Background. The epidemiology of nosocomial bloodstream infections (NBSIs) in patients with coronavirus disease 2019 (COVID-19) is poorly understood, due in part to substantial disease heterogeneity resulting from multiple potential pathogens.

Methods. We identified risk factors for NBSIs and examined the association between NBSIs and mortality in a retrospective cohort of patients hospitalized with COVID-19 in 2 New York City hospitals during the height of the pandemic. We adjusted for the potential effects of factors likely to confound that association, including age, race, illness severity upon admission, and underlying health status.

Results. Between January 1 and October 1, 2020, 1403 patients had a positive blood culture, and 79 and 101 met the stringent criteria for NBSI among non-COVID-19 and COVID-19 patients, respectively. NBSIs occurred almost exclusively among patients who were severely ill with COVID-19 at hospital admission. NBSIs were associated with elevated mortality, even after adjusting for baseline differences in COVID-19 illness (55% cases vs 45% controls; P = .13). Mortality was concentrated in patients with early-onset pneumonia caused by S. aureus and gram-negative bacteria. Less virulent Candida (49%) and Enterococcus (12%) species were the predominant cause of NBSI in the latter stages of hospitalization, after antibiotic treatment and COVID-19 treatments that attenuate immune response. Most Enterococcus and Candida infections did not have an identifiable source and were not associated with common risk factors for infection by these organisms.

Conclusions. Pathogen species and mortality exhibited temporal differences. Early recognition of risk factors among COVID-19 patients could potentially decrease NBSI-associated mortality through early COVID-19 and antimicrobial treatment.

Keywords. SARS-CoV-2; COVID-19; nosocomial; bloodstream infection.

Since the pandemic onset, coronavirus disease (COVID-19) mortality rates in US hospitals have declined owing to increasing experience with the disease, decreased patient-to-caregiver ratios, new treatments, and vaccination [1–4]. However, vaccine hesitancy, along with the emergence of new viral variants, could undo such progress [5]. A better understanding of the factors associated with poor COVID-19 outcomes could reduce vulnerability during recurrent COVID-19 outbreaks and build resilience against future pandemic pathogens.

Bloodstream infections (BSIs) are among the most serious medical complications in COVID-19 patients [6–10]. Recent work by us and others suggests that gut microbiome dysbiosis is associated with bacterial translocation into the blood during COVID-19 [11, 12]. Consistent with this idea, a high frequency of Candida and Enterococcus species BSI has been described among hospitalized COVID-19 patients [13–15]—a finding otherwise seen primarily in patients with dysbiosis from cancer treatment, in which these microbes translocate from the gut [16–18]. The natural history of BSI is poorly defined, in part because of substantial disease heterogeneity resulting from multiple potential pathogens, sites of infection, and the clinical time course of COVID-19.

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Pathogen-associated Mortality in NBSI Patients With COVID-19 • OFID • 1
In March 2020, New York City emerged as an epicenter of the COVID-19 pandemic [19]. To explore relationships between COVID-19, BSI risk, and mortality, we assembled a retrospective cohort of COVID-19 patients to study BSI epidemiology using both matched and unmatched controls. We excluded patients having a SARS-CoV-2-positive PCR test result but non-COVID illness. We focused on nosocomial BSI (NBSI) because nosocomial infection, rather than coinfection upon hospital admission, is the primary threat to COVID-19 patients [20]. We also excluded skin microbiota from the analysis (eg, coagulase-negative staphylococci, Bacillus), because skin microbiota can represent a high proportion of contaminants in overstretched hospitals managing many COVID-19 patients [21], and these organisms may not contribute to mortality [22]. These stringent criteria enabled us to examine temporal trends between COVID-19 and NBSIs.

METHODS

Setting and Design
We screened for NBSI among all adult COVID-19 patients admitted to 2 New York University Langone Health (NYULH) hospitals—one that serves an affluent population (Manhattan) and 1 that serves an underserved population (Brooklyn). Floor beds are able to provide intensive care unit (ICU)–level care; consequently, both floors and ICUs managed critically ill patients.

To determine the impact of NBSI on mortality, we compared COVID-19 patients with recorded NBSIs with COVID-19 patients with no record of BSIs. To establish a more comparable control group, we generated a subset of matched COVID-19 patients with no record of NBSI using propensity score matching [23].

Data Collection and Definitions
Patient data were extracted from electronic health records and by manual chart review. We obtained data on baseline clinical characteristics (within 72 hours of admission) and underlying comorbidities. Oxygen use was categorized as follows: none (no supplementary oxygen), low oxygen (low-flow noninvasive supplementary devices), high oxygen (high-flow), noninvasive ventilation (Bi-PAP, CPAP), and invasive ventilation (intubated). Time-varying data (eg, steroid use) were collected from the admission date forward.

Cases were defined as all patients with a COVID-19 diagnosis at the time of admission, a positive SARS-CoV-2 PCR result, and a positive blood culture obtained >48 hours after admission to the hospital (Figure 1). Infectious disease consultation notes, admission and primary team notes, and discharge summaries were reviewed by 2 infectious diseases physicians (T.D.F. and B.S.) to verify (1) that acute COVID-19 was the primary reason for hospitalization, (2) nosocomial onset of BSI (eg, no signs/symptoms of BSI at the time of hospital admission), and (3) presumed source of NBSI [24]. Patients were categorized as having a central venous catheter if it was present within 48 hours before bacteremia. Mortality was defined as death from any cause occurring after the onset of NBSI until December 31, 2020.

Microbiology
Microorganisms typically belonging to the skin flora, identified according to Centers for Disease Control and Prevention National Healthcare Safety Network Patient Safety Component Manual criteria (eg, coagulase-negative staphylococci, Micrococcus species, Bacillus species, or diphtheroids [corynebacteria or propionibacteria]) [25], were considered contaminants and were excluded.

Candidemia was identified by both culture and the T2Candida panel, a sensitive molecular assay [26, 27], in patients verified to have infection and to have received treatment by chart review. Polymicrobial NBSI was defined by the isolation of a second microbial species (excluding skin microbiota) within 72 hours of initial positive blood culture. Patients with >1 episode of NBSI during their admission were classified as “multiple” NBSI. S. aureus and Enterococcus were considered antimicrobial-resistant if they were nonsusceptible to methicillin or vancomycin, respectively. Gram-negative bacteria were defined as antimicrobial-resistant if they were nonsusceptible to ceftriaxone, piperacillin-tazobactam, ceftazipime, ceftazidime, or a carbapenem.

Statistical Analysis
The Pearson χ² test was used to compare microorganism frequencies. To examine the independent effect of NBSI on mortality, we first created a predictive model of NBSI that included the following set of potentially confounding variables: age, race, illness severity upon admission (eg, supplemental oxygen), and underlying health status (Charlson Comorbidity index) [28–30] using the complete COVID-19 cohort. We then calculated the estimated propensity score for each subject using nearest neighbor propensity score matching (4 controls per case) to identify an NBSI-negative control group [31]. To evaluate the covariate distribution for the unmatched and matched groups, standardized differences were calculated. We also determined the effect of COVID-19 treatments before the positive blood culture (eg, steroids, interleukin [IL]-6 inhibitors) on NBSI risk and mortality.

Kaplan-Meier curves were used to present mortality risk over time. Log-rank tests accounting for matched pairing were used to test the group difference in mortality risk. We ran a Cox proportional hazard model, matching between cases and their respective controls and adjusting for covariates, including type of microorganism (using “none” as a control), age, and sex. We tested the assumption of proportionality using the function “cox.zph()” in R package “survival.” We also performed
an accelerated failure time model, which does not require such stringent assumptions, using the Weibull distribution to evaluate survival time [32]. Time ratios (TRs) and 95% CIs were calculated to assess the percent change in survival time (100% * [TR-1]). Logistic regression was used to estimate odds ratios of NBSI onset for different treatments. All statistical analyses were performed in R, version 3.6.3 (R Project for Statistical Computing).

**RESULTS**

**COVID-19 NBSI Study Population**

Between January 1 and October 1, 2020, 1403 inpatients had a positive blood culture. We excluded 606 patients with cultures positive for microorganisms likely to be contaminants or low-virulence pathogens (Figure 1). Of the 797 remaining patients, 224 were not tested for SARS-CoV-2, mostly during the period of January to late March 2020, when testing was not widely available. Of the 573 BSI patients with a SARS-CoV-2 PCR test result, 456 tested negative and 117 were positive. Chart review confirmed the clinical diagnosis of COVID-19 and nosocomial acquisition in 101 of 117 cases. Most patients with a negative SARS-CoV-2 PCR test and positive culture results did not meet our >48-hour criteria for nosocomial infection (374/456). Chart review of SARS-CoV-2-negative BSI cases (n = 82) occurring >48 hours after admission identified 79 patients who met inclusion criteria for NBSI controls.

**Microbiology of NBSI**

Among the 101 COVID-19 patients with NBSI, *Candida* (49%) and *Enterococcus* (12%) were the leading pathogens (Table 1). The proportion of BSIs that were due to Candida (Figure 2) or antimicrobial-resistant bacteria was significantly higher after the first week of hospitalization, post-treatment with empiric antibiotics, steroids, and/or an IL-6 inhibitor, compared with the first week (4/22 [18.2%] vs 51/79 [64.6%]; P = .001). In contrast, BSI cases in the first week of hospitalization were usually caused by antimicrobial-susceptible bacteria. These observations suggest that, over time, COVID-19 patients are at increasing risk of antimicrobial-resistant NBSI pathogens.

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Figure 1. Flowchart of patient inclusion. Abbreviations: BSI, bloodstream infection; NBSI, nosocomial bloodstream infection; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
Table 1. Distribution of Pathogens in Bloodstream Infections in Patients With and Without COVID-19, 2019–2020

| Characteristic                | 2020 COVID-19 (-) (n = 79), No. (%) | 2020 COVID-19 (+) (n = 101), No. (%) | 2019 vs 2020 COVID-19 (+) P Value | 2019 vs 2020 COVID-19 (-) P Value | P Value |
|------------------------------|-------------------------------------|--------------------------------------|-----------------------------------|-----------------------------------|---------|
| Organisms                    |                                     |                                      |                                   |                                   |         |
| Gram-positive                |                                     |                                      |                                   |                                   |         |
| Overall                      | 23 (29.1)                           | 21 (20.8)                            | .197                              |                                   | .102    |
| Enterococcus spp.            | 10 (12.7)                           | 12 (11.9)                            | .874                              |                                   | .693    |
| Enterococcus faecalis        | 4 (5.1)                             | 5 (5.0)                              | 9 (7.7)                           |                                   | .837    |
| Enterococcus faecium         | 6 (7.6)                             | 7 (6.9)                              | 7 (6.0)                           |                                   | .804    |
| Staphylococcus aureus        | 13 (16.5)                           | 9 (8.9)                              |                                   |                                   | .095    |
| Gram-negative                |                                     |                                      |                                   |                                   |         |
| Overall                      | 26 (32.9)                           | 11 (10.9)                            | .001                              | 35 (29.9)                         | .657    |
| Acinetobacter baumannii      | 0 (0.0)                             | 1 (1.0)                              | 9 (7.7)                           |                                   | .095    |
| Enterobacter cloacae         | 5 (6.3)                             | 1 (1.0)                              |                                   |                                   | .095    |
| Escherichia coli             | 8 (10.1)                            | 0 (0.0)                              | 9 (7.7)                           |                                   | .095    |
| Klebsiella spp.              | 8 (10.1)                            | 4 (4.0)                              |                                   |                                   | .095    |
| Pseudomonas aeruginosa       | 3 (3.8)                             | 2 (2.0)                              |                                   |                                   | .095    |
| Morganella morganii          | 0 (0.0)                             | 0 (0.0)                              | 1 (0.9)                           |                                   | .804    |
| Proteus mirabilis            | 2 (2.5)                             | 0 (0.0)                              | 1 (0.9)                           |                                   | .804    |
| Serratia marcescens          | 0 (0.0)                             | 3 (3.0)                              |                                   |                                   | .804    |
| Candida spp.                 |                                     |                                      |                                   |                                   | .804    |
| Overall                      | 18 (22.8)                           | 49 (48.5)                            | .001                              | 18 (22.8)                         | .189    |
| Candida albicans             | 3 (3.8)                             | 11 (10.9)                            | 9 (7.7)                           |                                   | .189    |
| Candida glabrata             | 2 (2.5)                             | 1 (1.0)                              | 5 (4.3)                           |                                   | .189    |
| Candida parapsilosis         | 2 (2.5)                             | 3 (3.0)                              | 1 (0.9)                           |                                   | .189    |
| Other Candida spp.           | 2 (2.5)                             | 1 (1.0)                              | 3 (2.6)                           |                                   | .189    |
| T2 Candida spp.              | 8 (10.1)                            | 32 (31.7)                            | 0 (0.0)                           |                                   | .189    |
| Candida albicans/Candida tropicalis | 2 (2.5)                            | 24 (23.8)                            |                                   |                                   | .189    |
| Candida parapsilosis         | 2 (2.5)                             | 5 (4.9)                              |                                   |                                   | .189    |
| Candida glabrata/Candida krusei | 1 (1.3)                             | 3 (2.9)                              |                                   |                                   | .189    |
| Anaerobes                    |                                     |                                      |                                   |                                   |         |
| Bacteroides spp.             | 1 (1.3)                             | 0 (0.0)                              | —                                 | 0 (0.0)                           | .095    |
| Polymicrobial infection      | 9 (11.4)                            | 11 (10.9)                            | 915                               |                                   | .423    |
| Multiple infection           | 2 (2.5)                             | 9 (8.9)                              | 0.76                              | 10 (8.5)                          | .924    |

Two-sided Pearson χ² tests were used to determine P values. Bold formatting indicates statistical significance where the chance of a type I error is 5% or less.

Abbreviation: COVID-19, coronavirus disease 2019.

- Six Enterococcus were vancomycin-resistant; 1 S. aureus was methicillin-resistant.
- T2 Candida positivity in 2019 was only observed in polymicrobial or multiple infections.
- Defined as isolation of >1 microorganism from blood within 72 hours.
- Defined as isolation of >1 microorganism from blood after 72 hours.
NBSI Cases Compared With Non-COVID-19 Controls

To determine whether COVID-19 patients are more likely than non-COVID-19 patients to have Candida and Enterococcus BSI, we compared clinical characteristics between patients from 2 time periods: (1) BSI without COVID-19 from February 15 to December 31, 2020, or (2) hospitalized for any reason from January 1 to December 31, 2019 (historical non-COVID-19 cohort) (Table 1). The historical non-COVID-19 cohort consisted of 117 control cases with NBSI from 2019 out of 1390 patients with positive blood cultures. We excluded 581 cases due to potentially contaminating or clinically insignificant organisms and 691 that occurred <48 hours after hospital admission.

The prevalence of Candida was >2 times higher in COVID-19 patients than in patients belonging to either control group (Table 1). We did not find significant differences of Enterococcus BSI frequencies. However, among patients with NBSI due to Candida or Enterococcus (Supplementary Table 1), there were significant differences between COVID-19 cases and non-COVID-19 controls in the 2020 cohort in terms of known risk factors for infection by these organisms, the latter having more gastrointestinal surgeries, active malignancies, chemotherapy, and higher Charlson index score. Gram-negative bacteria were more abundant among non-COVID-19 controls. The abundance of Candida and Enterococcus in the absence of obvious risk factors suggests that Candida and Enterococcus represent distinct complications of COVID-19.

Candida and Enterococcus causing NBSI in COVID-19 patients were recovered from the urine or sputum in only 4 of 62 instances (6%). COVID-19 patients with NBSI were more likely to have a central venous catheter (CVC) than controls (Supplementary Table 1). Less than 5% were associated with femoral catheters, which are highest risk for BSI.

In contrast to NBSI with Candida and Enterococcus, where few patients had these organisms isolated from sites other than blood, COVID-19 patients with S. aureus or gram-negative NBSI had the same organisms recovered in respiratory cultures in 7 of 9 (77%) and 9 of 11 (80%) instances, respectively. NBSI in these cases most often occurred after endotracheal intubation, an important risk factor for bacterial pneumonia [33]. Indeed, all patients with S. aureus or gram-negative NBSI developed clinical signs of pneumonia (eg, fever, purulent secretions, radiology changes) and were treated for nosocomial pneumonia.

Mortality of NBSI Among Patients With and Without COVID-19

During the study period, we identified a control population of 3273 SARS-CoV-2 PCR test-positive patients without BSI who were admitted for COVID-19. Baseline inflammatory markers (eg, C-reactive protein) were elevated in almost all patients (Table 2). COVID-19 patients with NBSI were substantially different from COVID-19 patients without NBSI before matching; patients with NBSI were younger, more likely to be male and non-Hispanic White, required more oxygen at the time of hospitalization, and had different comorbidities.

Propensity score matching resulted in a well-balanced control group of 404 patients (SDS < 0.1 for all matching covariates). The number of patients requiring a ventilator at admission between groups was not significantly different (49.5% among cases vs 47.0% among matched controls; SDS = 0.08). The absolute difference in in-hospital mortality risk between BSI (+) patients and BSI (-) unmatched patients was 31.5% (54.5% vs 23.0%; 95%
Table 2. Patient Demographic and Clinical Characteristics Before and After Propensity Score Matching

| Variablesa                  | COVID-19 (+) & BSI (+) 2020 (n = 101) | COVID-19 (+) & BSI (-) 2020 (n = 3273) | SDS | COVID-19 (+) & BSI (-) 2020 (n = 404) | SDS |
|-----------------------------|---------------------------------------|----------------------------------------|-----|---------------------------------------|-----|
| Demographic characteristic  |                                       |                                        |     |                                       |     |
| Age, mean (SD), y           | 61.0 (15.5)                           | 64.1 (16.9)                            | 0.2 | 60.8 (15.4)                           | 0.01|
| Sex, No. (%)                |                                       |                                        | 0.36|                                       | 0.03|
| Female                      | 24 (23.8)                             | 1327 (40.5)                            |     | 91 (22.5)                             |     |
| Male                        | 77 (76.2)                             | 1946 (59.5)                            |     | 313 (77.5)                            |     |
| Race, No. (%)               |                                       |                                        |     |                                       |     |
| Asian                       | 10 (9.90)                             | 213 (6.51)                             |     | 32 (7.92)                             |     |
| Black                       | 7 (6.93)                              | 497 (15.2)                             |     | 30 (7.43)                             |     |
| Hispanic                    | 28 (27.7)                             | 923 (28.2)                             |     | 116 (28.7)                            |     |
| Other/multiracial           | 9 (8.91)                              | 298 (9.10)                             |     | 37 (9.16)                             |     |
| Unknown                     | 4 (3.96)                              | 96 (2.93)                              |     | 12 (2.97)                             |     |
| White                       | 43 (42.6)                             | 1246 (38.1)                            |     | 177 (43.8)                            |     |
| Clinical characteristic     |                                       |                                        |     |                                       |     |
| Maximum oxygenb (first 72 h), No. (%) | 1.48                                    | 11 (2.72)                              |     | 117 (28.9)                            |     |
| None                        | 2 (1.98)                              | 426 (13.6)                             |     |                                       | 0.08|
| Low oxygen                  | 3 (2.97)                              | 1315 (42.0)                            |     | 11 (2.72)                             |     |
| High oxygen                 | 20 (19.8)                             | 646 (20.6)                             |     | 79 (19.6)                             |     |
| Noninvasive ventilation     | 26 (25.7)                             | 381 (12.2)                             |     | 113 (28.0)                            |     |
| Mechanical ventilation      | 50 (49.5)                             | 365 (11.7)                             |     | 190 (47.0)                            |     |
| Charlson score, mean (SD)   | 2.57 (1.84)                           | 2.13 (2.12)                            | 0.24| 2.49 (2.15)                           | 0.06|
| BMI, mean (SD), kg/m^2      | 29.4 (6.69)                           | 30.4 (7.00)                            | 0.15| 30.2 (7.45)                           | 0.01|
| Temperature, mean (SD), °F  | 99.9 (1.82)                           | 99.5 (1.97)                            |     | 99.4 (3.57)                           | 0.18|
| Fever, No. (%)              | 92 (8.11)                             | 2914 (93.3)                            | 0.06| 367 (92.0)                            | 0.03|
| Demographic characteristic  |                                       |                                        |     |                                       |     |
| Age group, No. (%)          |                                       |                                        | 0.22|                                       | 0.13|
| 0–39                        | 12 (11.9)                             | 268 (8.57)                             |     | 44 (10.9)                             |     |
| 40–49                       | 9 (8.91)                              | 317 (10.1)                             |     | 47 (11.6)                             |     |
| 50–59                       | 15 (14.9)                             | 572 (18.3)                             |     | 70 (17.3)                             |     |
| 60–69                       | 31 (30.7)                             | 737 (23.6)                             |     | 124 (30.7)                            |     |
| 70+                         | 34 (33.7)                             | 1234 (39.5)                            |     | 119 (29.5)                            |     |
| Comorbidity, No. (%)        |                                       |                                        |     |                                       |     |
| Myocardial infarction       | 23 (22.8)                             | 458 (14.0)                             | 0.23| 67 (16.6)                             | 0.16|
| Congestive heart failure    | 11 (10.9)                             | 572 (17.5)                             | 0.18| 43 (10.6)                             | 0.01|
| PVD                         | 12 (11.9)                             | 485 (14.8)                             | 0.08| 68 (16.8)                             | 0.14|
| Cerebrovascular disease     | 31 (30.7)                             | 424 (13.0)                             | 0.45| 98 (24.3)                             | 0.15|
| Dementia                    | 9 (8.91)                              | 324 (9.90)                             | 0.03| 26 (6.44)                             | 0.02|
| Pulmonary disease           |                                       |                                        | 0.1 |                                       |     |
| Chronic disease             | 21 (20.8)                             | 824 (25.2)                             | 0.1 | 88 (21.8)                             | 0.02|
| Variables                  | COVID-19 (+) & BSI (+) 2020 (n = 101) | COVID-19 (+) & BSI (-) 2020 (n = 3273) | SDS | COVID-19 (+) & BSI (-) 2020 (n = 404) | SDS |
|---------------------------|--------------------------------------|---------------------------------------|-----|--------------------------------------|-----|
| Asthma                    | 5 (4.95)                             | 377 (12.03)                          | 0.52| 47 (11.6)                           | 0.51|
| COPD                      | 10 (9.90)                            | 369 (11.8)                           | 0.07| 32 (7.9)                            | 0.11|
| RA/CVD                    | 2 (1.96)                             | 114 (3.48)                           | 0.09| 15 (3.71)                           | 0.1  |
| Liver disease             | 9 (8.91)                             | 57 (1.74)                            | 0.33| 15 (3.71)                           | 0.26|
| Peptic ulcer disease      | 6 (5.94)                             | 106 (3.24)                           | 0.14| 17 (4.21)                           | 0.08|
| Diabetes                  | 49 (48.5)                            | 1256 (38.4)                          | 0.2 | 214 (53.0)                          | 0.09|
| Hemiplegia/paraplegia     | 14 (13.9)                            | 94 (2.87)                            | 0.42| 18 (4.46)                           | 0.3 |
| Renal disease             | 24 (2.38)                            | 865 (26.4)                           | 0.06| 131 (32.4)                          | 0.18|
| End-stage renal disease   | 3 (2.97)                             | 198 (6.32)                           | 0.14| 40 (9.90)                           | 0.08|
| Cancer                    | 11 (10.9)                            | 360 (11.0)                           | 0.00| 45 (11.1)                           | 0.03|
| Metastatic tumor          | 2 (1.98)                             | 105 (3.21)                           | 0.07| 13 (3.22)                           | 0.02|
| AIDS/HIV                  | 1 (0.99)                             | 19 (0.58)                            | 0.05| 5 (1.24)                            | 0.05|
| Index                     |                                     |                                      |     |                                      |     |
| ≥5                        | 31 (30.7)                            | 836 (25.9)                           | 133 | 32 (9.2)                            |     |
| 3–4                       | 26 (25.7)                            | 516 (15.8)                           | 52  | 12 (3.2)                            | 0.34|
| 1–2                       | 33 (32.7)                            | 1112 (34.0)                          | 175 | 43 (11.5)                           | 0.34|
| 0                         | 11 (10.9)                            | 809 (24.7)                           | 44  | 10 (2.9)                            |     |
| DNR status                |                                     |                                      |     |                                      | 0.17|
| DNR                       | 30 (29.7)                            | 718 (21.9)                           | 121 | 80 (2.2)                            |     |
| No DNR                    | 71 (70.3)                            | 2555 (78.1)                          | 283 | 72 (78.0)                           | 0.03|
| Laboratory values         |                                     |                                      |     |                                      |     |
| WBC, mean (SD), 1 x 10⁹ cells | 9.39 (5.49)                         | 8.46 (10.2)                          | 0.12| 10.6 (2.6)                          |     |
| Neutrophil, mean (SD), %  | 81.8 (9.89)                          | 76.9 (11.4)                          | 0.44| 80.7 (10.5)                         | 0.05|
| Lymphocyte, mean (SD), %  | 10.7 (7.97)                          | 14.1 (9.36)                          | 0.38| 11.8 (9.22)                         | 0.07|
| Hemoglobin, mean (SD), g/dL | 13.5 (11.0)                         | 10.0 (6.0)                           | 0.3 | 12.9 (2.23)                         | 0.07|
| Platelets (x1000), mean (SD), µL | 230 (108)                          | 1230 (121)                          | 0.06| 227 (101)                           | 0.08|
| Troponin, mean (SD), ng/mL| 0.19 (0.43)                          | 0.26 (1.62)                          | 0.06| 0.37 (1.08)                         | 0.27|
| AST, mean (SD), U/L       |                                     | 970 (875)                            | 0.13| 59.6 (62.9)                         | 0.03|
| LDH, mean (SD), U/L       | 514 (193)                            | 566 (305)                            | 0.18| 529 (275)                           | 0.22|
| ALT, mean (SD), U/L       | 16.9 (14.4)                          | 13.9 (10.5)                          | 0.21| 14.6 (15.9)                         | 0.72|
| Inflammatory markers      |                                     |                                      |     |                                      | 0.4 |
| Procalcitonin, mean (SD), ng/mL | 2.84 (15.9)                        | 1.22 (5.58)                          | 0.13| 2.24 (11.7)                         | 0.19|
| CRP, mean (SD), ng/dL     | 163 (39.3)                           | 159 (86.9)                           | 0.07| 158 (80.1)                          | 0.14|
| D-dimer, mean (SD), ng/mL | 1783 (2705)                          | 1322 (6694)                          | 0.13| 2078 (5315)                         | 0.44|
| Ferritin, mean (SD), ng/mL| 1414 (1638)                          | 1982 (3184)                          | 0.21| 1741 (2846)                         | 0.07|
| Outcome, No. (%)          |                                     |                                      |     |                                      | 0.07|
| Alive                     | 44.0 (31.9)                          | 10.6 (15.3)                          | 1.41| 127 (18.4)                          | 0.09|
| Alive                     | 64.6 (32.8)                          | 9.66 (12.3)                          | 20.8 | 21.4 (32.8)                         |     |
When compared with propensity-scored BSI (-) matched controls, mortality risk among those with NBSI remained higher by 9.5% (54.5% vs 45.0%), but the adjusted observed difference was not statistically significant, as confidence intervals were wide and overlapped (95% CI, 44.2%–64.4% vs 40.1%–50.0%). Thus, while NBSI may be associated with moderately increased risk of mortality in patients with COVID-19, we cannot rule out the possibility that the observed difference was due to chance.

Kaplan-Meier mortality curves for cases and matched controls indicated no overall difference between the 2 curves (Figure 3A). However, curves stratified by microorganism species (Figure 3B) indicated that mortality was significantly concentrated in Staphylococcus aureus and gram-negative NBSI early after hospitalization. Patients with Candida alone did not have a higher risk of mortality compared with those without NBSI. Thus, although Candida and Enterococcus were the predominant pathogens in NBSI, S. aureus and gram-negative bacteria were possibly the most deadly.

COVID-19-positive patients were administered several types of antibiotics, antifungals, and immunosuppressive agents, namely steroids and the IL-6 inhibitor tocilizumab (the most commonly used IL-6 inhibitor at our institution). Sensitivity analyses using different treatments to stratify mortality revealed that tocilizumab significantly reduced mortality in both the NBSI and non-NBSI COVID-19 patient groups (Supplementary Figure 1).

### Adjusted Mortality Models

To define potential independent predictors of mortality, we initially compared COVID-19 NBSI and matched cases using an accelerated failure time (AFT) Weibull model using type of microorganism, age, and sex as covariates, as cases and the matched control group did not meet the assumption of proportionality required for Cox-PH modeling ($P < .001$). Both the AFT model and the Cox-PH model (shown for comparative purposes) showed that patients with NBSI had a decreased survival time for all organisms except Candida. Additionally, older age and male gender decreased survival (Table 4).

Gram-negative and S. aureus NBSI time ratios (TRs) were shortened, the latter significantly (TR, 0.51 and 0.15; $P = .22$ and $.<.01$, respectively). In contrast, the TR for Candida was 1.33 ($P = .41$). Time ratios were also decreased with age (TR, 0.94; $P < .01$) and male gender (TR, 0.71; $P = .2$). In sum, patients with S. aureus and gram-negative NBSI had a shorter survival compared with both patients without NBSI and patients with NBSI due to Candida.

### Length of Stay

The average length of stay (SD) was 44 (31.9) days among NBSI cases, compared with 10.6 (15.3) days and 17.2 (18.4) days for unmatched and matched non-NBSI controls, respectively.
Figure 3. Kaplan-Meier survival curves. A, Mortality of COVID-19 patients with NBSI vs matched controls without NBSI. B, Mortality of COVID-19 patients with NBSI by microorganism. Log-rank tests were used to determine P values. Abbreviations: COVID-19, coronavirus disease 2019; NBSI, nosocomial bloodstream infection; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
| Antibiotic | COVID-19 (+) BSI (+) | COVID-19 (+) BSI (-) (Matched Controls) | Days of Treatment, Mean (SD) (n = 101) | No. (%) | Days of Treatment, Mean (SD) (n = 389) | No. (%) | Days, P Value | Patients, P Value | Cases–Controls, % Treated |
|-----------|----------------------|------------------------------------------|----------------------------------------|--------|----------------------------------------|--------|--------------|------------------|------------------------|
| **Gram-positive coverage** | | | | | | | | | |
| Daptomycin | — | 0 (0.00) | 0.85 (6.29) | 4 (1.03) | — | — | — | — | 103 |
| Linezolid | 3.67 (2.80) | 6 (5.94) | 8.12 (3.83) | 8 (2.06) | .191 | .048 | 3.88 |
| Vancomycin | 6.31 (7.58) | 88 (87.13) | 5.96 (6.33) | 180 (46.27) | .708 | <.001 | 40.86 |
| **Gram-negative coverage** | | | | | | | | | |
| Amoxicillin/clavulanate | — | 0 (0.00) | 3.17 (2.23) | 6 (1.54) | — | — | — | — | 154 |
| Ampicillin/sulbactam | 2.75 (1.58) | 8 (7.92) | 4.67 (5.82) | 12 (3.08) | 298 | .5 | 4.84 |
| Ampicillin | 6.00 (0) | 1 (0.99) | 6.00 (5.66) | 2 (0.51) | — | — | — | — | 0.48 |
| Cefepime | 3.53 (2.61) | 15 (14.86) | 5.20 (3.35) | 50 (12.85) | .053 | .717 | 2.00 |
| Ceftazidime/piperacillin | — | 0 (0.00) | 8.00 (2.63) | 2 (0.51) | — | — | — | — | 0.51 |
| Ceftolozane/tazobactam | 1.00 (0) | 1 (0.99) | 2.13 (7.77) | 3 (0.77) | — | — | — | — | 0.22 |
| Ceftriaxone | 3.89 (2.61) | 65 (64.36) | 3.62 (2.55) | 248 (63.75) | .488 | .9 | 0.60 |
| Levofloxacin | 5.33 (4.03) | 9 (8.91) | 6.50 (6.29) | 16 (4.11) | .578 | .089 | 4.80 |
| Meropenem | 10.2 (15.66) | 50 (49.50) | 10.9 (11.17) | 96 (24.68) | .776 | <.001 | 24.83 |
| Piperacillin/tazobactam | 6.16 (4.05) | 80 (79.21) | 5.97 (4.00) | 144 (37.02) | .735 | <.001 | 42.19 |
| Polymyxin B | 2.00 (0) | 0.99 | 1.00 (0) | 1 (0.26) | — | — | — | — | 0.73 |
| **Antifungal coverage** | | | | | | | | | |
| Fluconazole | 6.19 (7.32) | 16 (15.84) | 11.3 (12.3) | 25 (6.43) | .103 | .044 | 9.41 |
| Isavuconazonium sulfate | — | 0 (0.00) | 5.00 (0) | 1 (0.26) | — | — | — | — | 0.26 |
| Micafungin | 9.93 (14.5) | 30 (29.70) | 8.25 (11.0) | 48 (12.34) | .588 | <.001 | 17.36 |
| Voriconazole | — | 0 (0.00) | 6.00 (5.66) | 2 (0.51) | — | — | — | — | 0.51 |
| **Atypical coverage** | | | | | | | | | |
| Azithromycin | 4.42 (1.54) | 89 (88.12) | 4.00 (1.69) | 288 (71.04) | .029 | <.001 | 14.08 |
| Doxycycline | 3.38 (3.54) | 8 (7.92) | 3.95 (4.32) | 57 (14.65) | .686 | .107 | –6.73 |
| Minocycline | — | 0 (0.00) | 7.20 (3.49) | 5 (1.29) | — | — | — | — | 1.29 |
| **Others** | | | | | | | | | |
| Hydroxychloroquine | 5.04 (1.60) | 93 (92.08) | 4.82 (1.42) | 297 (76.35) | .234 | <.001 | 15.73 |
| Trimethoprim/sulfamethoxazole | 12.0 (14.8) | 3 (2.97) | 5.88 (6.76) | 16 (4.11) | .55 | .776 | –1.14 |

Bold formatting indicates statistical significance where the chance of a type I error is 5% or less.

Abbreviations: BSI, bloodstream infection; COVID-19, coronavirus disease 2019; NBSI, nosocomial bloodstream infection.

*Antibiotic use was measured before onset of NBSI. For NBSI-negative cases, antibiotic use was measured for the whole period of hospital admission.

Includes gram-positive coverage but not methicillin-resistant S. aureus coverage.
When stratified by living status, NBSI cases who survived had the longest hospitalizations (64.6 [32.8] days), while those who did not survive averaged 26.8 (17.9) days in the hospital. Likewise, matched survivors had longer lengths of stay compared with those who died (20.8 [21.4] days and 12.9 [12.7] days, respectively). Unmatched controls showed the opposite pattern: Whereas those who died stayed 11.7 (11.0) days, survivors stayed 9.66 (12.3) days. Thus, survival increases with increasing length of stay in NBSI patients and matched controls with severe COVID-19, but not in unmatched controls with mild disease, with implications for prediction of hospital mortality and length of stay from risk factors on admission.

**Antibiotic and Tocilizumab Use Before NBSI and Risk of NBSI**

Ceftriaxone, azithromycin, and hydroxychloroquine were widely prescribed among both cases and controls (Table 3). In contrast, NBSI cases received tocilizumab and steroids, broad-spectrum antimicrobials (vancomycin, meropenem, and piperacillin-tazobactam), and antifungals (micafungin and fluconazole) more frequently. Thus, NBSI cases received more aggressive treatment than non-NBSI controls. We also analyzed the odds of developing NBSI linked to COVID-19 treatments using a univariate logistic model with NBSI as the outcome. Tocilizumab did not predict NBSI (Supplementary Table 2). However, patients treated with piperacillin-tazobactam, vancomycin, meropenem, and hydrocortisone had higher odds of having NBSI compared with those not receiving those treatments.

**DISCUSSION**

Our results suggest that, early on, intubation promotes bacteremic pneumonia by *S. aureus* and gram-negative bacteria. Later, COVID-19 creates an environment that promotes intestinal acquisition and/or expansion of pathogenic microbes, especially resistant bacteria and organisms intrinsically resistant to antibiotics, such as *Candida*. Our data also show that NBSI in COVID-19 patients is dominated by *Candida* and *Enterococcus* that arise without a defined portal of entry into the host.

Although it is not possible to definitively state to what extent translocation played a role in *Candida* and *Enterococcus* NBSIs, at least 4 observations suggest that such infections are primarily translocation-associated. First, use of femoral catheters that are high risk for catheter-associated NBSI was uncommon in our population. Second, COVID-19 patients with *Candida* or *Enterococcus* NBSI showed an imbalance in conditions known to facilitate translocation (e.g., abdominal surgery, cancer chemotherapy) and alternative routes (e.g., urinary tract infection) that predispose patients to infection with these organisms, compared with COVID-19-negative controls. Third, NBSIs due to *Candida* and antimicrobial-resistant bacteria, especially vancomycin-resistant *Enterococcus*, arose in the later stages of hospitalization, after treatment with antimicrobials, steroids, or IL-6 inhibitors. SARS-CoV-2 infection and treatments targeting the COVID-19 hyperinflammatory state may fuel gut injury (e.g., steroids, IL-6 inhibitors) [34–37], and intestinal overgrowth under antimicrobial pressure is known to precede translocation of *Candida* and *Enterococcus* [16–18]. Finally, an analysis of gut microbiota in patients with COVID-19 belonging to our study cohort showed that BSI was associated with gastrointestinal overgrowth by the same organisms [12], as seen in patients undergoing allogeneic hematopoietic stem cell transplantation [17, 18]. Additionally, recent work demonstrates that COVID-19 patients have increased bacterial products [38] and gut microbes [11] in their bloodstream. Collectively, these observations support the hypothesis that gut translocation may contribute to the pathogenesis of NBSI in patients with COVID-19. An alternative but non–mutually exclusive hypothesis is that environmental contamination leads to exogenous entry of the organism into the bloodstream via catheter use [39].

Our data also suggest that NBSI increases mortality; COVID-19 patients who developed NBSI had an increased risk of death compared with propensity-matched controls. However, while mortality between the COVID-19 patients with NBSI and matched controls without NBSI was not significant, the slope declined most precipitously in patients without NBSI. This finding could reflect survivor bias (patients must survive long enough to be classified as acquiring NBSI). However, patients without NBSI who died early were older and more frail than those with NBSI, which suggests a potential interaction between COVID-19 treatment and subsequent NBSI. In this scenario, treatment improves survival of otherwise healthy but critically ill COVID-19 patients but might also have negative consequences for immune and microbiota-based clearance mechanisms that control...
infection, thereby predisposing patients to NBSI. Consistent with this idea, length of stay and mortality were inversely correlated in COVID-19 patients with NBSI. This finding may explain why mortality does not increase with candidemia, which primarily occurred after a prolonged length of hospital stay.

NBSI mortality was found to be significantly concentrated in patients with S. aureus and gram-negative nosocomial pneumonia (NP). S. aureus NP is a frequent complication in mechanically ventilated COVID-19 patients [40–42], and bacteremia is an independent risk factor for mortality in NP [43]. Evidently, COVID-19/bacteremic NP is a combination that kills patients at high frequency.

The present work has several limitations. First, our observational cohort data were obtained from 2 hospitals during the pandemic surge; whether NBSI patterns predict outcome in different scenarios, such as in a partially vaccinated population, will need to be tested. Second, correlations between NBSI and outcome may reflect factors we did not account for, such as managing high numbers of critically unwell patients and digression from infection prevention procedures. Third, use of clinical criteria and the T2Candida panel for the diagnosis of pneumonia and candidemia, respectively, may lead to overdiagnosis, potentially increasing the rate of overall disease detected and the proportion of cases that may be linked to NBSI and mortality.

In conclusion, NBSI is associated with mortality in hospitalized patients with severe COVID-19, depending on the species. Our findings suggest that early recognition of risk factors and treatment of NBSI are indicated. However, without accurate predictors of NBSI to guide clinicians, increased use of active agents could further shift species from a preponderance of susceptible organisms to more frequent isolation of antibiotic-resistant and Candida species. Accordingly, improved prediction models, potentially using immunological and microbiota markers, are needed. Improved prediction of NBSI could decrease morbidity and mortality by increasing early antimicrobial treatment for COVID-19 patients at risk for BSI and by reducing unnecessary antimicrobials for patients at low risk of infection.

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