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Risk Factors and Outcomes of Hospitalized Patients With Severe Coronavirus Disease 2019 (COVID-19) and Secondary Bloodstream Infections: A Multicenter Case-Control Study

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Background. Coronavirus disease 2019 (COVID-19) has become a global pandemic. Clinical characteristics regarding secondary infections in patients with COVID-19 have been reported, but detailed microbiology, risk factors, and outcomes of secondary bloodstream infections (sBSIs) in patients with severe COVID-19 have not been well described.

Methods. We performed a multicenter case-control study including all hospitalized patients diagnosed with severe COVID-19 and blood cultures drawn from 1 March 2020 to 7 May 2020 at 3 academic medical centers in New Jersey. Data collection included demographics, clinical and microbiologic variables, and patient outcomes. Risk factors and outcomes were compared between cases (sBSI) and controls (no sBSI).

Results. A total of 375 hospitalized patients were included. There were 128 sBSIs during the hospitalization. For the first set of positive blood cultures, 117 (91.4%) were bacterial and 7 (5.5%) were fungal. Those with sBSI were more likely to have altered mental status, lower mean percentage oxygen saturation on room air, have septic shock, and be admitted to the intensive care unit compared with controls. In-hospital mortality was higher in those with an sBSI versus controls (53.1% vs 32.8%, $P = .0001$).

Conclusions. We observed that hospitalized adult patients with severe COVID-19 and sBSI had a more severe initial presentation, prolonged hospital course, and worse clinical outcomes. To maintain antimicrobial stewardship principles, further prospective studies are necessary to better characterize risk factors and prediction modeling to better understand when to suspect and empirically treat for sBSIs in severe COVID-19.

Keywords. COVID-19; SARS-CoV-2; coronavirus; bloodstream infections; secondary infections.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), etiology of coronavirus disease 2019 (COVID-19), was first identified in Wuhan, China, in December 2019 [1]. COVID-19 has since become a global pandemic affecting over 21 million lives and resulting in over 776 000 deaths as of 17 August 2020 [2]. COVID-19 has a wide spectrum of manifestations that contribute to increased morbidity and mortality [3, 4]. Complications range from mild symptoms to hypoxic respiratory failure, acute respiratory distress syndrome, thromboembolic disease, cytokine release syndrome (CRS), multiorgan failure, and in some, secondary infections [5, 6].

Secondary bloodstream infections (sBSIs) are well described in patients with influenza or other viral respiratory illnesses, which occur due to alteration in the epithelial surfaces and immune response, resulting in severe inflammation and acquisition of secondary infections [5, 6]. A systematic review in 2018 revealed that 1 in 4 patients with influenza A (H1N1)pmd09 infection had a secondary bacterial infection that led to serious adverse outcomes including intensive care unit (ICU) admission or death [7].

Severe COVID-19 is associated with immune dysregulation, which can predispose patients to concurrent bacterial or fungal infections. There are limited data regarding secondary infections in patients with severe COVID-19 [3, 8, 9]. Zhang et al [10] described patients with severe COVID-19 who suffered a higher rate of secondary infections compared with patients

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with non–severe COVID-19. Another study of patients with COVID-19 revealed that 50% of nonsurvivors had a secondary bacterial infection [4]; however, it did not specify the organism or predisposing risk factors associated with the infection. Thus, there is a gap in the literature regarding secondary infections, specifically sBSIs, in hospitalized patients with severe COVID-19. In this study, we aim to describe epidemiology, risk factors, clinical features, microbiology, and outcomes of patients with severe COVID-19 and sBSIs.

METHODS

Study Design

This is a multicenter case-control study of bacterial and fungal sBSIs in hospitalized patients diagnosed with severe COVID-19 from 1 March 2020 to 7 May 2020. All patients were followed through 3 June 2020. Eligible patients included those with confirmed COVID-19 by a positive SARS-CoV-2 polymerase chain reaction (PCR) test via a nasopharyngeal swab, age 18 years or older, hospitalized, blood cultures drawn during hospitalization, and presence of severe COVID-19 defined as mean oxygen saturation percentage (SpO_2) of 94% or less on room air or requiring supplemental oxygen. The following were excluded: negative COVID-19 test or a presumed COVID-19 infection without a confirmed positive test result, outpatient, or patients requiring hospitalization but without blood cultures drawn.

Cases were defined as patients with confirmed sBSI. Controls were patients with severe COVID-19 without sBSI. Controls were randomly selected from the same day of admission as cases in a 2:1 ratio. After obtaining institutional review board approval from Rutgers University, we reviewed electronic medical records (EMRs) on patients admitted with severe COVID-19 who had blood cultures drawn at 3 different academic medical centers in New Jersey: Robert Wood Johnson University Hospital (RWJUH), University Hospital (UH), and Robert Wood Johnson University Hospital–Somerset (RWJ-S). Key epidemiological, demographic, clinical, laboratory, microbiologic, and outcome data were abstracted from the EMR using a standardized data-collection tool.

Variables

Bloodstream infection was defined as bacterial or fungal infection identified on blood cultures. Blood cultures were performed using BACTEC FX (Beckton, Dickinson and Co., Franklin Lakes, NJ) Blood Culture Systems. Direct molecular detection of *Candida* spp. (*Candida albicans/Candida tropicalis, Candida glabrata/Candida krusei*, and *Candida parapsilosis*) from whole blood was performed using the T2Candida Panel (only available at RWJUH). Blood cultures were considered a contaminant if there was presence of coagulase-negative *Staphylococcus* species in only 1 out of 2 blood cultures without clinical evidence of a true bacteremia as deemed by the treating clinical team. Source of BSIs included surgical site infection (based on Centers for Disease Control and Prevention/National Healthcare Safety Network criteria) [11], pneumonia (clinical evidence of pulmonary infection with radiographic imaging and a compatible organism identified on respiratory culture), central line–associated BSI (CLABSI; positive blood cultures in the presence of a central line documented by the treating physician), urinary tract infection, intra-abdominal infection, or unknown/not reported if no clinical source of BSI was identified by the treating physician.

Statistical Analysis

Descriptive statistics were used to describe the sample of patients with COVID-19, including mean and standard deviation, median and interquartile range (IQR) for continuous variables, and proportions for categorical variables. Risk factors and outcomes were compared between cases (sBSI) and controls (no sBSI). Group comparisons were performed using 2-sample *t* tests for normally distributed continuous variables and Mann–Whitney *U* tests for non–normally distributed continuous variables. Differences in proportions were compared using a chi-square test or Fisher's exact test. Logistic regression was used to calculate odds ratios and 95% confidence intervals for associations between risk factors and sBSIs adjusted for age, sex, and race. All tests of significance are 2-tailed. The α level was set at .05. Propensity score matching was performed using the radius method in SAS (SAS Institute, Cary, NC) [12, 13]. Analyses were performed using SAS version 9.4.

RESULTS

A total of 1735 adult patients were identified at 3 centers in New Jersey (34.7% RWJUH, 24.0% RWJ-S, and 41.3% UH) with COVID-19 between 1 March 2020 and 7 May 2020. After applying exclusion criteria, 375 patients were included (Figure 1). Participant characteristics are shown in Table 1. The median age was 64 years (IQR, 53–75 years), and 61.1% were male. Most participants were African American (30.4%) or Hispanic/Latino (29.3%). The mean duration of symptoms was 5.6 days. Demographic characteristics were similar by site (data not shown).

Most blood cultures were drawn on the day of admission. The median time from admission to the first blood culture draw was 0 days (IQR, 0–1 days), of which 69 (53.9%) were positive. There were a number of contaminants before or after the first positive blood culture for a true pathogen: 13 (10.7%) on the first blood draw, 12 (23.1%) on the second, 2 (13.3%) on the third, and 1 (16.7%) on the fourth. The median time from admission to the first positive blood culture was 6 days (IQR, 1–13 days), ranging from 0 to 36 days. For the first set of positive blood cultures, 117 (91.4%) were bacterial and 7 (5.5%) were fungal. The most common pathogens isolated from the first set of positive blood culture were *Staphylococcus epidermidis,* methicillin-sensitive *Staphylococcus aureus* (MSSA), *Enterococcus faecalis, Escherichia*

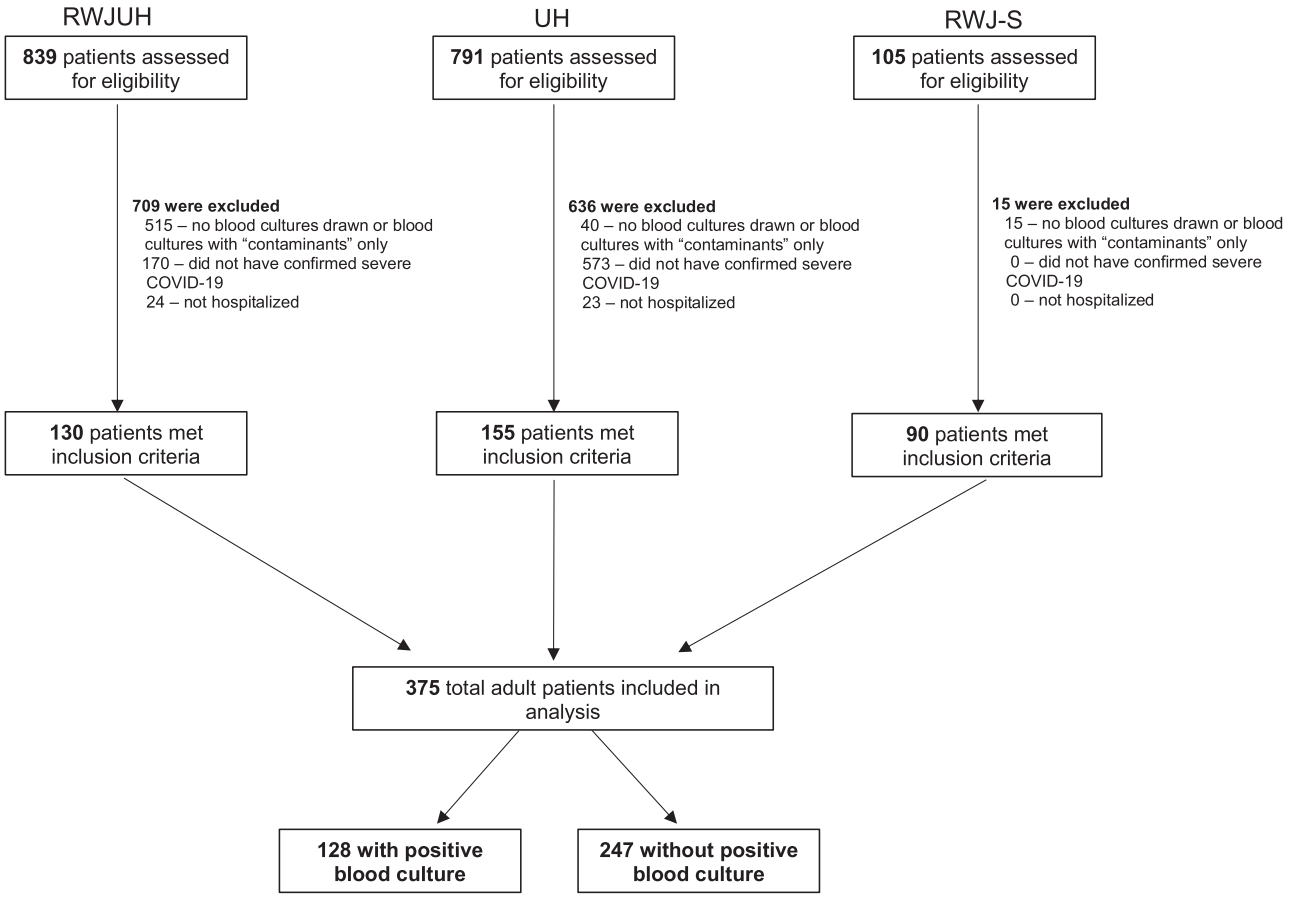

Figure 1. Flow chart of patients with severe COVID-19 who were assessed for eligibility (N = 1735) and included in the study (N = 375) from 3 academic centers. Abbreviations: COVID-19, coronavirus disease 2019; RWJ-S, Robert Wood Johnson University Hospital–Somerset; RWJUH, Robert Wood Johnson University Hospital; UH, University Hospital.

coli, methicillin-resistant *Staphylococcus aureus* (MRSA), *C. albicans*, and *C. glabrata*. The most common presumed source was unknown/not reported, followed by line-related and lungs. Data regarding the second, third, and fourth set of blood cultures are available in Figure 2 and Supplementary Table 1. The median time from admission to a positive T2 *Candida* PCR was 13 days (IQR, 12–25 days). Twelve T2 *Candida* PCR tests were ordered, of which 5 (41.7%) were positive for *C. albicans/C. tropicalis* (4; 80%) and *C. parapsilosis* (1; 20%). None of the positive T2 *Candida* PCR tests were considered to be a contaminant. The most common presumed source was unknown/not reported followed by abdomen. The overall median time of sBSI in our cohort was 3 days (IQR, 2–6 days). Among all patients with sBSIs, 50.8% were considered nosocomial acquisition as defined by positive blood cultures more than 48 hours from time of admission.

Cases and controls were compared to evaluate for risk factors for sBSI (Table 2). Patients with sBSIs were less likely to have cough (45.3% vs 65.2%, $P = .0002$) and fever (54.7% vs 66.8%, $P = .02$) as a presenting symptom compared with those without sBSIs; however, AMS (23.4% vs 11.7%, $P = .003$) was more common in those with sBSIs. The number of patients with diarrhea or abdominal pain as a presenting symptom was not different between groups. The mean percentage oxygen saturation on room air upon initial presentation was lower in those with sBSI compared with controls (82.5% vs 86.1%). More patients with sBSIs were intubated compared with controls (23.8% vs 8.1%; $P < .0001$) on the day of positive COVID-19 test. Mean baseline white blood cell (WBC) count (10.9 vs 8.6, $P < .001$) and creatinine (2.23 vs 1.49, $P = .001$) were higher in the patients with sBSIs than in controls. Those with an sBSI were more likely to have a central line (78.1% vs 32%, $P < .0001$), with a mean duration of 7.1 days prior onset of BSI. Invasive procedures including endotracheal intubation (65.6% vs 29.6%, $P < .0001$) and continuous veno-venous hemofiltration/hemodialysis (35.9% vs 9.3%, $P < .0001$) were common in those with sBSI compared with controls. All findings remained consistent in multivariable logistic regression models adjusting for age, sex, and race.

Data for treatment and outcomes are shown in Table 3. Septic shock requiring vasopressors (55.5% vs 14.2%, $P < .001$), use of antimicrobial therapy (99.2% vs 70.5%, $P < .001$), and

Table 1. Characteristics of Patients With Severe COVID-19 and Blood Cultures Drawn During Hospitalization

Characteristics	Total (N = 375)
Demographic	
Site, n (%)	
RWJUH	130 (34.7)
UH	155 (41.3)
RWJ-S	90 (24.0)
Sex, n (%)	
Male	229 (61.1)
Female	146 (38.9)
Age, mean (SD), years	63.2 (16.2)
Race/ethnicity, n (%)	
Hispanic or Latino	110 (29.3)
White	98 (26.1)
African American	114 (30.4)
Asian	30 (8.0)
Native Hawaiian	1 (0.3)
Unknown/not reported	22 (5·9)
Insurance status, n (%)	
Medicare only	123 (32.8)
Medicaid only	49 (13.1)
Private only	122 (32.5)
More than 1	19 (5.1)
Uninsured	43 (11.5)
Other	11 (2.9)
Unknown	8 (2.1)
BMI, mean (SD), kg/m^2	29.6 (7.5)
Comorbidities, n (%)	
Diabetes mellitus	131 (34.9)
Lung disease	60 (16.0)
Coronary artery disease	48 (12.8)
Hypertension	219 (58.4)
Hyperlipidemia	105 (28.0)
Congestive heart failure	22 (5.9)
Cerebrovascular disease/history of stroke	31 (8.3)
Malignancy	41 (10.9)
Solid-organ transplant recipient	8 (2.1)
Bone marrow transplant recipient	0 (0.0)
Autoimmune disease	14 (3.7)
Active gastrointestinal disease	27 (7.2)
HIV	6 (1.6)
CKD stage 3 or more	38 (10.1)
Immunosuppressant use	20 (5.3)
Symptoms	
Duration of symptoms, mean (SD), days	5.6 (4.5)
Duration (range), days	0–28
Abdominal pain, n (%)	23 (6.1)
Diarrhea, n (%)	52 (13.9)
Cough, n (%)	219 (58.4)
Fever, n (%)	235 (62.7)
Shortness of breath, n (%)	158 (42.1)
Hypoxia, n (%)	90 (24.0)
Acute mental status change, n (%)	59 (15.7)
SaO_2	
SaO_2, mean (SD), %	85.0 (11.8)
Needed O_2 on room air on admission, n (%)	256 (68.3)
If yes, type of O_2 on admission, n (%)	
Nasal cannula	167 (65.5)
Non-rebreather	49 (19.2)
High-flow nasal cannula	6 (2.4)
BiPAP	6 (2.4)
Intubated	27 (10.6)
SaO_2 at time of positive COVID-19 test, %	89.9 (10.6)
Required O_2 on date of positive COVID-19 test, n (%)	315 (84.0)
Type of O_2 required on date of COVID-19 test, n (%)	
Nasal cannula	197 (62.5)
Non-rebreather	64 (20.3)
High-flow nasal cannula	6 (1.9)
BiPAP	6 (1.9)
Intubated	42 (13.3)

Abbreviations: BiPAP, bilevel positive airway pressure; BMI, body mass index; CKD, chronic kidney disease; COVID-19, coronavirus disease 2019; HIV, human immunodeficiency virus; RWJ-S, Robert Wood Johnson University Hospital–Somerset; RWJUH, Robert Wood Johnson University Hospital; SaO_2, oxygen saturation; SD, standard deviation; UH, University Hospital.

use of systemic glucocorticoids (32% vs 17.8%, $P = .002$) was more common in those with sBSI. The most common empirical antimicrobials were ceftriaxone, azithromycin, and piperacillin-tazobactam. The median length of hospital stay was significantly longer in the sBSI group (18.5 vs 7 days, $P < .001$). Patients with sBSIs were also more likely to require ICU admission (71.1% vs 35.6%, $P < .001$) with a longer median length of ICU stay (17 vs 6.5 days, $P < .001$). More patients with sBSIs died in-hospital compared with those without (53.1% vs 32.8%, $P = .0001$). As of 3 June 2020, more patients without sBSIs were alive and discharged from the hospital (98.8% vs 63.3%, $P < .0001$), whereas those with sBSIs were still hospitalized (36.7% vs 1.2%, $P < .0001$). All findings, including mortality, remained consistent in multivariable logistic regression models adjusting for age, sex, and race as well as a propensity score–matched analysis (Supplementary Table 2). Additionally, among patients with sBSIs, the proportion who died did not vary by nosocomial acquisition status.

DISCUSSION

To our knowledge, this is the first study to assess the microbiology, risk factors, and outcomes in hospitalized patients with severe COVID-19 with sBSIs. We observed that patients with more advanced types of supplemental oxygen on admission were associated with higher odds of sBSI. Interestingly, there were significantly fewer patients with sBSIs presenting with cough and fever but rather with AMS, higher WBC count, and higher serum creatinine. Additionally, in our secondary descriptive analysis, we observed that patients with sBSIs were more likely to require intubation and renal replacement therapy and had worse clinical outcomes including septic shock requiring vasopressors, admission to the ICU, longer hospital length of stay, longer length of ICU stay, and greater in-hospital mortality. In summary, patients with sBSIs were significantly

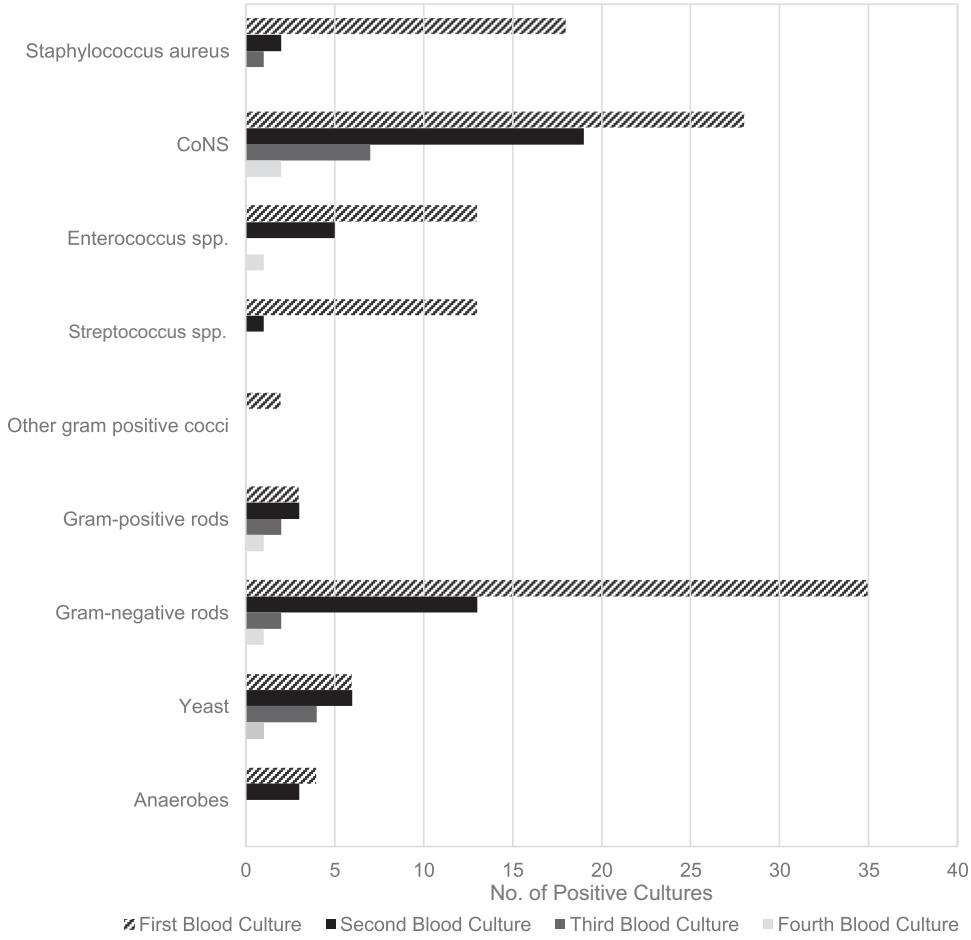

Figure 2. Identification of organisms from all blood cultures in hospitalized patients with COVID-19 and secondary BSI. Abbreviations: BSI, bloodstream infection; CoNS, coagulase-negative *Staphylococci*; COVID-19, coronavirus disease 2019.

more ill upon presentation and had poorer outcomes. The sBSIs observed in patients with COVID-19 may have contributed to the more severe presentation and clinical course and/or reflect other underlying physiological and immunological complications of COVID-19. Alternatively, a complicated hospital course may have contributed to acquiring more risk factors for developing sBSI.

In our cohort, the majority of BSIs had an unknown source. However, CLABSI was found to be the most common presumed source of sBSI. Prior studies report bacterial pneumonia as the primary source of bacteremia in those with influenza or other coronaviruses [14]. This has infection-control implications as the presence of airborne/contact precautions and fear of prolonged patient contact and aerosolization could be a barrier to good catheter hygiene and maintenance, increasing the risk of CLABSI. Alternatively, patients with sBSIs were more likely to require longer hospitalization or ICU stay, thus predisposing them to a prolonged indwelling line and developing CLABSI. As previously reported [15], we also found that the most common cause of bacteremia was due to *S. aureus*, *E. faecalis*, and *E. coli*.

We observed numerous cases of fungemia caused by *Candida* species, which is in contrast to previous reports [14, 16]. One notable finding was a positive blood culture for *Cryptococcus neoformans*. Invasive fungal infections in patients with COVID-19, such as *Aspergillus* spp., have been reported [17–20] but there are limited data regarding cryptococcemia. Our patient was a 70-year-old human immunodeficiency virus–negative female with decompensated liver cirrhosis secondary to nonalcoholic steatohepatitis and hepatocellular carcinoma who presented with AMS. She was tested positive for COVID-19 on admission and was hypotensive requiring vasopressors. Patient expired on day 2 of hospitalization however 5 days after admission, blood cultures were positive for *Cryptococcus neoformans*. To the best of our knowledge, this is the first reported case of disseminated *Cryptococcus* in a patient with COVID-19.

A recent study assessing blood culture utilization in New York City observed a significant proportion of contaminant blood cultures [15]. In our study, we noted a large number of blood cultures deemed to be a contaminant before or after the first positive blood culture with true pathogen. At the time of this study, New Jersey was experiencing a surge in cases along

Table 2. Risk Factors Associated With Secondary Bloodstream Infection in Patients With Severe COVID-19

Risk factor	No sBSI (n = 247)	sBSI (n = 128)	*P*
Characteristics and comorbidities			
Sex, n (%)			
Male	149 (60.3)	80 (62.5)	.68
Female	98 (39.7)	48 (37.5)	
Age, mean (SD), years	62.0 (16.8)	65.6 (14.7)	.043
Race, n (%)			
Hispanic or Latino	68 (27.5)	42 (32.8)	.15
White	64 (25.9)	34 (26.6)	
African American	83 (33.6)	31 (24.2)	
Asian	21 (8.5)	9 (7.0)	
Native Hawaiian	1 (0.4)	0 (0.0)	
Unknown/not reported	10 (4.1)	12 (9.4)	
Insurance status, n (%)			
Medicare only	83 (33.6)	40 (31.3)	.06
Medicaid only	38 (15.4)	11 (8.6)	
Private only	78 (31.6)	44 (34.4)	
More than 1	7 (2.8)	12 (9.4)	
Uninsured	27 (10.9)	16 (12.5)	
Other	9 (3.6)	2 (1.6)	
Unknown	5 (2.0)	3 (2.3)	
BMI, mean (SD), kg/m^2	30.0 (7.3)	28.6 (8.0)	.09
Diabetes mellitus, n (%)	81 (32.8)	50 (39.1)	.23
Lung disease, n (%)	37 (15.0)	23 (18.0)	.45
Coronary artery disease, n (%)	29 (11.7)	19 (14.8)	.39
Hypertension, n (%)	148 (59.9)	71 (55.5)	.41
Hyperlipidemia, n (%)	75 (30.4)	30 (23.4)	.16
Congestive heart failure, n (%)	13 (5.3)	9 (7.0)	.49
Cerebrovascular disease/history of stroke, n (%)	19 (7.7)	12 (9.4)	.57
Malignancy, n (%)	26 (10.5)	15 (11.7)	.73
Solid-organ transplant recipient, n (%)	5 (2.0)	3 (2.3)	.84
Bone marrow transplant recipient, n (%)	0 (0.0)	0 (0.0)	…
Autoimmune disease, n (%)	8 (3.2)	6 (4.7)	.48
Active gastrointestinal disease, n (%)	15 (6.1)	12 (9.4)	.24
HIV, n (%)	3 (1.2)	3 (2.3)	.41
CKD stage 3 or more, n (%)	24 (9.7)	14 (10.9)	.71
Immunosuppressant use, n (%)	14 (5.7)	6 (4.7)	.69
Symptoms			
Duration of symptoms, mean (SD), days	5.8 (4.5)	5.1 (4.5)	.18
Abdominal pain, n (%)	18 (7.3)	5 (3.9)	.20
Diarrhea, n (%)	38 (15.4)	14 (10.9)	.24
Cough, n (%)	161 (65.2)	58 (45.3)	.0002
Fever, n (%)	165 (66.8)	70 (54.7)	.02
Shortness of breath, n (%)	107 (43.3)	51 (39.8)	.52
Hypoxia, n (%)	60 (24.3)	30 (23.4)	.85
Acute mental status change, n (%)	29 (11.7)	30 (23.4)	.003
SaO_2			
SaO_2, mean (SD), %	86.1 (10.5)	82.5 (13.9)	.007
Needed O_2 on room air on admission, n (%)	156 (63.2)	100 (78.1)	.003
If yes, type of O_2 on admission, n (%)			
Nasal cannula	114 (73.1)	53 (53.5)	.003
Non-rebreather	27 (17.3)	22 (22.2)	
High-flow nasal cannula	3 (1.9)	3 (3.0)	
BiPAP	4 (2.6)	2 (2.0)	
Intubated	8 (5.1)	19 (19.2)	
SaO_2 at time of positive COVID-19 test	89.7 (10.3)	90.2 (11.2)	.72
Required O_2 on date of positive COVID-19 test, n (%)	210 (85.0)	105 (82.0)	.45
Type of O_2 required on date of COVID-19 test			

Table 2. Continued

Risk factor	No sBSI (n = 247)	sBSI (n = 128)	*P*
Nasal cannula	151 (71.9)	46 (43.8)	<.0001
Non-rebreather	36 (17.1)	28 (26.7)	
High-flow nasal cannula	3 (1.4)	3 (2.9)	
BiPAP	3 (1.4)	3 (2.9)	
Intubated	17 (8.1)	25 (23.8)	
Labs (on date of positive COVID-19 test)			
WBC count, mean (SD), $\times 10^9$/L	8.6 (4.7)	10.9 (6.1)	<.0001
Creatinine, mean (SD), mg/dL	1.49 (1.8)	2.23 (2.5)	.001
CRP,[a] mean (SD), mg/dL	67.4 (94.6)	173.2 (25.4)	.30
D-Dimer,[b] mean (SD), ng/mL	2976 (7191)	5437 (13 148)	.06
Ferritin,[c] mean (SD), ng/mL	1197 (1935)	1854 (5301)	.12
Abdominal imaging, n (%)			
Colitis	0 (0.0)	3 (2.3)	.04
Cholecystitis	1 (0.4)	1 (0.8)	1.00
Pancreatitis	1 (0.4)	0 (0.0)	1.00
Intra-abdominal or pelvic abscess	0 (0.0)	2 (1.6)	.12
Pyelonephritis	0 (0.0)	2 (1.6)	.12
Small bowel obstruction or ileus	1 (0.4)	2 (1.6)	.27
Ascites	2 (0.8)	5 (3.9)	.048
Central line and procedures			
Central line, n (%)	79 (32.0)	100 (78.1)	<.0001
If yes to central line, duration of central line, mean (SD), days	7.7 (6.4)	7.1 (8.7)	.71
EGD, n (%)	0 (0.0)	1 (0.8)	.34
PEG, n (%)	2 (0.8)	8 (6.3)	.004
Percutaneous cholecystostomy tube, n (%)	1 (0.4)	1 (0.8)	1.0
Coronary catherization, n (%)	1 (0.4)	0 (0.0)	1.0
ECMO, n (%),	0 (0.0)	1 (0.8)	.34
Endotracheal tube/intubation, n (%)	73 (29.6)	84 (65.6)	<.0001
Tracheostomy, n (%)	0 (0.0)	12 (9.4)	<.0001
Chest tube placement, n (%)	6 (2.4)	7 (5.5)	.14
Paracentesis, n (%)	1 (0.4)	0 (0.0)	1.00
Abscess drainage, n (%)	0 (0.0)	2 (1.6)	.12
TPN, n (%)	3 (1.2)	3 (2.3)	.41
CVVH or hemodialysis, n (%)	23 (9.3)	46 (35.9)	<.0001
Peritoneal dialysis, n (%)	0 (0.0)	9 (7.0)	<.0001

Abbreviations: BiPAP, bilevel positive airway pressure; BMI, body mass index; CKD, chronic kidney disease; CRP, C-reactive protein; COVID-19, coronavirus disease 2019; CVVH, continuous veno-venous hemofiltration; ECMO, extracorporeal membrane oxygenation; EGD, esophagogastroduodenoscopy; HIV, human immunodeficiency virus; PEG, percutaneous endoscopic gastrostomy; SaO_2, oxygen saturation; sBSI, secondary bloodstream infection; SD, standard deviation; TPN, total parenteral nutrition; WBC, white blood cell.

[a]Missing values: n = 85.

[b]Missing values: n = 126.

[c]Missing values: n = 70.

with New York City. This undoubtedly caused a strain on the healthcare system, causing a lack of personal protective equipment (PPE) and affecting how some of the blood cultures may have been drawn. Additionally, the presence of airborne/contact isolation likely affected the quality of blood culture draws at the time.

Presenting symptoms such as fever, cough, and dyspnea have been widely reported in severe COVID-19 [4, 10, 21]. However, our findings indicated that AMS was a more common presenting symptom in patients with sBSIs, while fever and cough were less common. Additionally, the higher prevalence of leukocytosis and acute kidney injury in the sBSI cohort represents classical markers of immune response to systemic infection and organ dysfunction secondary to impending onset of septic shock as noted in prior epidemiological studies of COVID-19 [4]. Last, we observed that patients with sBSIs present to the hospital in more severe respiratory distress as noted by lower oxygen saturation and need for advanced oxygen supplementation. These presenting symptoms may reflect a superimposed effect of bacterial or fungal sepsis with severe COVID-19 or a marker of critical illness due to COVID-19 itself. Similar clinical manifestations of respiratory failure and sepsis have been noted in patients with secondary infections and influenza [22, 23], but there are limited data describing this level of critical illness in other viral infections. We hypothesized that the presence of abdominal pain or diarrhea on admission may be a risk factor for developing sBSI due to an enteric organism; however, this was not observed. Diabetes mellitus plays a significant role

Table 3. Treatment and Outcomes in Hospitalized Patients With Severe COVID-19 With or Without a Secondary Bloodstream Infection

Variable	All (N = 375)	No sBSI (n = 247)	sBSI (n = 128)	*P*
Ever received intravenous antimicrobial therapy, n (%)	301 (80.3)	174 (70.5)	127 (99.2)	<.001
Ever received systemic glucocorticoids, n (%)	85 (22.7)	44 (17.8)	41 (32.0)	.002
Ever received tocilizumab, n (%)	88 (23.5)	54 (21.9)	34 (26.6)	.309
Length of hospital stay, median (IQR), days	9 (5, 17)	7 (4, 12)	18.5 (9, 33.5)	<.001
Admission to ICU, n (%)	179 (47.7)	88 (35.6)	91 (71.1)	<.001
Length of ICU stay, median (IQR), days	9 (5, 19)	6.5 (4, 11)	17 (7, 26)	<.001
Septic shock requiring vasopressors, n (%)	106 (28.3)	35 (14.2)	71 (55.5)	<.001
In-hospital death, n (%)	149 (39.7)	81 (32.8)	68 (53.1)	.0001
Of those who died, died <7 days (admission to death)	73 (49.0)	51 (63.0)	22 (32.3)	<.001
Of those who died, died 8–14 days (admission to death)	28 (18.8)	17 (21.0)	11 (16.2)	
Of those who died, died >15 days (admission to death)	48 (32.2)	13 (16.1)	35 (51.5)	
Alive as of 3 June 2020, n (%)	226 (60.3)	166 (67.2)	60 (46.9)	.0001
Of those alive, discharged	202 (89.4)	164 (98.8)	38 (63.3)	<.0001
Of those alive, still hospitalized as of 3 June 2020	24 (10.6)	2 (1.2)	22 (36.7)	
Readmission with bacteremia, n (%)	2 (1.0)	1 (0.6)	1 (2.7)	.337

Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care unit; IQR, interquartile range; sBSI, secondary bloodstream infection.

in the severity of COVID-19 [24–27]; however, our study did not find it to be a risk factor for sBSIs.

A review of secondary infections in patients with coronavirus infections, including COVID-19, reported that approximately 70% of patients received antimicrobials [28]. This is consistent with our study finding that 80% of patients received antimicrobials at some point during hospitalization. More notably, most patients received antimicrobials despite having negative blood cultures. This likely reflects the clinician's inclination to administer empiric antimicrobial coverage given the limited information on the natural course of this novel disease. Suspicion of bacterial sepsis without positive blood cultures may be confounded by the viral sepsis presentation associated with severe COVID-19. This supports the fact that antimicrobial stewardship remains crucial during this unprecedented time [28]. Given the scale of the pandemic, indiscriminate antimicrobial use will inevitably lead to widespread complications such as adverse drug reactions, antimicrobial resistance, and *Clostridium difficile* infections. To enable a better understanding of the antibiogram and appropriate empiric antimicrobial choices in patients at high risk of sBSI across different regions in the United States and globally, larger prospective studies and public health surveillance strategies are urgently required.

Increased morbidity and mortality associated with secondary bacterial infections have been well described for prior influenza pandemics, but there are limited data for SARS-CoV-2 [29]. In our study, clinical outcomes were significantly worse for patients with sBSI as noted by a higher percentage of septic shock, admission to ICU, longer length of hospital and ICU stay, and higher in-hospital mortality. The significant differences remained consistent with both multivariable regression and propensity score–matched analyses. While previous studies [16, 30] have described coinfections in patients with COVID-19, a number of cases lack detailed case descriptions. Across 3 academic medical centers in New Jersey, we were able to examine 128 patients with sBSIs. The in-hospital mortality rate was over 50% for these patients. We emphasize caution in conclusions related to clinical outcomes such as mortality, as the primary intent of our case-control study was to examine risk factors associated with sBSIs in patients with COVID-19 and was not a cohort study intended to examine predictors of mortality.

Our study had some limitations. First, the retrospective, observational design limits understanding of clinical decisions. Many patients had missing variables depending on their clinical course or physician's discretion at time of care. We did not collect data such as cultures of other types of secondary infections or cause of mortality as this information was incomplete in the EMR. We focused on sBSIs given the higher level of diagnostic certainty for retrospective investigation. Second, lack of standardized care given the novelty of the virus resulted in heterogenous management within and among hospitals. This may have also contributed to poor clinical outcomes, which we are unable to reasonably distinguish. Third, although our sample size is relatively large for this complication, our study does not use a nationally representative sample. Therefore, results must be carefully interpreted before generalizing to differing populations or geographical regions. Fourth, misclassification between contaminant versus pathogens was possible as we relied on the documentation of the clinical team's interpretation at the time of data collection. Last, the source of sBSI was primarily based on correlation to other positive body-site cultures with the same organism and the clinical team's assessment. It is difficult to discern the true source for a retrospective study.

Our study has several strengths. First, to the best of our knowledge, this is the first multicenter study to examine detailed microbiology, risk factors, and outcomes in hospitalized patients with severe COVID-19 with sBSIs. This adds to the

limited literature for COVID-19 and provides clinically relevant data for antimicrobial stewardship to better assess appropriate antimicrobial therapy in patients with COVID-19 suspected of having sBSI. Second, there was higher reliability in the case definition of sBSI in comparison to studies evaluating a broad scope of secondary or coinfections. Although microbiologically diagnosed infections were noted in most studies describing secondary infections in COVID-19, this could be clinically biased as there may be difficulty distinguishing between colonization versus a true infection [8, 31, 32]. Third, the 3 centers in this study are geographically diverse and serve suburban to inner-city communities providing a diverse study population.

In summary, hospitalized adult patients with severe COVID-19 with sBSIs had a more severe initial presentation, prolonged hospital course, and worse clinical outcomes. To maintain antimicrobial stewardship principles, further prospective studies are necessary to better characterize risk factors and prediction modeling to better understand when to suspect and empirically treat for sBSIs in severe COVID-19.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. P. J. B. and N. N. had the idea for and designed the study. P. J. B., L. B., Y. X., K. S., S. K., S. M., P. H. A., C. P., P. U., and R. N. collected the data. N. N. and S. S. analyzed the data. P. J. B., N. N., and S. S. prepared the manuscript. P. U. provided guidance on the microbiology content of the manuscript and figures. All authors critically reviewed the manuscript for content and gave final approval for publication.

Potential conflicts of interest. P. J. B. reports a research grant from Gilead outside the submitted work. N. N. serves on the speaker's bureau for Astellas Pharma. R. N. reports advisory/speaking fees as a consultant for Gilead, Merck, Abbvie, and ViiV and research grants from Gilead, Merck, Abbvie, ViiV, and Alkermes outside the submitted work. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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