove difficult because of the frequently absent fever and reduced serum concentrations of classical inflammatory markers. Further study will clarify if the increased risk of BSI we detected in COVID-19 patients treated with anti-inflammatory drugs is outweighed by the benefits of reducing any possible pro-inflammatory dysregulation of the host response induced by SARS-CoV-2.

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CONFLICT OF INTEREST
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AUTHORS’ CONTRIBUTION
DRG made substantial contributions to the study concept and design, acquisition of data, analysis and interpretation of data, first drafting of the manuscript and critical revision of the manuscript for important intellectual content. MB and PP made substantial contributions to the study concept and design and critical revision of the manuscript for important intellectual content. DB, LT, LM, AS and AV made substantial contributions to the study concept and design, and analysis and interpretation of data. LM, BB, FC, GC, CD, LM, CR, AV and LT made substantial contributions to the acquisition of data and critical revision of the manuscript for important intellectual content. LB, IB, GI, ADM, ADB, AM, MM, NP and AO made substantial contributions to the interpretation of data and critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT
The data sets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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