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Bacterial infections and death among patients with Covid-19 versus non Covid-19 patients with pneumonia



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ABSTRACT

Background: Many patients with Coronavirus disease-2019 (Covid-19) present with radiological evidence of pneumonia. Because it is difficult to determine co-existence of bacterial pneumonia, many of these patients are initially treated with antibiotics. We compared the rates of bacterial infections and mortality in Covid-19 patients with pulmonary infiltrates versus patients diagnosed with 'pneumonia' the year previously.

Methods: We conducted a medical record review of patients admitted with Covid-19 and a pulmonary infiltrate and compared them with patients diagnosed with pneumonia admitted in the prior year before the pandemic. Data abstracted included baseline demographics, comorbidities, signs and symptoms, laboratory and microbiological results, and imaging findings. Outcomes were bacterial infections and mortality. Patients presenting with and without Covid-19 were compared using univariable and multivariable analyses.

Results: There were 1398 and 1001 patients admitted through the emergency department (ED) with and without Covid-19 respectively. Compared with non-Covid-19 patients, those with Covid-19 were younger (61 ± 18 vs. 65 ± 25 years, $P < 0.001$) and had a lower Charlson Comorbidity Index (0.7 vs. 1.2 , $P < 0.001$). Bacterial infections were present in fewer Covid-19 than non-Covid-19 patients (8% vs. 13% , $P < 0.001$), and most infections in Covid-19 were nosocomial as opposed to community acquired in non-Covid-19 patients. CXR was more often read as abnormal and with bilateral infiltrates in patients with Covid-19 (82% vs. 70% , $P < 0.001$ and 81% vs. 48% , $P < 0.001$, respectively). Mortality was higher in patients with Covid-19 vs. those without (15% vs. 9% , $P < 0.001$). Multivariable predictors (OR [95%CI]) of mortality were age (1.04 [1.03 – 1.05]/year), tachypnea (1.55 [1.12 – 2.14]), hypoxemia (2.98 [2.04 – 4.34]), and bacterial infection (2.80 [1.95 – 4.02]). Compared with non-Covid-19 patients with pneumonia, patients with Covid-19 were more likely to die (2.68 [1.97 – 3.63]).

Conclusions: The rate of bacterial infections is lower in Covid-19 patients with pulmonary infiltrates compared with patients diagnosed with pneumonia prior to the pandemic and most are nosocomial. Mortality was higher in Covid-19 than non-Covid-19 patients even after adjusting for age, tachypnea, hypoxemia, and bacterial infection.

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1. Introduction

First reported in December 2019, SARS-CoV-2, the etiologic agent of the novel coronavirus infectious disease 2019 (Covid-19), has been responsible for the greatest pandemic in over a century. Covid-19 results in a wide spectrum of disease from asymptomatic carriers through pneumonia, Acute Respiratory Distress Syndrome (ARDS) and death leading to many hospitalizations and ICU admissions [1]. In the hospital as part of the work up, biological specimens (such as blood and sputum)

are sent for microbiological culture to determine the presence of co-existing, or superimposed bacterial infections in patients diagnosed with Covid-19. To date, data on the prevalence of bacterial superinfection in Covid-19 positive patients is not well established [2–4].

Historically, patients hospitalized for influenza and influenza-like viral syndromes have been shown to be more susceptible to bacterial super-infection [5]. In the last 20 years, the world has experienced at least six major viral epidemics, including SARS-CoV, MERS, H1N1, Ebola, Zika, and the current SARS-CoV-2. Bacterial super-infections during these viral illnesses have been associated with poor outcomes [6–8]. Thus, bacterial superinfection is a poor prognostic factor for patients and increases the likelihood for ICU admission and mortality [1,7]. The Centers for Disease Control and Prevention (CDC) reported during the

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2009 H1N1 influenza pandemic that between 29 and 55% of deaths were due to secondary bacterial infections. Of five studies done during the original 2002 SARS-CoV outbreak, 11% of cases were associated with secondary bacterial infections [6]. *Staphylococcus aureus*, in particular, has been shown to be isolated from hospitalized patients with influenza virus infection [9,10]. *Streptococcus pneumoniae*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Enterobacter* and *Citrobacter* spp., and *Haemophilus influenzae* are also common bacteria isolated from blood and sputum cultures in patients with a bacterial superinfection on top of a respiratory viral infection [2,3,5,8].

The goal of the current study was to determine the rate of co-existent bacterial infections in admitted patients with Covid-19 and a pulmonary infiltrate and compare it to the rate of bacterial infections in a control cohort of patients admitted with a diagnosis of pneumonia in the year prior to the Covid-19 pandemic. We also sought to establish if Covid-19 and bacterial infection were independently associated with increased mortality.

2. Methods

2.1. Study design

We performed a structured, retrospective electronic medical record review (Cerner, Kansas City, MO) examining all patients presenting to our ED with confirmed Covid-19 based on a positive SARS-CoV-2 PCR. This study followed the Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines for cross-sectional studies [11]. We also followed the recommended methodology of Kaji et al. for retrospective chart reviews [12]. Due to the retrospective nature of this study, we received IRB approval with waiver of informed consent.

2.2. Patients and setting

All patients admitted to our hospital between 2/2020–5/2020 with SARs-CoV-2 PCR confirmed Covid-19 infection were included in the study. For the control group, we used a cohort of all patients admitted to the hospital between 2/2019 and 5/2019 with a diagnosis of pneumonia based on International Classification of Diseases version 10 (ICD-10) codes. We specifically excluded patients with an ICD-10 code consistent with a viral pneumonia. We chose patients from the previous year prior to the pandemic with a diagnosis of pneumonia as the control group since many such patients have a pulmonary infiltrate and have traditionally presumed to have a bacterial etiology and started on antibiotics. Our hospital is a tertiary academic medical center with 650 hospital beds located in Eastern Long-Island approximately 60 miles from New York City, with a catchment area of 1.5 million inhabitants.

2.3. Data source and collection

A computerized search and a manual retrospective chart review of our electronic medical records to identify patients meeting all inclusion criteria was performed. For eligible patients, we extracted patient demographic information, including race, ethnicity, sex, comorbidities (expressed as a Charlson Comorbidity Index [CCI]), symptoms, vital signs, lab results, bacterial cultures and antigens, chest XR and chest CT imaging results, disposition, (discharge to home, admission to a non-intensive floor, admission to an ICU), and survival to hospital discharge. Study data and variables were defined prior to initiating the study and extracted by trained abstractors using a library of definitions. We periodically monitored data collection and determined the inter-observer agreement on the outcomes on a randomly selected sample of 200 study patients. Interobserver agreement (Kappa statistic) ranged from 0.96 (95%CI, 0.90–0.99) to 1.0.

2.4. Study outcomes

The primary outcome was the presence of a culture or antigen confirmed bacterial infection. Secondary outcomes were in-hospital mortality, ICU admission, and hospital length of stay. All results of blood, sputum, and pleural bacterial cultures as well as urinary bacterial antigens were reviewed by a two-member committee including an emergency medicine and infectious disease provider to determine whether the positive cultures or antigens were ‘true positives’ and due to infection.

Infections were defined as nosocomial if the positive culture was obtained >48 h after hospital admission. Patients with a first positive culture within 48 h who were admitted from home or from long term care facilities were deemed to have community-acquired infections. A patient with a positive culture was classified as an infection if the bacteria was isolated from blood or any other sterile source (e.g., pleural). Blood cultures with coagulase negative *Staphylococcus* species, *Corynebacterium*, or *Bacillus* (not anthracis) species were deemed to be contaminants from commensal skin flora [13].

For patients with positive sputum cultures, we required sputum samples to exhibit <9 epithelial cells per high power field and moderate-many WBCs to indicate infection. Sputum samples with more epithelial cells were deemed to represent inadequate sample collection. If no-few WBCs were present, we deemed positive bacterial cultures to represent colonization [13,14]. However, if the same bacterial species was also isolated in sterile site cultures (blood or pleural fluid), then sputum cultures were classified as infection. These definitions were consistent with those proposed from IDSA/ATS Society guidelines [14].

2.5. Data analysis

Data are summarized as numbers and frequencies for nominal data and means with standard deviations (SD) for continuous data. For all variables and models, we only used the initial findings at ED presentation. Comparisons between groups were performed using logistic regression. Exploratory multivariate analysis of primary and secondary outcomes was performed using potential predictor variables chosen based on biological plausibility and previous reports. Variables significantly associated with outcomes on bivariable analyses were also entered into the model. Level of significance was defined as a *P* value of 0.05 or less.

3. Results

3.1. General patient characteristics

The study cohort included 1389 patients who were admitted through the ED with PCR confirmed Covid-19 infection between February and May 2020. The total number of ED visits during this time period was 25,902. The control cohort included 1001 non-Covid-19 patients with pneumonia admitted to the hospital through the ED during the corresponding time period one year earlier. The total number of ED visits during this time period was 25,024. Table 1 compares patients with and without Covid-19. Compared with non-Covid-19 patients with pneumonia, patients with Covid-19 were younger (61 vs. 65 years), had a lower mean [SD] CCI (0.7 [0.8] vs. 1.2 [0.8]), and were more likely to present with fever (22% vs. 9%), hypoxemia defined as oxygen saturation less than 94% (40% vs. 31%), leukopenia (9% vs. 5%), abnormal chest X-rays (82% vs. 70%), and bilateral findings both on chest X-rays (81% vs. 48%) and chest CT (87 vs. 63%) respectively; *P* < 0.001 for all comparisons. In contrast, patients with non-Covid-19 pneumonia were more likely than patients with Covid-19 to present with elevated creatinine (24% vs. 19%), elevated procalcitonin (33% vs 19%), and elevated cardiac troponin (18% vs. 10%) respectively; *P* < 0.001 for all comparisons.

Table 1
Comparison of baseline patient characteristics

	Non Covid-19	Covid-19	P value
Male	562 (56)	799 (58)	0.50
Mean (SD) age, years	65 (25)	61 (18)	<0.001
VITAL SIGNS/LAB TESTS			
Fever	82 (9)	304 (22)	<0.001
Tachypnea	236 (24)	332 (24)	0.88
Oxygen saturation			<0.001
>94%	689 (69)	842 (61)	
89–93%	211 (21)	344 (25)	
<89%	101 (10)	202 (15)	
Leukopenia < 4000/ml	46 (5)	124 (9)	<0.001
Lymphocytopenia <1000/ml	458 (47)	503 (36)	<0.001
Platelets <150,000/ml	182 (19)	245 (18)	0.59
Creatinine >1.5 mg/dL	234 (24)	256 (19)	0.002
D-Dimer > 750 mg/L	35 (32)	310 (24)	0.06
CRP > 8.2 mg/dL	119 (42)	641 (48)	0.06
Procalcitonin > 0.5 ng/mL	228 (33)	248 (19)	<0.001
AST > 40 Units/L	214 (26)	682 (50)	<0.001
Troponin >0.06 mg/mL	143 (18)	123 (10)	<0.001
IMAGING			
CXR performed	950 (95)	1328 (96)	0.43
CXR positive	665 (70)	1094 (82)	<0.001
Finding bilateral	322 (48)	888 (81)	<0.001
CT performed	493 (49)	370 (27)	<0.001
CT positive	429 (87)	320 (86)	0.84
Finding bilateral	269 (63)	277 (87)	<0.001
Mean (SD) Charlson Comorbidity Index	1.2 (0.8)	0.7 (0.8)	<0.001

Values are presented as number (%) or mean (standard deviation).

3.2. Bacterial infections

Bodily fluid (blood, sputum, and pleural) cultures and urinary antigens were tested in 1325 (95%) Covid-19 patients and 859 (89%) non-Covid-19 patients respectively (Table 2). Positive results consistent with bacterial infections were found in a higher proportion of patients with non-Covid-19 pneumonia than in patients with Covid-19 (129 [13%] vs. 117 [8%] respectively, $P < 0.001$). A summary of the respective bacterial species identified in the study and control patients is presented in Table 3.

Patients with non-Covid-19 pneumonia presented with bacterial infections significantly earlier in their hospital course than patients with Covid-19. Median (IQR) days from admission to positive blood and sputum cultures in control and Covid-19 patients were 0 (0–1) vs. 12.5 (0–21) and 1 (0–2) vs. 10 (7–19) respectively, $P < 0.001$ for both. Among 128 patients with non-Covid-19 pneumonia, 91 (71%) had evidence of infection within the first 48 h of admission. Of these, about one third ($n = 31$) had bacteremia while the others showed evidence of infection in the respiratory system whether based on positive sputum

Table 2
Results of bacterial cultures and antigens

	Non-Covid-19 ($n = 1001$)	Covid-19 ($n = 1389$)	P value
Blood			
Tested	858 (86)	1272 (92)	<0.001
True positive	53 (6)	76 (6)	0.85
Sputum			
Tested	322 (32)	200 (22)	<0.001
True positive	80 (25)	88 (44)	<0.001
Urinary antigen			
Tested	451 (45)	1050 (76)	<0.001
True positive	17 (4)	5 (0.5)	<0.001
Pleural fluid			
Tested	45 (4)	13 (1)	<0.001
True positive	5 (11)	2 (15)	0.65
Any test performed	895 (89)	1325 (95)	<0.001
Any True Positive	129 (13)	117 (8)	<0.001

Table 3
Bacterial Isolates Identified (excludes contaminants)

Most frequent type of bacteria given as a percent of all patients.			
	Non-Covid-19 (2019)	Covid-19 (2020)	P value
Gram positive organisms	71 (55)	50 (43)	0.08
Gram negative organisms	37 (29)	49 (42)	
Both gram positive and negative organisms	20 (16)	17 (15)	
Total patients	128 (100)	116 (100)	
Most frequent bacteria identified given as a percent of all true positive bacterial tests. Only bacteria with 10 or more occurrences are listed.			
Non-Covid-19 (2019)		Covid-19 (2020)	
<i>Staphylococcus aureus</i>	60 (31%)	<i>S. aureus</i>	44 (25%)
<i>Pseudomonas Aeruginosa</i>	20 (10%)	<i>Klebsiella pneumoniae</i>	25 (14%)
<i>Streptococcus pneumoniae</i>	17 (9%)	<i>Pseudomonas Aeruginosa</i>	21 (12%)
<i>Escherichia coli</i>	17 (9%)	<i>Enterococcus faecalis</i>	17 (10%)
<i>K. pneumoniae</i>	10 (5%)	<i>E. coli</i>	12 (7%)
<i>Stenotrophomonas Maltophilia</i>	10 (5%)	<i>Klebsiella (Enterobacter) aerogenes</i>	12 (7%)

cultures ($n = 44$), urinary antigens ($n = 17$) or positive pleural cultures ($n = 2$). The remaining 37 (29%) non-Covid-19 patients developed infection >48 h of admission, of which 9 had bacteremia, 34 had a positive sputum culture, and three patients had a positive pleural culture. Among 116 Covid-19 patients, only 28 (24%) had evidence of infection within the first 48 h and the remaining 88 (76%) developed infection at least 48 h after admission. Among 28 Covid-19 patients who were diagnosed early with infections, 15 had bacteremia, 11 had positive sputum cultures, and three had a positive urinary antigen. In contrast among 88 Covid-19 patients who presented late with infection, 33 had bacteremia, 75 had positive sputum cultures, 20 had a positive urinary antigen and two had a positive pleural culture. Thus, community acquired bacterial infections were more common in non-Covid-19 pneumonia patients while bacterial nosocomial infections were more common in Covid-19 patients.

Gram positive organisms represented the majority of infections found in our study in both the blood and sputum cultures. Among gram positive bacteria, *Staphylococcus aureus* was the predominant isolate both in non-Covid-19 and Covid-19 patients (Table 3). Among gram negative bacteria *Pseudomonas aeruginosa* was the predominant isolate from non-Covid-19 patients while *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* were the predominate species in Covid-19 patients (Table 3).

3.3. Mortality

The number (%) of deaths was higher in Covid-19 patients than control patients without Covid-19; 211 (15%) vs. 86 (9%) respectively, $P < 0.001$ (Table 4). A summary of the multivariable analyses is presented in Table 5. Predictor variables associated with death after adjusting for confounding variables (OR, 95%CI) were age (1.04, 1.03–1.05/year), tachypnea (1.55, 1.12–2.14), and oxygen saturation less than 89% (2.98–2.04–4.34). Presence of a bacterial infection (2.80, 1.95–4.02) and Covid-19 (2.68, 1.97–3.63) were independently associated with mortality even after adjusting for confounders.

3.4. ICU admission and hospital length of stay

The number (%) of patients who required ICU level of care among patients with and without Covid-19 was 327 (24%) vs. 275 (27%)

Table 4
Outcomes

	Non Covid-19	Covid-19	P value
Hospital discharge disposition			
Discharged	896 (90)	1172 (84)	<0.001
Died	86 (9)	211 (15)	0.55
Median (IQR) time to death, days	8.3 (3.4–15.9), range 0–47	9.3 (4.3–20), range 0–112	
LAMA	19 (2)	6 (0.4)	
ICU (admit or upgrade)	275 (27)	327 (24)	0.03
Patients with no + test ^a	137 (21) [643]	156 (15) [1051]	0.001
Patients with 1 or more + test	138 (39) [358]	171 (51) [338]	0.002
Mean (SD) Total LOS, days	10.6 (14.9)	11.6 (15.6)	0.13

LAMA: left against medical advice; ICU: intensive care unit; SD: standard deviation; LOS: length of stay.

^a Includes untested patients; brackets indicate sample size.

Table 5
Multivariable analyses.

Mortality	Odds ratio	95% CI
Age	1.04	1.03–1.05
Bacterial infection	2.80	1.95–4.02
Non-Covid-19	Reference	
Covid-19	2.68	1.97–3.63
Fever	0.59	0.38–0.91
Tachypnea	1.55	1.12–2.14
O ₂ saturation (%)		
94–100	Reference	
89–93	1.23	0.87–1.72
<89	2.98	2.04–4.34
ICU admission	Odds ratio	95% CI
Male	1.45	1.19–1.78
O ₂ saturation (%)		
94–100	Reference	
89–93	1.10	0.87–1.40
<89	2.40	1.82–3.16
Bacterial infection	6.08	4.56–8.10
Non-Covid-19	Reference	
Covid-19	0.83	0.68–1.01
Hospital length of stay (days)	Coefficient	95% CI
ICU admission	13.7	12.4–15
Bacterial infection	11.2	9.3–13
Pre-Covid-19	Reference	
Covid-19	1.8	0.7–2.9
O ₂ saturation (per % decrease)		
94–100	Reference	
89–93	0.7	–0.6–2.0
<89	2.7	1.0–4.3

respectively, $P = 0.03$. Patient variables independently associated with ICU admission at any time during admission included male sex (1.45, 1.19–1.78), oxygen saturation less than 89% (2.40, 1.82–3.16), and a bacterial infection (6.08, 4.56–8.10). After adjusting for confounding variables, Covid-19 was not associated with ICU admission (0.83, 0.68–1.01).

Mean total hospital length of stay did not differ between the two study groups based on univariable analysis (Table 4). Predictor variables associated with prolonged length of stay after adjusting for confounding variables included oxygen saturation less than 89%, ICU admission, and bacterial infection (Table 5).

4. Discussion

In this retrospective study we compared a cohort of admitted patients with Covid-19 during 2020 and another cohort of admitted patients with non-Covid-19 pneumonia in 2019. We found that non-

Covid-19 patients with pneumonia were more likely to have a bacterial infection than Covid-19 patients and were more likely to present with a community acquired infection on arrival to the hospital. In contrast, Covid-19 patients were less likely to present with evidence of bacterial infection and when bacterial infection was evident, it was more likely to be nosocomial occurring later in the hospital admission. This suggests that bacterial superinfection occurred in the majority of Covid-19 patients. Given the appearance of bacteremia later in the hospital course of Covid-19 patients, line infection with skin flora translocation to the bloodstream is a possible likely etiology in many patients. This is similar to other respiratory viral infections such as influenza, in which superinfection is not uncommon, particularly with *Staph. aureus* [9,10]. Not surprisingly, we also found that the evidence of a bacterial coinfection was independently associated with mortality both in patients with and without Covid-19. Another possible explanation for the reduced rates of bacterial co-infection during the Covid-19 study period is the widespread use of masks and social distancing that may have further reduced bacterial co-infections and superinfections.

Evidence of bacterial infection based on blood, sputum and pleural bacterial cultures as well as urinary antigens was only present in 13% of those with non-Covid-19 pneumonia that were tested. This is consistent with prior similar studies in which positive blood cultures have been reported in 5–14% of those tested [15,16]. Prior studies have found that *Strep. pneumoniae* is the most common bacterial etiology of pneumonia [16]. However, in our study other less typical bacteria were commonly found such as *Staph. aureus*, both in patients with and without Covid-19.

Studies have shown that infection with SARS-CoV-2 can lead to an impairment in immune function by damaging lymphocytes, especially B cells, T cells, and NK cells [17]. This decrease in immune function likely contributes to increased susceptibility to bacterial coinfection [18]. Our study is unique in that it directly compared patients with non-Covid-19 pneumonia who did not have a confirmed diagnosis of viral infection with patients with a confirmed diagnosis of Covid-19. A study preceding the Covid-19 pandemic found that among patients infected with other respiratory viruses, the number of cases of primary coinfection or secondary bacterial pneumonia was between 11 and 35% [19]. Another study from 2003, reported that more than 20% of the patients who were positive for SARS-CoV had evidence of bacterial and fungal coinfection [20]. A single-center, retrospective case series study including 55 severe patients and 166 non-severe patients with laboratory-confirmed SARS-CoV-2 pneumonia, found that in all 221 patients the bacterial coinfection rate was 7.7% [21]. A study from Italy that included 16,654 patients who died of SARS-CoV-2 infection, reported that 11% had coinfection [22]. A retrospective, single-center study of 99 Covid-19 cases from Wuhan reported coinfections with *Acinetobacter baumannii* and *Klebsiella pneumoniae* [23]. Regardless of the rate and cause of bacterial co-infections in patients with Covid-19, there is evidence that bacterial co-infection is proportional to the severity of the disease [24], and that coinfection can increase the mortality [25].

5. Limitations

Our study has several notable limitations. Due to its retrospective nature, we cannot exclude selection bias or residual confounding. While most patients were cultured, some were not. This may have underestimated the number of patients with bacterial infection. We also cannot exclude errors in data entry and reporting. We used commonly suggested criteria to distinguish between true bacterial infection and contamination [14]. However, these criteria may have overestimated or underestimated the true number of infections. In addition, our study is representative of a single, academic suburban hospital near one of the first epicenters of the Covid-19 pandemic and may not be representative of other settings.

6. Conclusions

We found higher rates of bacterial infection in patients with non-Covid-19 pneumonia presenting in the year prior to the global Covid-19 pandemic than in Covid-19 patients presenting early in the pandemic. Of Covid-19 patients who developed bacterial infection many were nosocomial acquired after hospital admission and were caused by less common bacteria such as *Staph. aureus* and gram-negative bacteria. Routine administration of antibiotics to Covid-19 patients on admission, especially those without severe disease, does not seem warranted.

Grants

None.

Author contributions

HS, BCF, and AJS conceived the study and designed the study. AJS and RF supervised the conduct of the study and data collection. HCT analyzed the data. HS and AJS drafted the manuscript and all authors contributed substantially to its revision. AJS takes responsibility for the paper as a whole.

Author statement

Hayley Scott: writing original-draft, data curation, formal analysis. *Allena Zahra*: formal analysis, writing-review & editing. *Rafael Fernandes*: supervision, data curation, writing-review & editing. *Bettina Fries*: conceptualization, formal analysis, writing-review & editing. *Henry Thode*: formal analysis. *Adam Singer*: conceptualization, formal analysis, writing-original draft, supervision.

Declaration of Competing Interest

None of the authors have any conflicts of interest related to this study.

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