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## Bloodstream infections in the COVID-19 era: results from an Italian multi-centre study



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### ABSTRACT

**Background:** Correlation between coronavirus disease 2019 (COVID-19) and superinfections has been investigated, but remains to be fully assessed. This multi-centre study reports the impact of the pandemic on bloodstream infections (BSIs).

**Methods:** This study included all patients with BSIs admitted to four Italian hospitals between 1 January and 30 June 2020. Clinical, demographic and microbiologic data were compared with data for patients hospitalized during the same period in 2019.

**Results:** Among 26,012 patients admitted between 1 January and 30 June 2020, 1182 had COVID-19. Among the patients with COVID-19, 107 BSIs were observed, with an incidence rate of 8.19 episodes per 1000 patient-days. The incidence of BSI was significantly higher in these patients compared with patients without COVID-19 (2.72/1000 patient-days) and patients admitted in 2019 (2.76/1000 patient-days). In comparison with patients without COVID-19, BSI onset in patients with COVID-19 was delayed during the course of hospitalization (16.0 vs 5 days, respectively). Thirty-day mortality among patients with COVID-19 was 40.2%, which was significantly higher compared with patients without COVID-19 (23.7%). BSIs in patients with COVID-19 were frequently caused by multi-drug-resistant pathogens, which were often centre-dependent.

**Conclusions:** BSIs are a common secondary infection in patients with COVID-19, characterized by increased risk during hospitalization and potentially burdened with high mortality.

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### Introduction

The worldwide spread of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection has caused a massive global health challenge (Lupia et al., 2020; Pasquini et al., 2020). By the end of February 2021, the Coronavirus Resource Center of the Johns Hopkins University in Baltimore, MD, USA reported that there had been 114,338,204 confirmed cases and 2,535,737 deaths globally (<https://coronavirus.jhu.edu/>). Patients affected by coronavirus disease 2019 (COVID-19) often require hospital admission, and a large

percentage need invasive treatment in intensive care units (ICUs) (Petrilli et al., 2020).

As shown by several studies on other respiratory viruses, primary infection confers increased susceptibility to develop co-infections (Lee et al., 2011; Chertow and Memoli, 2013) and secondary infections due to bacteria and fungi (Lee et al., 2011; Chertow and Memoli, 2013). Co-infection is defined as acute infection detected on presentation of the primary infection (Langford et al., 2020), and secondary infection is defined as an infection detected  $\geq 48$  h after admission with a positive culture of a new pathogen from a lower respiratory tract specimen or blood taken  $\geq 48$  h after hospital admission (Huang et al., 2020; Lansbury et al., 2020). These conditions contribute to increase

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both disease severity and mortality (Lee et al., 2011; Chertow and Memoli, 2013), and their burden during the SARS-CoV-2 pandemic has not been fully assessed to date (Bassetti et al., 2020; Bengoechea and Bamford, 2020; Chen et al., 2020). Several studies and two systemic reviews have already attempt to assess the risk of co-infections and secondary infections (Bartoletti et al., 2020; Langford et al., 2020; Lansbury et al., 2020; Timsit et al., 2020; Vaughn et al., 2020). Based on these studies, co-infections are generally uncommon in patients with COVID-19, while secondary infections are favoured by many factors such as disease severity, ICU admission, need for mechanical ventilation and longer hospital stay. Bloodstream infections (BSIs) have also been evaluated, but only in small studies (Engsbro et al., 2020), and particularly in patients hospitalized in ICUs (Buetti et al., 2021; Giacobbe et al., 2020; Timsit et al., 2020).

The aim of this study was to evaluate the burden of BSI in patients with COVID-19 in terms of incidence, ecology and mortality in four Italian hospitals during the first wave of the SARS-CoV-2 pandemic.

## Methods

### Study population

This observational retrospective multi-centre study was conducted in four hospitals in the Marche region of Italy. The hospitals involved were: Azienda Ospedaliera Ospedali Riuniti Marche Nord, which consists of two secondary hospitals (Pesaro Hospital and Fano Hospital; hereafter referred to as 'Marche Nord hospitals'; Azienda Ospedaliera Universitaria Ospedali Riuniti di Ancona, a tertiary university hospital, hereafter referred to as 'Ancona hospital'; and Ospedale Augusto Murri, a secondary hospital, hereafter referred to as 'Fermo hospital'.

All adult patients (age >18 years) with bacterial or fungal BSIs admitted to these hospitals between 1 January and 30 June 2020 were included in this study. Epidemiological data were compared with data from the same time period in 2019. Patients admitted in 2020 were classified as 'patients with SARS-CoV-2 infection' or 'patients with COVID-19' and 'patients without SARS-CoV-2 infection' or 'patients without COVID-19'. Patients were further divided into two subgroups: those who were hospitalized in ICUs at the time of infection, and those who were hospitalized on normal wards at the time of infection.

### Outcome

The primary objective of this study was to estimate the incidence of BSI in patients with COVID-19 admitted to four Italian hospitals. Secondary outcomes included the evaluation of risk factors, mortality and ecology of these infections.

### Data collection

Patients with bacterial or fungal BSI were identified retrospectively through the hospitals' patient management software. The institutional review board for each centre granted retrospective access to the data without the need for individual informed consent. Consent was not required as the data were analysed anonymously. This study was undertaken in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments.

The following data were collected for each patient: demographic characteristics, Charlson Comorbidity Index, arterial hypertension, date of first positive swab for SARS-CoV-2, date of hospital admission, date of ICU admission, date of hospital discharge, date of death, date of first BSI, isolated pathogens, hospital ward

at time of BSI, days between hospitalization and first BSI, days between first BSI and discharge, days between first BSI and death, and death within 30 days of BSI.

### Laboratory techniques

All patients with COVID-19 had SARS-CoV-2 infection confirmed by reverse-transcriptase polymerase chain reaction assay. Blood cultures from peripheral access or central venous catheters (CVCs) were performed as requested by a physician for patients presenting clinical deterioration associated with suggestive laboratory findings. Cultured micro-organisms were identified using standard techniques. Single blood cultures from contaminant pathogens such as coagulase-negative staphylococci (CoNS) were not considered.

### Statistical analysis

Normally distributed continuous data are reported as mean  $\pm$  standard deviation, and were compared using two-sided Student's *t*-test. Non-normally distributed continuous data are reported as median and interquartile range (IQR), and were compared using the Mann-Whitney *U*-test. Categorical variables were analysed using Chi-squared test or Fisher's exact test, depending on best applicability.

Time of BSI onset in patients with and without SARS-CoV-2 infection was evaluated using the Kaplan-Meier method, and compared using the log-rank test. SPSS Version 24 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Statistical significance was set at  $P < 0.05$ .

## Results

### Study population

Between 1 January and 30 June 2020, 26,012 patients were hospitalized in the four hospitals, 616 of whom were admitted to an ICU (2.37%). In total, 1182 (4.54%) patients had confirmed SARS-CoV-2 infection, 155 (13.22%) of whom needed intensive care. In contrast, between 1 January and 30 June 2019, 34,712 patients were hospitalized in these hospitals and 628 (1.81%) were admitted to an ICU (Table 1).

The relative increase in ICU admissions between 2019 and 2020 (1.81% vs 2.37%, respectively;  $P < 0.001$ ), although minimal, led to an increase in the number of ICU beds from 44 to 91.

In total, 665 hospitalized patients had BSIs in 2020, 107 of whom were patients with COVID-19 (Table 2). Their median age was 71.2 years (IQR 60.9–80.0), 59.1% were male, the median Charlson Comorbidity Index was 5.0 (IQR 3.0–7.0), and 116 patients (17.4%) were hospitalized in an ICU at the time of BSI. The median interval between hospital admission and BSI occurrence was 5.0 days (IQR 0.0–17.0), the median interval between BSI and hospital discharge was 14.0 days (IQR 7.0–28.0), and the median interval between BSI and death was 7.0 days (IQR 2.0–20.0).

Significant differences were observed between patients with and without COVID-19 for Charlson Comorbidity Index (4.0 vs 5.0, respectively;  $P < 0.001$ ), hospitalization in ICU at the time of BSI (38.2% vs 12.7%, respectively;  $P < 0.001$ ), days between hospital admission and BSI occurrence (16.0 vs 5.0, respectively;  $P < 0.001$ ), and days between BSI occurrence and hospital discharge (23.0 vs 14.0, respectively;  $P = 0.038$ ) (Table 2).

Similarly, among the 116 patients hospitalized in an ICU at the time of BSI, significant differences were observed between patients with and without COVID-19 for Charlson Comorbidity Index (2.0 vs 4.0, respectively;  $P = 0.013$ ), days between hospital admission and

**Table 1**  
Study population

	First half of 2019, n	First half of 2020		
		All patients, n	Patients without COVID-19, n	Patients with COVID-19, n
Hospitalization – overall	34,712	26,012	24,830	1,182
Hospitalization – normal ward	34,084	25,396	24,369	1,027
Hospitalization – ICU	628	616	461	155

ICU, intensive care unit; COVID-19, coronavirus disease 2019.

**Table 2**  
Demographic and clinical characteristics of patients with bloodstream infections (BSIs) in the first half of 2020.

Characteristics	All patients (n=665)	Patients without COVID-19 (n=558)	Patients with COVID-19 (n=107)	P-value
Age, median (IQR), years	71.2 (60.9–80.0)	71.5 (61.1–79.9)	69.6 (59.8–81.3)	0.260
Male sex, n (%)	393 (59.1%)	327 (58.6%)	66 (61.7%)	0.984
CCI, median (IQR)	5.0 (3.0–7.0)	5.0 (4.0–8.0)	4.0 (2.0–6.0)	<0.001
Patient in ICU at time of BSI, n (%)	116 (17.4%)	71 (12.7%)	45 (38.2%)	<0.001
Interval between admission and BSI, median (IQR), days	5.0 (0.0–17.0)	5.0 (0.0–15.0)	16.0 (6.0–27.5)	<0.001
Interval between BSI and discharge, median (IQR), days	14.0 (7.0–28.0)	14.0 (8.3–27.0)	23 (12.0–42.0)	0.038
Interval between BSI and death, median (IQR), days	7.0 (2.0–20.0)	7.0 (2.8–15.5)	5 (2.0–20.3)	0.904

IQR, interquartile range; CCI, Charlton Comorbidity Index; ICU, intensive care unit; COVID-19, coronavirus disease 2019.

**Table 3**  
Incidence of bloodstream infections (BSIs).

	BSIs in first half of 2019, n per 1000 patient-years	BSIs in first half of 2020, n per 1000 patient-years		
		All patients	Patients without COVID-19	Patients with COVID-19
BSIs – overall	751 (2.76)	665 (3.05)	558 (2.72)	107 (8.19) <sup>a,b</sup>
BSIs – normal ward	675 (2.52)	555 (2.60)	492 (2.44)	63 (5.46) <sup>a,b</sup>
BSIs – ICU	76 (18.17)	110 (23.56)	66 (21.01)	44 (28.82) <sup>c</sup>

COVID-19, coronavirus disease 2019; ICU, intensive care unit.

<sup>a</sup> P<0.01 compared with 2019.

<sup>b</sup> P<0.01 compared with patients in 2020 without COVID-19.

<sup>c</sup> P<0.05 compared with 2019.

BSI occurrence (18.0 vs 12.0, respectively; P=0.038), and days between BSI occurrence and hospital discharge (25.0 vs 43.0, respectively; P=0.024) (data not shown).

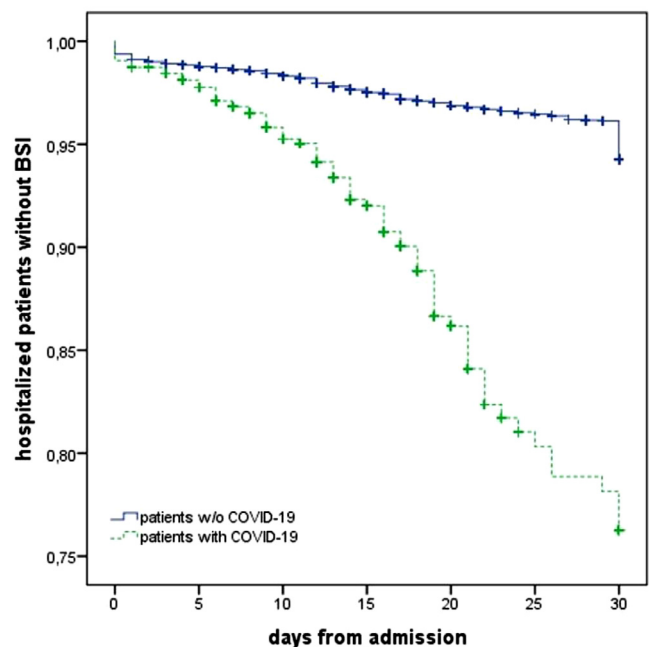
**BSI incidence and mortality**

Among the 1182 patients with SARS-CoV-2 infection hospitalized in the four study hospitals, there were 107 BSIs, the duration of hospitalization was 11.05 days, and the incidence rate was 8.19 BSIs per 1000 patient-days (Table 3). This incidence rate was higher than that for patients admitted in the same time period without COVID-19 (2.72 BSIs per 1000 patient-days, P<0.001) and for patients admitted in 2019 (2.76 BSIs per 1000 patient-days, P<0.001) (Table 3). The duration of hospitalization in these two groups was 8.25 and 7.83 days, respectively.

Analysis of the incidence of BSI according to the department of onset revealed a significant increase in normal wards for patients without COVID-19 admitted in 2020 (5.46 vs 2.44 BSIs per 1000 patient-days, P<0.001) and for patients admitted in 2019 (5.46 vs 2.52 BSIs per 1000 patient-days, P<0.001). For ICU patients, the increase was only significant in comparison with 2019 (28.82 vs 18.17 BSIs per 1000 patient-days, P<0.001) (Table 3).

Correlation between BSI onset and time after hospital admission was also analysed using Kaplan–Meier curves (Figure 1). Up to the third day of hospitalization, the incidence of BSIs was similar between patients with and without COVID-19, and thereafter, incidence increased significantly in patients with COVID-19 (Figure 1).

Overall mortality in patients with COVID-19 was 40.2%, which was significantly higher compared with patients admitted during the same period without COVID-19 (23.7%, P<0.001) and patients admitted in 2019 (25.2%, P<0.001). For patients hospitalized in normal wards, there was a significant increase in mortality for



**Figure 1.** Time to bloodstream infection (BSI) in hospitalized patients with and without coronavirus disease 2019. Patients who were discharged or who died before 30 days were censored (log rank P<0.001). COVID-19, coronavirus disease 2019.

patients with COVID-19 (41.3% vs 23.6% and 24.3%, respectively; P<0.001), while the difference was not significant for patients hospitalized in ICUs (Table 4).

**Table 4**  
Thirty-day mortality for bloodstream infections (BSIs).

	Death within 30 days of BSI in 2019, n (%)	Death within 30 days of BSIs in 2020, n (%)		
		All patients	Patients without COVID-19	Patients with COVID-19
BSIs – overall	189 (25.2%)	175 (26.3%)	132 (23.7%)	43 (40.2%) <sup>a,b</sup>
BSIs – normal ward	164 (24.3%)	142 (25.6%)	116 (23.6%)	26 (41.3%) <sup>a,b</sup>
BSIs – ICU	25 (32.9%)	33 (30.0%)	16 (24.2%)	17 (38.6%)

COVID-19, coronavirus disease 2019; ICU, intensive care unit.

<sup>a</sup>  $P < 0.01$  compared with 2019.<sup>b</sup>  $P < 0.01$  compared with patients in 2020 without COVID-19.**Table 5**  
Pathogens isolated in bloodstream infections.

	Pathogens isolated in 2019, n (n per 1000 hospitalizations)	Pathogens isolated in 2020, n (n per 1000 hospitalizations)		
		All patients	Patients without COVID-19	Patients with COVID-19
MSSA	79 (2.3)	56 (2.2)	49 (2.0)	7 (5.9) <sup>a</sup>
MRSA	23 (0.7)	24 (0.9)	18 (0.7)	6 (5.1) <sup>a</sup>
CoNS	122 (3.5)	129 (5.0) <sup>a</sup>	111 (4.5)	18 (15.2) <sup>a</sup>
<i>Enterococcus faecalis</i>	47 (1.4)	47 (1.8)	39 (1.6)	8 (6.8) <sup>a</sup>
<i>Enterococcus faecium</i>	24 (0.7)	44 (1.7) <sup>a</sup>	38 (1.5) <sup>a</sup>	6 (5.1) <sup>a</sup>
Carbapenem-resistant <i>Klebsiella pneumoniae</i>	18 (0.5)	30 (1.2) <sup>a</sup>	13 (0.5)	17 (14.4) <sup>a</sup>
Other Enterobacteriaceae	297 (8.6)	220 (8.5)	205 (8.3)	15 (12.7) <sup>a</sup>
<i>Acinetobacter baumannii</i>	19 (0.5)	26 (1.0) <sup>b</sup>	7 (0.3)	19 (16.1) <sup>a</sup>
<i>Pseudomonas aeruginosa</i>	29 (0.8)	28 (1.1)	20 (0.8)	8 (6.8) <sup>a</sup>
<i>Candida</i> spp.	63 (1.8)	59 (2.3)	44 (1.8)	15 (12.7) <sup>a</sup>
Polymicrobial	84 (2.4)	74 (2.8)	55 (2.2)	19 (16.1) <sup>a</sup>
Others	114 (3.3)	76 (2.9)	69 (2.8)	7 (5.9) <sup>a</sup>

MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; CoNS, coagulase-negative staphylococci.<sup>a</sup>  $P < 0.01$  compared with 2019.<sup>b</sup>  $P < 0.05$  compared with 2019.

### Epidemiological changes in BSIs between 2019 and 2020

Table 5 shows the pathogens causing BSIs in 2019 and 2020. Overall, the incidence rates (per 1000 hospitalizations) of four pathogens increased significantly from 2019 to 2020: *Enterococcus faecium* (from 0.7 to 1.7,  $P < 0.001$ ), carbapenem-resistant *Klebsiella pneumoniae* (from 0.5 to 1.2,  $P = 0.009$ ), *Acinetobacter baumannii* (from 0.5 to 1.0,  $P = 0.043$ ) and CoNS (from 3.5 to 5.0,  $P = 0.006$ ). Considering patients with COVID-19 alone, the incidence rate of all pathogens increased significantly from 2019 to 2020 ( $P < 0.001$ ).

The highest increase in incidence was observed for *A. baumannii* (29.3 fold, from 0.5 to 16.1 per 1000 hospitalizations), followed by carbapenem-resistant *K. pneumoniae* (27.7 fold), *Pseudomonas aeruginosa* (8.10 fold), methicillin-resistant *Staphylococcus aureus* (MRSA) (7.66 fold), *E. faecium* (7.34 fold), *Candida* spp. (6.99 fold), polymicrobial BSIs (6.64 fold), *Enterococcus faecalis* (5.0 fold), CoNS (4.33 fold), methicillin-susceptible *Staphylococcus aureus* (MSSA) (2.60 fold), other pathogens (1.80 fold), and other Enterobacteriaceae (1.48 fold).

For patients without COVID-19, the only significant difference between 2019 and 2020 was a 2.2-fold increase in *E. faecium* (from 0.7 to 1.5 per 1000 hospitalizations,  $P = 0.003$ ) (Table 5).

The variation of incidence for specific pathogens was centre-dependent (Figure 2). The Marche Nord hospitals showed a 43.6-fold increase in the incidence of carbapenem-resistant *K. pneumoniae* from 2019 to 2020 (from 0.34 to 14.73 per 1000 hospitalizations,  $P < 0.001$ ), a 40.9-fold increase in the incidence of *A. baumannii* (from 0.76 to 31.30 per 1000 hospitalizations,  $P < 0.001$ ), and a 15.5-fold increase in the incidence of *P. aeruginosa* (from 0.42 to 6.55 per 1000 hospitalizations,  $P < 0.001$ ) (Figure 2a). Ancona hospital showed a 29.7-fold increase in the incidence of carbapenem-resistant *K. pneumoniae* (from 0.47 to 13.81 per 1000 hospitalizations,  $P < 0.001$ ), a 20.4-fold increase in the incidence of MRSA (from 0.41 to 8.29 per 1000 hospitalizations,  $P < 0.001$ ), and a 11.9-fold increase in the incidence of *Candida* spp. (from 1.86 to 22.10

per 1000 hospitalizations,  $P < 0.001$ ) (Figure 2b). Finally, Fermo hospital showed a 54.3-fold increase in the incidence of *E. faecium* (from 0.18 to 9.57 per 1000 hospitalizations,  $P < 0.001$ ), a 13.6-fold increase in the incidence of carbapenem-resistant *K. pneumoniae* (from 1.06 to 14.35 per 1000 hospitalizations,  $P < 0.001$ ), and a 7.7-fold increase in the incidence of *E. faecalis* (from 1.23 to 9.57 per 1000 hospitalizations,  $P = 0.038$ ) (Figure 2c).

### Main difference between the three centres

The burden of the SARS-CoV-2 epidemic over the study period differed between the three centres. The percentage of patients with SARS-CoV-2 infection in the Marche Nord hospitals was significantly higher compared with Ancona hospital (7.0% vs 2.8%, respectively;  $P < 0.001$ ) and Fermo hospital (7.0% vs 4.6%, respectively;  $P < 0.001$ ). Fermo hospital had more hospitalizations with SARS-CoV-2 infection than Ancona hospital (4.6% vs 2.8%, respectively;  $P < 0.001$ ) (Table 6).

The pressure on ICUs was also different. The Marche Nord hospitals and Fermo hospital had similar rates of hospitalization in ICUs (20.0% and 20.1%, respectively), while only 9.1% of patients with COVID-19 were admitted to ICUs at Ancona hospital.

Despite these differences, there was an increase in BSIs in patients with COVID-19 in all three centres, both in comparison with other patients hospitalized in 2020 and with patients admitted in 2019. In the Marche Nord hospitals, the incidence of BSI among patients with SARS-CoV-2 was 9.27 per 1000 patient-days vs 2.13 and 3.07, respectively; equivalent figures for Ancona hospital and Fermo hospital were 9.42 vs 2.88 and 2.39, respectively, and 4.17 vs 3.14 and 3.52, respectively (data not shown).

On the contrary, large differences in mortality were observed between the centres. The Marche Nord hospitals and Fermo hospital showed higher mortality rates in patients with COVID-19 (51.8% and 41.7%, respectively) compared with Ancona hospital, which showed 30-day mortality in line with SARS-CoV-2-negative pa-

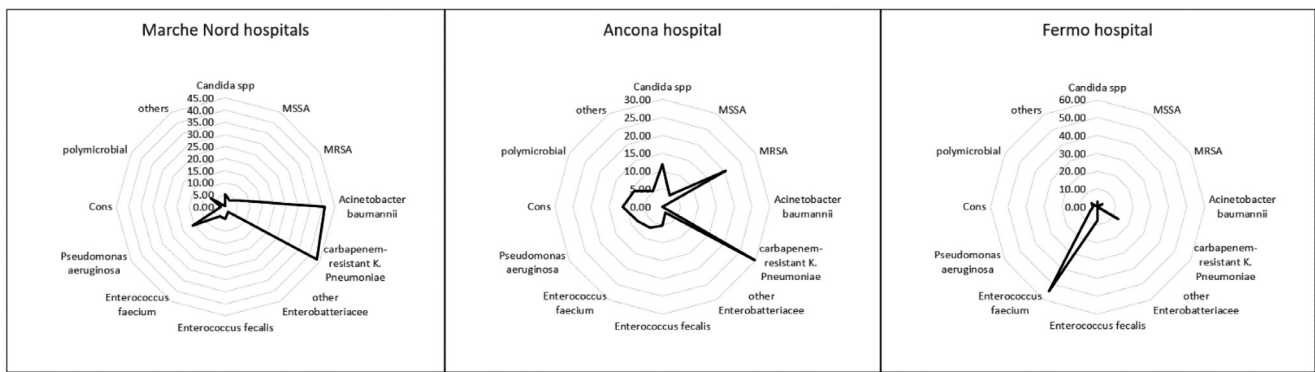


Figure 2. Changes in incidence of pathogens isolated from bloodstream infections of patients with coronavirus disease in 2020 compared with 2019 in the three study centres.

Table 6  
Hospitalization in the three hospital centres

	Hospitalizations in first half of 2019, n	Hospitalizations in first half of 2020		
		All patients	Patients without COVID-19, n (%)	Patients with COVID-19, n (%)
Marche Nord hospitals	11,838	8,696	8085 (93.0%)	611 (7.0%)
Ancona hospital	17,204	12,741	12,379 (97.2%)	362 (2.8%)
Fermo hospital	5,670	4,575	4,366 (95.4%)	209 (4.6%)
Overall	34,712	26,012	24,830 (95.5%)	1,182 (4.5%)

COVID-19, coronavirus disease 2019.

tients (23.1 vs 19.9, respectively;  $P=0.802$ ) and with patients admitted in 2019 (23.1 vs 24.6, respectively;  $P=0.983$ ).

Discussion

The study data show that BSIs are a common complication in patients with COVID-19. The increased incidence of BSI was evident both in normal wards and in ICUs compared with the same time period of 2019. BSIs in patients with COVID-19 were mainly secondary infections, and the increase in incidence was observed from the third day of admission and continued to increase over time, well beyond the viral infection itself. This trend differs greatly from that observed for seasonal influenza, where superinfections usually occur in the first 6 days after symptom onset (Chertow and Memoli, 2013; MacIntyre et al., 2018). This difference may suggest that the altered microbiological clearance of lung alveolar epithelium, due to the viral cytopathic effect, in patients with COVID-19 plays a minor role in promoting superinfections compared with other respiratory viruses (Wilder-Smith et al., 2004; Rynda-Apple et al., 2015; Morris et al., 2017). The increased risk of secondary infection in patients with COVID-19 could be explained by four factors (not mutually exclusive). First, immune system dysregulation, mainly due to two mechanisms: the ‘cytokine storm’, triggered in response to the virus (Fajgenbaum and June, 2020; López-Collazo et al., 2020; McGonagle et al., 2020), and the marked reduction in IFN- $\gamma$  production with the consequent reduction of Th1 polarization of CD4+ T cells and cytotoxic activity (Diao et al., 2020; Qin et al., 2020; Yao et al., 2021). Second, the longer hospitalization time with higher rate of ICU admission, which increases the risk of contracting nosocomial infections (Timsit et al., 2020; Ripa et al., 2021). Third, the high use of immunosuppressive treatments (e.g. corticosteroids, anti-IL6 drugs) (Bengoechea and Bamford, 2020; Campochiaro et al., 2020; Rojas-Marte et al., 2020). Fourth, the gut-lung axis dysfunction due to changes in the gut microbiota (Dumas et al., 2018; Ahlawat and Asha, 2020; Dhar and Mohanty, 2020; Zuo et al., 2020).

Although this study is not sufficiently strong to assess the burden of these four factors, an attempt has been made to limit some potential confounders to better describe the increase in incidence. First, the incidence of BSIs was analysed in terms of the number of cases per 1000 patient-days in order to adjust the different lengths of hospitalization. Second, the incidence rates of BSIs in ICUs and normal wards were calculated separately in order to limit the effect of the higher rate of ICU admission for patients with COVID-19. Doing this showed that the increase in incidence was more evident for normal wards, while it was only significant in ICUs if compared with 2019 rather than with patients without COVID-19 hospitalized in the first half of 2020. Similarly, mortality only showed a significant increase in normal wards, suggesting that particular attention is required for BSIs occurring in non-intensive settings.

With regard to mortality, contrary to what was observed for the incidence of BSIs, large differences were observed between centres. The Marche Nord hospitals and Fermo hospital, which were worst hit by the pandemic, had higher mortality in patients with COVID-19 compared with Ancona hospital, where the pandemic did not impact the regular functioning of the hospital. This confirms that a higher hospitalization rate has an independent harmful impact on mortality in patients with COVID-19 (Carenzo et al., 2020; Ji et al., 2020; Wu et al., 2020; Soria et al., 2021).

From a microbiological view, there was wide variation in the pathogens causing BSIs in patients with COVID-19, with a high proportion of multi-drug-resistant organisms. Interestingly, as carbapenem-resistant *K. pneumoniae* isolates increased significantly at all centres, the prevalence of aetiology was centre-dependent. This suggests that the use of antibiotics and the local ecology play a fundamental role in the selection of multi-drug-resistant pathogens among patients with COVID-19. These data confirm the importance of limiting the use of antibiotics in patients with COVID-19, as suggested by Vaughn et al. (2020).

Despite efforts to limit some of the potential confounders, this study still has numerous limitations, mainly related to the retrospective cohort design and the lack of clinical data such as SOFA score; presence of CVCs; data about source control; laboratory and

radiographic data; and records about the treatments performed, particularly regarding immunosuppressive agents (e.g. dexamethasone, tocilizumab, baricitinib).

These limitations do not enable further investigation with multi-variate analysis of risk factors related to the increased incidence of BSIs and mortality. Further studies are needed to identify which risk factors affect the development of BSIs and which measures are best to limit this.

#### Conflict of interest statement

None declared.

#### Funding

None.

#### Ethical approval

The institutional review board for each centre granted retrospective access to the data without the need for individual informed consent. Consent was not required as the data were analysed anonymously. This study was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments.

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