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The association of a positive respiratory or bloodstream culture on outcome in a large, single-center study of predominately rural Georgia patients admitted with COVID-19 in 2020

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ABSTRACT

In early 2020, Albany Georgia, located in a predominately rural part of Georgia, had the 4th highest per capita rate of COVID-19 infection in the United States. Many of these patients developed secondary infections or presented with concomitant infections, which were noted anecdotally to be associated with a worse outcome compared to those who did not develop secondary infections. We conducted a retrospective chart review of all patients admitted to Phoebe Putney Memorial Hospital in the calendar year 2020. We were primarily interested in the effect of respiratory and bloodstream culture positivity on the outcome. We recorded data for other variables potentially contributing to a bad outcome, including Charlson Comorbidity Index (CCI), Body Mass Index (BMI), age, sex, and race. Variables initially identified as significantly associated with bad outcomes (defined as either need for mechanical ventilation or death) were then analyzed by multinomial regression. During a 10-month period (March to December), 1,431 patients were admitted. Of these, 155 (10.8%) had a positive blood culture and 142 (9.9%) had a positive respiratory culture at any time during admission. Odds ratios (OR) for death or mechanical ventilation without death were 43.0 and 86.1, respectively, for a positive respiratory culture and 4.5 and 3.3, respectively, for a positive blood culture. Age > 70 and CCI also were associated with an increased risk of death, with OR of 2.0 and 1.3, respectively. In conclusion, in our large, single-center study of patients admitted with COVID-19 in the calendar year 2020, positive respiratory culture or a positive blood culture had the highest OR associated with the bad outcome of all the variables considered.

Keywords: COVID-19, risk factors, inpatients.

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INTRODUCTION

There are many identified conditions or indices that are associated with severe disease and death in patients with COVID-19: a Charlson Comorbidity Index score of greater than zero (Kuswardhani et al., 2020; Christensen et al., 2020), age greater than 65 (or 70 or 75) (Centers for Disease Control and Prevention, nd), obesity

(Kompaniyets et al., 2020), and nosocomial infections (He et al., 2020), to list just a few. It is not clear if all of these identified conditions are independently associated with an increased risk of more severe disease, although recent data for age, in particular, suggest that age is an independent risk factor (Starke et al., 2021). The Charlson Comorbidity Index, on the other hand, weights various comorbid conditions (e.g., diabetes, dementia, chronic obstructive lung disease among 19 that were included in the original index) to predict the risk of death within 1 year of hospitalization (Charlson et al., 1987).

In early 2020, Albany, Georgia, located in Dougherty County, was at the epicenter of the COVID-19 epidemic. Two large funerals on consecutive weekends in late February - early March of 2020 were later determined to be super-spreader events (Rapier, 2020; Willis and Williams, 2020). On April 7th, 967 persons were hospitalized in Albany, the majority of them at the Phoebe Putney Memorial Hospital. At that time, the Albany per capita COVID-19 case rate was 659 per 100,000 persons, the 4th highest rate in the United States. Per the 2010 US Census, Dougherty County is 67% black compared to 30% non-Hispanic white; per capita income is around $19,000; almost 30% of the population is below the poverty line. Dougherty County ranks 152nd out of 159 Georgia counties in health outcomes (Blomme et al., 2020). Many of those hospitalized died, likely due in part to underlying comorbid conditions and/or racial disparities (Porter et al., 2021), but also due to the development of secondary infections.

The primary aim of the study was to investigate the impact of positive respiratory cultures and positive blood cultures on outcomes in a cohort of patients admitted to Phoebe Putney Memorial Hospital during the first year of the pandemic. The working hypothesis was that patients with either positive respiratory culture or a positive blood culture at any time during admission would have worse outcomes than those without either of those positive cultures.

METHODS

The study was approved by the Augusta University Institutional Review Board (PI: DF Linder, IRB#: 1606780-1). All patients admitted to Phoebe Putney Memorial Hospital in 2020 with the diagnosis of COVID-19 were included. All data were collected retrospectively from a review of the electronic medical record. For culture results, only those results felt to represent true infection were coded as “positive”. Blood culture was considered to be contaminated if one of the following criteria were met: (i) only one culture bottle out of the four bottles [two sets of anaerobic and aerobic bottles] obtained grew a typically non-pathogenic organism, such as coagulase-negative staphylococcus, (ii) an isolate was considered falsely positive by the medical team as indicated in the clinician documentation, or (iii) a positive culture was not acknowledged in clinician documentation and was not treated with antibiotics for seven or more days. A respiratory culture was considered to be contaminated if one of the following criteria were met: (i) a non-pathogenic organism (coagulase-negative staphylococcus) was grown, (ii) Candida species were isolated with no evidence of disseminated candidiasis, (iii) the isolate was considered false positive by the medical team as indicated in the clinician documentation, or (iv) positive culture was not acknowledged in clinician documentation and was not treated with antibiotics for seven or more days. We did not record the specific pathogen(s) or pathogen class (e.g., bacteria vs fungi). We also did not record whether the cultures were obtained on admission or subsequently.

The mean and standard deviation for continuous variables as well as the frequency and percent for categorical variables in tables are presented in the results section. The severity of the disease was classified into three levels: (i) the patient had neither mechanical ventilation nor in-hospital mortality, (ii) the patient required mechanical ventilation but lived, and (iii) in-hospital mortality. These levels correspond to the least severe, more severe, and most severe disease outcomes accordingly. For bivariate analyses between severity and each of the predictors, we used ANOVA for continuous variables and the Pearson chi-square test for categorical variables. To assess the independent effects of positive blood culture and positive respiratory culture on disease severity, as defined by the above three categories, we fit a multinomial logistic regression model, with least severe as the baseline category, that included blood culture and respiratory culture variables as predictors and adjusted for demographics and comorbidities using the updated (2011) Charlson comorbidity index (CCI) (Quan et al., 2011). We computed each patient’s CCI by first determining whether there was an ICD-9 or ICD-10 code in the patient’s medical record for each of the comorbidities that comprise the index, and then calculated their weighted score. We also included the following demographic variables in the analyses: (i) age > 70 years (Y/N), (ii) sex, (iii) race, and (iv) BMI. Seventy years was chosen as the age cut point somewhat arbitrarily, although others have used this cut point as well, especially early in the COVID-19 pandemic (Zhu et al., 2021). The multinomial logistic regression model was applied to the entire dataset for which we had complete information, as well as for the subset of patients for which we had complete information who had spent any amount of time in the intensive care unit (ICU). All statistical analyses were performed using R version 3.6.0.

RESULTS

Out of the 1431 records for patients hospitalized with

COVID-19 during the study period, 155 (10.8%) had a positive blood culture and 142 (9.9%) had a positive respiratory culture. Of notice, there were 255 (17.8%) patients who had either a positive blood culture, or a positive respiratory culture, and 42 (2.9%) patients who had both positive blood culture and a positive sputum culture during hospitalization (often concomitantly). The mean age (SD) of our patients was 61.5 (16.7); mean (SD) BMI was 33.2 (10.3); mean (SD) CCI was 1.7 (2.0). Seventy percent of our patients were black; 27% non-Hispanic white; 3% other. Fifty-two percent were women. Results of bivariate analyses of demographics, CCI and positive culture by disease severity are reported in Table 1.

Patients with in-hospital mortality (most severe) were more likely to have had a positive culture – blood or respiratory (48.6% vs. 7.9%; $p < 0.001$), more likely to have had a positive blood culture (23.9% vs. 6.6%; $p < 0.001$), more likely to have had a positive respiratory culture (36.5% vs. 1.2%; $p < 0.001$), more likely to be over 70 years of age (51.6% vs. 28.7%; $p < 0.001$), and have higher CCI (mean 2.61 vs. 1.48; $p < 0.001$), compared to those who lived and did not require mechanical ventilation (least severe disease). Patients requiring mechanical ventilation, but without in-hospital mortality (more severe), were more likely to have had a positive culture - blood or respiratory - (66.3% vs. 7.9%; $p<0.001$), more likely to have positive blood culture (31.5% vs. 6.6%; $p < 0.001$), more likely to have had a positive respiratory culture (52.8% vs. 1.2%; $p < 0.001$), compared to those who lived and did not require mechanical ventilation (least severe) (Table 2).

Table 1. Severity level by culture, demographics and CCI.

	Severity level			Total (N=1431)	p-value
	No mechanical ventilation or death (N=1120)	Mechanical ventilation w/o death (N=89)	Death (N=222)		
Positive Blood Culture	74 (6.6%)	28 (31.5%)	53 (23.9%)	155 (10.8%)	< 0.001
Positive Respiratory Culture	14 (1.2%)	47 (52.8%)	81 (36.5%)	142 (9.9%)	< 0.001
Positive Blood or Respiratory Culture	88 (7.9%)	59 (66.3%)	108 (48.6%)	255 (17.8%)	< 0.001
Age > 70					
Yes	321 (28.7%)	20 (22.5%)	114 (51.6%)	455 (31.8%)	< 0.001
No	798 (71.3%)	69 (77.5%)	107 (48.4%)	974 (68.2%)	
Sex					
F	590 (52.7%)	55 (61.8%)	101 (45.7%)	746 (52.2%)	0.084
M	529 (47.3%)	34 (38.2%)	120 (54.3%)	683 (47.8%)	
Race					
African American	791 (70.7%)	73 (82.0%)	141 (63.8%)	1005 (70.3%)	
Caucasian	294 (26.3%)	15 (16.9%)	73 (33.0%)	382 (26.7%)	0.084
Other	34 (3.0%)	1 (1.1%)	7 (3.2%)	42 (2.9%)	
CCI					
Mean (SD)	1.48 (1.87)	1.81 (2.06)	2.61 (2.14)	1.68 (1.97)	< 0.001
BMI					
Mean (SD)	33.24 (10.49)	35.05 (11.79)	32.02 (8.74)	33.16 (10.33)	0.084

P-values were adjusted for multiplicity.

Table 2. Multinomial logistic regression of severity level on culture, demographics and CCI.

	Severity level	
	Mechanical ventilation w/o death	**Death**
Positive Blood Culture	4.54 (1.87, 11.00)***	3.29 (1.67, 6.49)***
Positive Respiratory Culture	86.07 (29.17, 253.92)***	43.02 (16.49, 112.28)***
Sex (Male)	0.54 (0.25, 1.19)	1.08 (0.70, 1.68)
Age > 70	0.60 (0.25, 1.45)	2.02 (1.15, 3.51)***
Race (Caucasian)	0.63 (0.26, 1.54)	1.33 (0.78, 2.28)
Race (Other)	0.25 (0.01, 5.07)	1.19 (0.34, 4.20)
CCI	1.06 (0.90, 1.25)	1.23 (1.09, 1.38)***
BMI	0.98 (0.95, 1.02)	1.00 (0.98, 1.02)

Reference level for severity is no mechanical ventilator or death (least severe).
*p < 0.05, **p < 0.01, ***p < 0.001.
P-values were adjusted for multiple testing.

A positive blood culture (OR 3.29; CI 1.67-6.50, p < 0.001), positive respiratory culture (OR 43.02; CI 16.49-112.28, p < 0.001), age > 70 (OR 2.02; CI 1.15-3.51, p < 0.001) and CCI (OR 1.23; CI 1.09-1.38, p < 0.001) were all associated with significantly increased odds of in-hospital mortality (most severe) compared to the least severe disease outcome. A positive blood culture (OR 4.54; CI 1.87-11.00, p < 0.001) and positive respiratory culture (OR 86.07; CI 29.17-253.92, p < 0.001) were associated with significantly increased odds of being alive but requiring mechanical ventilation (more severe), compared to the least severe disease outcome (Table 3).

In this smaller sample size group of patients who spent any time in an ICU, a positive blood culture (OR 3.82; CI 1.32-11.02, p < 0.001), and a positive respiratory culture (OR 13.16; CI 3.90-44.43, p < 0.001) were both associated with significantly increased odds of in-hospital mortality (most severe) compared to the least severe disease outcome. A positive blood culture (OR 4.14; CI 1.25-13.79, p < 0.001) and a positive respiratory culture (OR 21.93; CI 5.71-84.18, p < 0.001) were associated with significantly increased odds of being alive but requiring mechanical ventilation (more severe), compared to the least severe disease outcome. No other variable, including age > 70 years and CCI, showed statistical significance.

Table 3. Multinomial logistic regression of severity level on culture, demographics and CCI on the subset of ICU patients (n = 391).

	Severity level	
	Mechanical ventilation w/o death	**Death**
Positive Blood Culture	4.14 (1.25, 13.79)***	3.82 (1.32, 11.02)***
Positive Respiratory Culture	21.93 (5.71, 84.18)***	13.16 (3.90, 44.43)***
Sex (Male)	0.40 (0.15, 1.07)	0.90 (0.46, 1.75)
Age > 70	0.39 (0.12, 1.27)	1.56 (0.69, 3.55)
Race (Caucasian)	0.89 (0.42, 1.92)	1.68 (0.74, 3.80)
Race (Other)	0.12 (0.01, 3.34)	0.58 (0.10, 3.35)
CCI	1.03 (0.85, 1.24)	1.13 (0.93, 1.36)
BMI	0.99 (0.94, 1.03)	1.01 (0.97, 1.05)

Reference level for severity is no mechanical ventilator or death (least severe).
*p < 0.05, **p < 0.01, ***p < 0.001.
P-values were adjusted for multiple testing.

DISCUSSION

Similar to others (He et al., 2020; Costa et al., 2022; Grasselli et al., 2021), we found that secondary infections, whether in the respiratory tract or blood, were associated with a substantially increased risk of a bad outcome, even after adjusting for other known risk factors. Unlike He et al. (2020), we cannot state that all of the positive culture results represented nosocomial acquisition of pathogens. Anecdotally, however, it is likely that over 90% of the pathogens isolated were obtained after the first two hospital days. The 17.8% rate of

positive blood or respiratory cultures (Table 1) is similar to the 14.3% rate of "secondary bacterial infections" reported by Langford et al in a recent meta-analysis[16]. Of notice, in their meta-analysis, they found that over 70% of patients early in the pandemic received antibiotics during the course of their hospitalization. It, therefore, needs to be emphasized that our results in no way support the use of empiric antibiotics to prevent infections, even as it needs to be noted the profound effect secondary infections have on patients admitted with COVID-19. Our positive respiratory and bloodstream culture rates were comparable to those reported by other investigators, who themselves noted rates in patients admitted with COVID-19 to be higher than either concurrent or historical controls (DeVoe et al., 2021; Marin-Corral et al., 2022). Our reported rate of positive respiratory cultures of 9.9% further suggests that clinicians were using appropriate criteria to determine whom to culture.

The substantially higher OR for bad outcomes with a positive respiratory culture compared with a positive blood culture may, initially, seem surprising. However, substantial damage to the lungs due to infection with SARS-CoV-2 and the host inflammatory response occurs throughout the hospital course of patients admitted with COVID-19. It is likely that additional insults to the lung from these secondary infections explain the higher OR compared to bacteremia. COVID-19 is, first and foremost, a respiratory illness associated with hypoxia in those hospitalized with it.

The demographics of our study population likely are broadly representative of the demographics of the Albany area. As such, they may not be generalizable to other populations (e.g., urban) in other parts of the United States and the world. Nevertheless, the 16% mortality rate in our study (222/1431) compares favorably to hospitals throughout the United States, suggesting that our patients received an appropriate level of care (Asch et al., 2021). Our study found that both older age and CCI are independent risk factors for bad outcomes in the entire cohort. Of notice, our study found that age greater than 70 was more strongly predictive of mortality than was the CCI. A recent meta-analysis of 59 studies also found that age over 70 was associated with more severe COVID-19 disease, more intensive care time, and a higher risk of death[20]. These findings support current recommendations to prioritize giving vaccinations to the elderly, regardless of underlying comorbid conditions. We were not surprised that BMI in our study was not found to be an independent predictor of bad outcomes, because our study population is predominantly obese, with a sample mean BMI of 33. It does need to be emphasized, however, that BMI is a recognized risk factor for bad outcomes in patients with COVID- (Kompaniyets et al., 2020). We also did not find sex to be a risk factor, although the meta-analysis by Pijls et al. (2021) referenced above did find that men had a higher risk of COVID-19 in general and a higher risk for severe disease. However, the relative risk (men vs women) in their pooled analysis of over 11,000 individuals was less than 1.20. Our study was likely underpowered to detect such relatively small differences.

Our study has quite a few strengths, including a large sample of patients enrolled over 10 months, as health care providers improved COVID-19-specific care (Asch et al., 2021). In addition, by controlling for the impact of known risk factors for a bad outcome in our multinomial logistic regression analyses (e.g., CCI), we were able to demonstrate the large role that secondary infections play in contributing to a worse outcome. Future studies need to investigate more effective ways to reduce nosocomial infections in this high-risk population.

The study does have a few weaknesses, some inherent to the retrospective chart review approach. Specific pathogens were not recorded, nor were the number of days of hospitalization before obtaining cultures, antibiotic information, specific complications (e.g., thrombotic events) contributing to mortality, etc. Nevertheless, this large, single-site study of a predominately rural group of patients severely impacted by COVID-19 early during the first phase of the epidemic clearly showed the need for increased vigilance to minimize the likelihood of developing nosocomial infections.

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Conflict of interest

None of the authors has anything to disclose or any conflicts of interest to report.

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