Risk Factors and Outcomes of Hospitalized Patients with Severe COVID-19 and Secondary Bloodstream Infections: A Multicenter, Case-Control Study

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Summary: Limited data are available regarding secondary bloodstream infections in hospitalized patients with severe COVID-19. COVID-19 patients with secondary bloodstream infections had more severe initial presentation, prolonged hospital course, and worse clinical outcomes compared to COVID-19 patients without secondary bloodstream infections

ABSTRACT

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 (sBSI) 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 March 1, 2020 to May 7, 2020 at three academic medical centers in New Jersey, USA. 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 percent oxygen saturation on room air, have septic shock and be admitted to the intensive care unit compared to the controls. In-hospital mortality was higher in those with a sBSI versus controls (53.1% vs 32.8%, p=0.0001).

Conclusions

We observed 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 sBSI in severe COVID-19.

Keywords: COVID-19, SARS-CoV-2, coronavirus, bloodstream infections, secondary infections

INTRODUCTION:

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 resulting in over 776,000 deaths as of August 17, 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), multi-organ failure, and in some, secondary infections.[5,6]

Secondary bloodstream infections (sBSI) 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 one in four patients with Influenza A (H1N1)pmd09 infection had a secondary bacterial infection which 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. described patients with severe COVID-19 suffered a higher rate of secondary infections compared to patients with non-severe COVID-19.[10] Another study of COVID-19 patients revealed that 50% of non-survivors 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 sBSI.

METHODS

Study design

This is a multicenter, case-control study of bacterial and fungal sBSI in hospitalized patients diagnosed with severe COVID-19 from March 1, 2020 to May 7, 2020. All patients were followed through June 3, 2020. Eligible patients included those with confirmed COVID-19 by a positive SARS-CoV-2 PCR test via a nasopharyngeal swab, age $\geq$ 18 years, hospitalized, blood cultures drawn during hospitalization and presence of severe COVID-19 defined as SpO2 $\leq$ 94% 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 severe COVID-19 patients 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 (EMR) on patients admitted with severe COVID-19 who had blood cultures drawn at three 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

BSI was defined as bacterial or fungal infection identified on blood cultures. Blood cultures were performed using BD BACTEC™ 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 CDC/NHSN 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 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 COVID-19 patients, including mean and standard deviation, median and interquartile range, range 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 two 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 sBSI adjusted for age, sex, and race. All tests of significance are two-tailed. Alpha was set at 0.05. Propensity score

matching was performed using the radius method in SAS.[12,13] Analyses were performed using SAS version 9.4 (Cary, North Carolina, USA).

RESULTS

A total of 1,735 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 March 1, 2020 and May 7, 2020. After applying exclusion criteria, 375 patients were included (**Figure 1**). Participant characteristics are shown in **Table 1**. Median age was 64 years (IQR 53-75), 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), 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. Median time from admission to the first positive blood culture was 6 days (IQR 1-13), 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 coli*, methicillin-resistant *Staphylococcus aureus* (MRSA), *Candida albicans and Candida glabrata*. The most common presumed source was unknown/not reported, followed by line-related and lungs. Data regarding 2nd, 3rd and 4th set of blood cultures are available in **Figure**

2 and **Supplementary Table 1.** Median time from admission to a positive T2 Candida PCR was 13 days (IQR 12-25). Twelve T2 Candida PCR tests were ordered, of which, 5 (41.7%) were positive for *Candida albicans/Candida tropicalis* (4, 80%) and *Candida parapsilosis* (1, 20%). None of the positive T2 Candida PCR 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). Among all patients with sBSI, 50.8% were considered nosocomial acquisition as defined by positive blood cultures >48 hours from time of admission.

Cases and controls were compared to evaluate for risk factors for sBSI (**Table 2)**. Patients with sBSI were less likely to have cough (45.3% vs 65.2%, p=0.0002) and fever (54.7% vs 66.8%, p=0.02) as a presenting symptom compared to those without sBSI, however AMS (23.4% vs 11.7%, p=0.003) was more common in those with sBSI. The number of patients with diarrhea or abdominal pain as a presenting symptom was not different between groups. The mean percent oxygen saturation on room air upon initial presentation was lower in those with sBSI compared to controls (82.5% vs 86.1%). More patients with sBSI were intubated compared to the controls (23.8% vs 8.1%; p<0.0001) on the day of positive COVID-19 test. Mean baseline white blood cell count (WBC) (10.9 vs 8.6, p<0.001) and creatinine (2.23 vs 1.49, p=0.001) was higher in the sBSI than the controls. Those with sBSI were more likely to have a central line (78.1% vs 32%; p<0.0001) with a mean duration of 7.1 days prior onset of BSI. Invasive procedures including endotracheal intubation (65.6% vs 29.6%, p<0.0001) and CVVH/hemodialysis (35.9% vs 9.3%, p<0.0001) were common in those with sBSI compared to 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<0.001), use of antimicrobial therapy (99.2% vs 70.5%, p<0.001) and use of systemic glucocorticoids (32% vs 17.8%, p=0.002) was more common in those with sBSI. The most common empirical antimicrobials were ceftriaxone, azithromycin, and piperacillin-tazobactam. Median length of hospital stay was significantly longer in the sBSI group (18.5 days vs 7 days, p<0.001). Patients with sBSI were also more likely to require ICU admission (71.1% vs 35.6%, p<0.001) with a longer median length of ICU stay (17 days vs 6.5 days, p<0.001). More patients with sBSI died in-hospital compared to those without (53.1% vs 32.8%, p=0.0001). As of June 3, 2020, more patients without sBSI were alive and discharged from the hospital (98.8% vs 63.3%, p<0.0001) whereas those with sBSI were still hospitalized (36.7% vs 1.2%, p<0.0001). 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 sBSI, proportion of death 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 was associated with higher odds of sBSI. Interestingly, there were significantly less patients with sBSI presenting with cough and fever but rather with AMS, higher WBC, higher serum creatinine. Additionally, in our secondary descriptive analysis, we observed patients with sBSIs were more likely to require intubation, renal replacement therapy, and had worse clinical outcomes including septic shock requiring vasopressors, admission

to ICU, longer hospital length of stay, longer length of ICU stay, and greater in-hospital mortality. In summary, patients with sBSI were significantly more ill upon presentation and had poorer outcomes. The sBSIs observed in COVID-19 patients 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 sBSI 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 *Staphylococcus aureus*, *Enterococcus faecalis* and *Escherichia 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 COVID-19 patients, such as *Aspergillus spp,,* have been reported [17-20] but there is limited data regarding cryptococcemia. Our patient was a 70-year-old HIV-negative female with decompensated liver cirrhosis secondary to non-alcoholic 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 with New York City. This undoubtedly caused a strain on the health care system causing a lack of 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 sBSI while fever and cough were less common. Additionally, the higher prevalence of leukocytosis and acute kidney injury in the sBSI cohort represent 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] Lastly, we observed that patients with sBSI 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 in the severity of COVID-19[24-27] however our study did not find it to be a risk factor for sBSI.

A review of secondary infections in patients with coronavirus infections, including COVID-19, reported 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 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 *C. 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 has 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 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 co-infections in COVID-19 patients, number of cases lack detailed case descriptions. Across three academic medical

centers in New Jersey, we were able to examine 128 patients with sBSI. 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 sBSI in COVID-19 patients 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 sBSI 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. Lastly, 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 our best knowledge, this is the first multicenter study to examine detailed microbiology, risk factors and outcomes in hospitalized patients with severe

COVID-19 with sBSI. This adds to the limited literature for COVID-19 and provides clinically relevant data for antimicrobial stewardship to better assess appropriate antimicrobial therapy in COVID-19 patients suspected to have sBSI. Second, there was higher reliability in the case definition of sBSI in comparison to studies evaluating a broad scope of secondary or co-infections. 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 three 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 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 sBSI in severe COVID-19.

Notes

Author contributions

PJB and NN had the idea for and designed the study. PJB, LB, YX, KS, SK, SM, PHA, CP, PU and RN collected the data. NN and SS analyzed the data. PJB, NN and SS prepared the manuscript. PU 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.

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Declaration of interests

None of the authors have a financial relationship with a commercial entity that has an interest in the subject of the submitted manuscript. PJB reports a research grant from Gilead outside the submitted work. NN serves on speaker bureau for Astellas Pharma. RN reports advisory/speaking fees as a consultant for Gilead, Merck, Abbvie and Viiv and research grant from Gilead, Merck, Abbvie, Viiv and Alkermes outside the submitted work. The other authors have no conflicts of interest to disclose.

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Figure 1: Flow chart of patients with severe COVID-19 who were assessed for eligibility (N= 1, 735) and included in the study (N=375) from three academic centers

RWJUH = Robert Wood Johnson University Hospital. UH= University Hospital. RWJ-S: Robert Wood Johnson University Hospital- Somerset

Figure 2: Identification of organisms from all blood cultures in hospitalized patients with COVID-19 and secondary BSI

CoNS= coagulase negative *Staphylococci.* Spp = species.

Table 1

Characteristic	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 in years, Mean (SD)	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 one	19 (5·1)
Uninsured	43 (11·5)
Other	11 (2·9)
Unknown	8 (2·1)
BMI, Mean (SD)	29·6 (7·5)
Co-morbidities	
Diabetes mellitus, N (%)	131 (34·9)
Lung disease, N (%)	60 (16·0)
Coronary artery disease, N (%)	48 (12·8)
Hypertension, N (%)	219 (58·4)
Hyperlipidemia, N (%)	105 (28·0)
Congestive heart failure, N (%)	22 (5·9)
Cerebrovascular disease / history of stroke, N (%)	31 (8·3)
Malignancy, N (%)	41 (10·9)
Solid organ transplant recipient, N (%)	8 (2·1)
Bone marrow transplant recipient, N (%)	0 (0·0)
Autoimmune disease, N (%)	14 (3·7)
Active gastrointestinal disease, N (%)	27 (7·2)
HIV, N (%)	6 (1·6)
CKD stage 3 or more, N (%)	38 (10·1)
Immunosuppressant use, N (%)	20 (5·3)
Symptoms	
Duration of symptoms in days, Mean (SD)	5·6 (4·5)
Duration in days (Range)	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)
SaO2	
SaO2(%), Mean (SD)	85·0 (11·8)
Needed O2 on room air on admission, N (%)	256 (68·3)
If yes, Type of O2 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)
SaO2 on at time of positive COVID-19 test	89·9 (10·6)
Required 02 on date of positive COVID-19 test, N (%)	315 (84·0)
Type of O2 required on date of COVID test	
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)

Table 1: Characteristics of patients with severe COVID-19 and blood cultures drawn during hospitalization

BiPAP = Bilevel positive airway pressure. BMI = body mass index. CKD = chronic kidney disease. COVID-19 = Coronavirus disease 19. HIV = human immunodeficiency virus. O2 = oxygen. RWJ-S: Robert Wood Johnson University Hospital-Somerset. RWJUH = Robert Wood Johnson University Hospital. SaO2 = oxygen saturation. SD = standard deviation. UH= University Hospital.

Table 2

Risk factor	No sBSI (n=247)	sBSI (n=128)	p value
Characteristics and Co-morbidities			
Sex, N (%)			
Male	149 (60·3)	80 (62·5)	0·68
Female	98 (39·7)	48 (37·5)	
Age in years, Mean (SD)	62·0 (16·8)	65·6 (14·7)	0·043
Race, N (%)			
Hispanic or Latino	68 (27·5)	42 (32·8)	
White	64 (25·9)	34 (26·6)	0·15
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)	
Medicaid only	38 (15·4)	11 (8·6)	0·06
Private only	78 (31·6)	44 (34·4)	
More than one	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)	30·0 (7·3)	28·6 (8·0)	0·09
Diabetes mellitus, N (%)	81 (32·8)	50 (39·1)	0·23
Lung disease, N (%)	37 (15·0)	23 (18·0)	0·45
Coronary artery disease, N (%)	29 (11·7)	19 (14·8)	0·39
Hypertension, N (%)	148 (59·9)	71 (55·5)	0·41
Hyperlipidemia, N (%)	75 (30·4)	30 (23·4)	0·16
Congestive heart failure, N (%)	13 (5·3)	9 (7·0)	0·49
Cerebrovascular disease / history of stroke, N (%)	19 (7·7)	12 (9·4)	0·57
Malignancy, N (%)	26 (10·5)	15 (11·7)	0·73
Solid organ transplant recipient, N (%)	5 (2·0)	3 (2·3)	0·84
Bone marrow transplant recipient, N (%)	0 (0·0)	0 (0·0)	--
Autoimmune disease, N (%)	8 (3·2)	6 (4·7)	0·48
Active gastrointestinal disease, N (%)	15 (6·1)	12 (9·4)	0·24
HIV, N (%)	3 (1·2)	3 (2·3)	0·41
CKD stage 3 or more, N (%)	24 (9·7)	14 (10·9)	0·71
Immunosuppressant use, N (%)	14 (5·7)	6 (4·7)	0·69
Symptoms			
Duration of symptoms in days, Mean (SD)	5·8 (4·5)	5·1 (4·5)	0·18
Abdominal pain, N (%)	18 (7·3)	5 (3·9)	0·20
Diarrhea, N (%)	38 (15·4)	14 (10·9)	0·24
Cough, N (%)	161 (65·2)	58 (45·3)	**0·0002**
Fever, N (%)	165 (66·8)	70 (54·7)	**0·02**
Shortness of breath, N (%)	107 (43·3)	51 (39·8)	0·52
Hypoxia, N (%)	60 (24·3)	30 (23·4)	0·85
Acute mental status change, N (%)	29 (11·7)	30 (23·4)	**0·003**
SAO2			
Sa02 (%), Mean (SD)	86·1 (10·5)	82·5 (13·9)	**0·007**
Needed O2 on room air on admission, N (%)	156 (63·2)	100 (78·1)	**0·003**
If yes, Type of O2 on admission, N (%)			
Nasal cannula	114 (73·1)	53 (53·5)	
Non-rebreather	27 (17·3)	22 (22·2)	**0·003**
High Flow Nasal Cannula	3 (1·9)	3 (3·0)	
BiPAP	4 (2·6)	2 (2·0)	
Intubated	8 (5·1)	19 (19·2)	
SaO2 on at time of positive COVID-19 test	89·7 (10·3)	90·2 (11·2)	0·72
Required 02 on date of positive COVID-19 test, N (%)	210 (85·0)	105 (82·0)	0·45
Type of O2 required on date of COVID test			
Nasal cannula	151 (71·9)	46 (43·8)	**<0·0001**
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 ($x10^9$/L), Mean (SD)	8·6 (4·7)	10·9 (6·1)	**<0·0001**
Creatinine (mg/dL), Mean (SD)	1·49 (1·8)	2·23 (2·5)	**0·001**
CRP[1] (mg/dL), Mean (SD)	67.4 (94.6)	173.2 (25.4)	0.30
D-Dimer[2] (ng/mL), Mean (SD)	2976 (7191)	5437 (13148)	0.06

Ferritin[3] (ng/mL), Mean (SD)	1197 (1935)	1854 (5301)	0.12
Abdominal Imaging			
Colitis, N (%)	0 (0·0)	3 (2·3)	0·04
Cholecystitis	1 (0·4)	1 (0·8)	1·00
Pancreatitis, N (%)	1 (0·4)	0 (0·0)	1·00
Intra-abdominal or pelvic abscess, N (%)	0 (0·0)	2 (1·6)	0·12
Pyelonephritis, N (%)	0 (0·0)	2 (1·6)	0·12
Small bowel obstruction or ileus, N (%)	1 (0·4)	2 (1·6)	0·27
Ascites, N (%)	2 (0·8)	5 (3·9)	**0·048**
Central line and procedures			
Central Line, N (%)	79 (32·0)	100 (78·1)	<0·0001
If Yes to central line, duration of central line, Mean (SD)	7·7 (6·4)	7·1 (8·7)	0·71
EGD, N (%)	0 (0·0)	1 (0·8)	0·34
PEG, N (%)	2 (0·8)	8 (6·3)	**0·004**
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)	0·34
Endotracheal Tube / Intubation, N (%)	73 (29·6)	84 (65·6)	**<0·0001**
Tracheostomy, N (%)	0 (0·0)	12 (9·4)	**<0·0001**
Chest Tube Placement, N (%)	6 (2·4)	7 (5·5)	0·14
Paracentesis, N (%)	1 (0·4)	0 (0·0)	1·00
Abscess Drainage, N (%)	0 (0·0)	2 (1·6)	0·12
TPN, N (%)	3 (1·2)	3 (2·3)	0·41
CVVH or Hemodialysis, N (%)	23 (9·3)	46 (35·9)	**<0·0001**
Peritoneal Dialysis, N (%)	0 (0·0)	9 (7·0)	**<0·0001**

Table 2: Risk factors associated with secondary bloodstream infection in severe COVID-19 patients

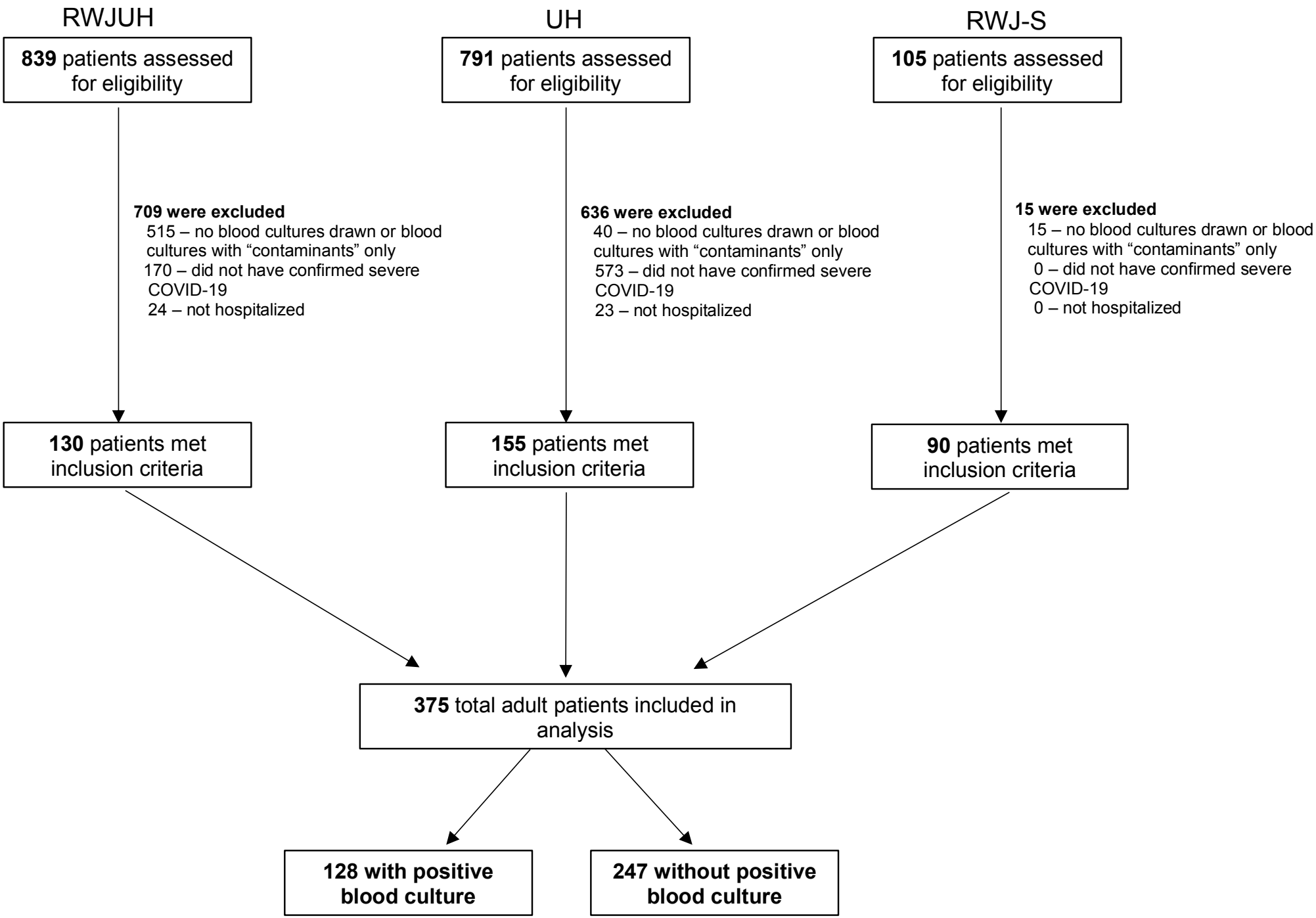
BiPAP = bilevel positive airway pressure. BMI = body mass index. CKD = chronic kidney disease. CRP = C-reactive protein. COVID-19 = Coronavirus disease 19. CVVH = continuous veno-venous hemofiltration. ECMO = extracorporeal membrane oxygenation. EGD = Esophagogastroduodenoscopy. HIV = human immunodeficiency virus. O2 = oxygen. PEG = percutaneous endoscopic gastrostomy. SaO2 = oxygen saturation. sBSI = secondary blood stream infection. SD = standard deviation. TPN = total parenteral nutrition. WBC = white blood cell. [1]missing values: n=85. [2]missing values: n=126. [3]missing values: n=70

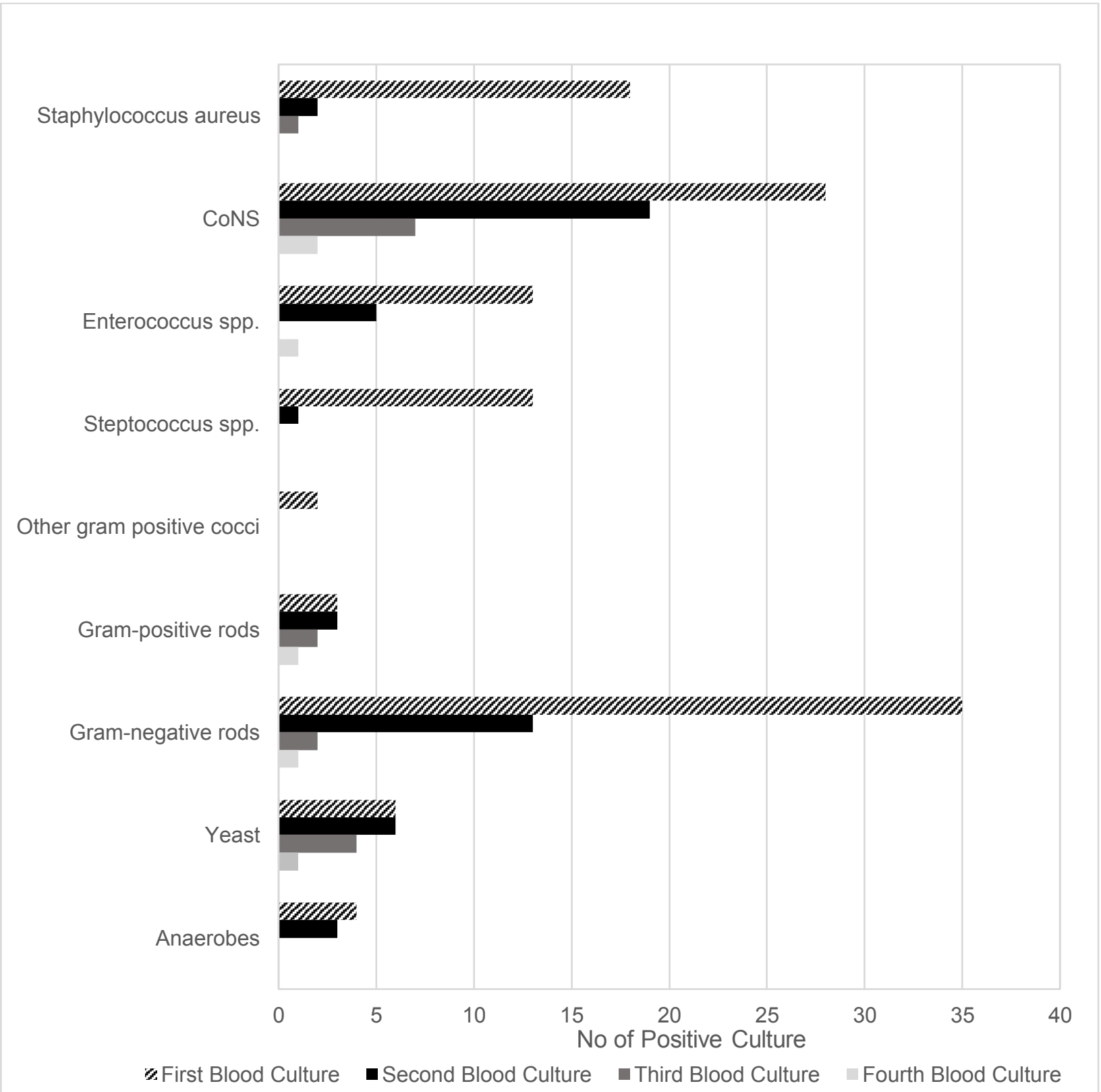
Table 3

Variable	All (n=375)	No sBSI (n=247)	sBSI (n=128)	p value
Ever received intravenous antimicrobial therapy, N (%)	301 (80·3)	174 (70·5)	127 (99·2)	**<0·001**
Ever received systemic glucocorticoids, N (%)	85 (22·7)	44 (17·8)	41 (32·0)	**0·002**
Ever received tocilizumab, N (%)	88 (23·5)	54 (21·9)	34 (26·6)	0·309
Length of hospital stay, Median (IQR), days	9 (5, 17)	7 (4, 12)	18.5 (9, 33·5)	**<0·001**
Admission to ICU, N (%)	179 (47·7)	88 (35·6)	91 (71·1)	**<0·001**
Length of ICU stay, Median (IQR), days	9 (5, 19)	6.5 (4, 11)	17 (7, 26)	**<0·001**
Septic shock requiring vasopressors, N (%)	106 (28·3)	35 (14·2)	71 (55·5)	**<0·001**
In-hospital death, N (%)	149 (39·7)	81 (32·8)	68 (53·1)	**0·0001**
Of those who died, died <7 days (admission to death)	73 (49·0)	51 (63·0)	22 (32·3)	**<0·001**
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 6/3/20, N (%)	226 (60·3)	166 (67·2)	60 (46·9)	**0·0001**
Of those alive, discharged	202 (89·4)	164 (98·8)	38 (63·3)	**<0·0001**
Of those alive, still hospitalized as of 6/3/20	24 (10·6)	2 (1·2)	22 (36·7)	
Readmission with bacteremia, N (%)	2 (1·0)	1 (0·6)	1 (2·7)	0·337

Table 3: Treatment and outcomes in hospitalized patients with severe COVID-19 with or without a secondary bloodstream infection

ICU = intensive care unit. IQR = interquartile range. sBSI = secondary bloodstream infection.


RWJUH
839 patients assessed for eligibility
709 were excluded
515 – no blood cultures drawn or blood cultures with "contaminants" only
170 – did not have confirmed severe COVID-19
24 – not hospitalized
130 patients met inclusion criteria
UH
791 patients assessed for eligibility
636 were excluded
40 – no blood cultures drawn or blood cultures with "contaminants" only
573 – did not have confirmed severe COVID-19
23 – not hospitalized
155 patients met inclusion criteria
RWJ-S
105 patients assessed for eligibility
15 were excluded
15 – no blood cultures drawn or blood cultures with "contaminants" only
0 – did not have confirmed severe COVID-19
0 – not hospitalized
90 patients met inclusion criteria
375 total adult patients included in analysis
128 with positive blood culture
247 without positive blood culture


Staphylococcus aureus
CoNS
Enterococcus spp.
Steptococcus spp.
Other gram positive cocci
Gram-positive rods
Gram-negative rods
Yeast
Anaerobes
0
5
10
15
20
25
30
35
40
No of Positive Culture
First Blood Culture
Second Blood Culture
Third Blood Culture
Fourth Blood Culture