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Bacteremia in Critically Ill Patients with SARS-CoV 2 Infection

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Abstract: *Background:* Since December 2019, the COVID-19 pandemic has caused the dead of 1 million people, from these critically ill patients have an increased risk of bacteremia. *Material and Methods:* This observational, retrospective, single-center study included 129 critically ill COVID-19 patients with a bacteremia. We studied the clinical characteristics, comorbidities, hospital and intensive care unit length of stay, days on invasive mechanical ventilation, maximum dose of norepinephrine and mortality. *Results:* From 129 patients were reported 17 patients (13.2%) with bacteremia. 35.3% were cataloged as a primary bacteremia. The source of secondary bacteremia was a ventilator associated pneumonia in 81.8%, central line-associated blood stream infection in 18.1% and urinary catheter infection in 9%. The patients with bacteremia, had a hospitalization stay of 23 days Vs. 20.5 days in the patients without bacteremia (p=0.19); 18 Vs. 13.5 days in the ICU (p=0.061); 15 Vs 11 days on IMV (p=0.053) and a maximum dose of norepinephrine of 0.28 Vs. 0.11 mcg/kg/min (p=0.02). We reported a 14.8% of mortality in patients with bacteremia vs. 12.7% in patients without bacteremia, odds ratio of 0.87 (p=0.75). *Conclusion:* Critically ill COVID-19 patients and bacteremia tend to increase the length of stay in the ICU and days on IMV with no change in mortality.

Keywords: COVID-19, SARS-CoV-2, Bacteremia, Critically III Patients

1. Introduction

Since December 2019, the COVID-19 pandemic has affected more than 42 million people and caused the death of approximately 164 million people. Se In Mexico there are 891 160 cumulative cases and 88 924 deaths until October 2020, according to the World Health Organization (WHO) [1].

It is known that the primary risk factors for clinical worsening and mortality in COVID-19 patients are advanced age and comorbidities, including obesity, hypertension, and diabetes [2]. In Mexican population people among 20 years have an overweight and an obesity prevalence of 72% with an increment in the period from 2000 to 2016 of 41.8% in overweight and a 290.5% in obesity prevalence [3].

There is an increased number of blood stream infections (BSI) in COVID-19 hospitalized patients in the intensive care unit (ICU) after their need of an invasive device like a central venous catheter, an extracorporeal membrane oxygenation (ECMO) or renal replacement therapy [4, 5]. But there are still few studies aiming on the detection and clinical relevance of bacteremias in COVID-19 patients.

The aim of this study is to describe the clinical and microbiological characteristics of critically III COVID-19 patients with a positive blood culture, identifying the source

of the bacteremia and the association of the outcome of these patients.

2. Objective

The objective of this study was to compare the clinical characteristics of critically III COVID-19 patients and a positive blood culture with patients with negative blood cultures, determining the source of the bacteremia, pathogen, and clinical outcomes, like hospital and ICU days of stay, days on IMV, maximum dose of vasopressor and hospital mortality.

3. Definitions

COVID-19 was defined as a patient with a positive RT-PCR test for SARS-CoV-2 on at least one respiratory specimen (either from a nasopharyngeal swab or a BAL). Primary bacteremia was cataloged as at least one positive blood culture with no confirmed source, assuming direct inoculation. Secondary bacteremia was cataloged as at least one positive blood culture with a confirmed source or other positive cultures in specific sites (respiratory or urinary cultures). These definitions and the categorization of the patient bacteremias were made by the HESU. Polymicrobial infections were considered as separate events, one for each causative organism isolated from the blood culture.

4. Material and Methods

We conducted a retrospective analysis on patients with COVID-19 admitted to the ICU of Medica Sur Hospital in Mexico City, from March to August 2020. The protocol was authorized by the Research and Ethics Committee of the hospital (2020-EXT-461). We collected the patient's data: gender, age, body mass index (BMI), comorbidities (including smoking, hypertension, heart arrhythmias, diabetes, ischemic cardiac disease, dyslipidemia, chronic pneumopathies, solid and hematologic neoplasm) from the digital medical records. We collected the positive blood culture during the first 14 days of stay in the ICU describing the causal microorganism and determining the source of the bacteremia concomitant with respiratory and urinary cultures. The final determination between a primary or secondary bacteremia was realized by the Hospital Epidemiological Surveillance Unit (HESU). Once determining the source of the bacteremia, we divided in two groups (patients with a bacteremia and patients without a bacteremia) for the comparison of clinical outcomes.

4.1. Inclusion Criteria

We included men and women of 18 years and older, with COVID-19 confirmed with a RT-PCR from a nasopharyngeal swab or bronchoalveolar lavage (BAL), requiring invasive mechanical ventilation (IMV), whit at least a 7 day in hospital stay.

4.2. Exclusion Criteria

There were excluded patients with blood cultures with isolation of Coagulase negative Staphylococcus, considered as a contaminant, we also excluded pregnant patients.

4.3. Statistical Analysis

All data analysis was anonymized and collected, the categorical data was reported in percentages and proportions, continuous data was expressed in medians and interquartile ranges (IQR). The Statistical analysis and associations were realized using Statistical Package for the Social Sciences (SPSS) software version 22.0, the quantitative data was analyzed with a Mann-Whitney U test and qualitative data was analyzed with a chi-square test. The graphics were realized on GraphPad Prism 5.07. The statistical significance on results was stablished with a p value below 0.05.

5. Results

Table 1. *Patient´s characteristics and comorbidities.*

Characteristics	Total (n=129)	Without bacteremia (n=112)	With bacteremia (n=17)
Age (years), median [interquartile range]	59 [48-68]	58.5 [48-67]	68 [43.5-74.5]
Gender			
Male	109 (84.5%)	95 (84.8%)	14 (82.4%)
Female	20 (15.5%)	17 (15.2%)	3 (17.6%)
BMI (kg/m^2), media [interquartile range]	29.7 [26.5-32.9]	29.7 [26.6-32.5]	29.4 [25.2-33.4]
Comorbidities			
Smokers	8 (6.2%)	6 (5.3%)	2 (11.7%)
Hypertension	42 (32.5%)	36 (32.1%)	6 (35.2%)
Cardiac arrhythmia	8 (6.2%)	7 (6.2%)	1 (5.8%)
Diabetes	36 (27.9%)	29 (25.8%)	7 (41.1%)
Prior acute ischemic cardiopathy	6 (4.6%)	5 (4.4%)	1 (5.8%)
Peripheric arterial disease	3 (2.3%)	3 (2.6%)	0 (0%)
Dyslipidaemias	9 (6.9%)	8 (7.1%)	1 (5.8%)
Chronic pneumopathy	3 (2.3%)	3 (2.6%)	0 (0%)
Ambulatory oxygen user	1 (0.7%)	1 (0.8%)	0 (0%)
Solid neoplasm	9 (6.9%)	8 (7.1%)	1 (5.8)
Hematologic neoplasm	1 (0.7%)	1 (0.8%)	0 (0%)

A total of 129 patients with confirmed SARS-CoV-2 were identified during the study period (March 1st to August 15th, 2020). The median of age was 57.9 years old [IQR 48 – 68], with 84.5% (n=109) male patients and 15.5% (n=20) female patients. The median of BMI was 30.23 kg/m^2 [IQR 26.5-32.9]. 32.5% (n=42) of the patients had hypertension, 27.9% (n=36) had diabetes, 6.2% (n=8) had a cardiac arrhythmia, 6.2% (n=8) were smokers, and 4.65% (n=6) had a prior acute ischemic cardiopathy (Table 1).

From all the 129 patients, 13.2% of patients (n=17) had a positive blood cultures; from those, 17 patients 35.3% (n=6) were cataloged as a primary bacteremia where Chryseobacterium indologenes was the most common pathogen (2 patients). E. coli, Streptococcus oralis, Streptococcus constellatus, and Streptococcus mitis represented one patient each. Secondary bacteremia was reported in 64.7% (n=11) of the patients; where the most common pathogens where Pseudomonas aeruginosa and Enterococcus faecalis (4 patients), Staphylococcus aureus (3 patients), Stenotrophomonas maltophilia, Enterococcus faecium, Escherichia coli, and Klebsiella pneumoniae (1 patient each).

In four patients two pathogens were isolated, two had a Gram-negative bacteremia and the other two had mixed microorganism bacteremia (Gram positive and Gram-negative rods) (Figure 1).

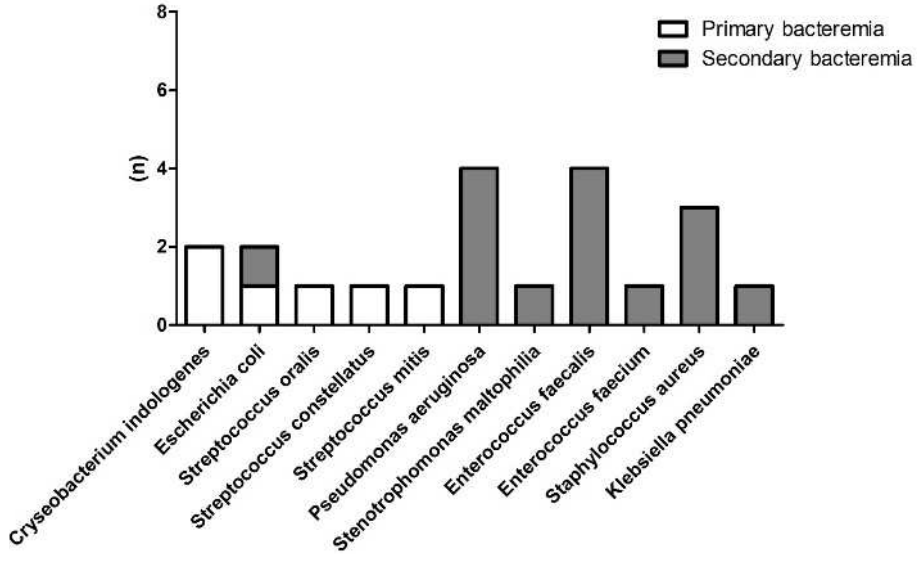

Figure 1. *Isolated microorganisms in blood cultures.*

The source of secondary bacteremia was a ventilator associated pneumonia (VAP) in 81.8% (n=9) with isolation of Enterococcus faecalis (n=3), Staphylococcus aureus (n=1), Pseudomonas aeruginosa (n=4) and Klebsiella pneumoniae (n=1); Central line-associated blood stream infection (CLABSI) in 18.1% (n=2) with isolation of Staphylococcus aureus (n=2); and urinary catheter infection (UCI) in 9% (n=1) with isolation of Enterococcus faecalis (n=1) (Figure 2).

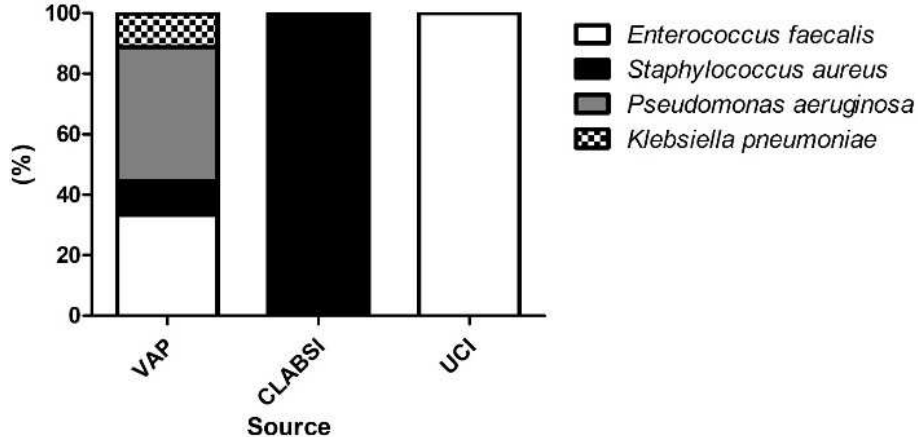

Figure 2. *Secondary bacteremias source of infection and pathogens.*

Overall, we found a median of 21 [IQR 15.5 - 31.5] days of hospitalization stay, 14 [IQR 9 - 21] days of ICU stay, with a median of 11 [IQR 6 - 19.5] days on IMV and a median of 0.14 [IQR 0.05 - 0.40] mcg/kg/min dose of norepinephrine. The patients with a positive blood culture, a median of total hospitalization stay was 23 days [IQR 15 - 31.7] compared to

20.5 days [IQR 20 - 31.5] in the patients with negative blood cultures (p=0.19). A median of 18 days [IQR 11 - 23.5] in the ICU was found in the group of positive blood cultures compared to 13.5 days [IQR 8 - 21] in the group of negative cultures. (p=0.061). The patients with a positive blood cultured had more days under IMV compared to the group of patients with negative blood cultures 15 days [IQR 8.5-19.5] vs 11 days [IQR 6-19.5] respectively (p=0.053). A median of maximum dose of norepinephrine were 0.28 mcg/kg/min [IQR 0.15-0.5] in the positive blood culture group vs. 0.11 mcg/kg/min [IQR 0.05-0.4] in the negative blood culture group (p=0.02) (Figure 3).

The mortality was reported in 13.2% (n=27) of all the patients; 14.8% (n=4) for the patients with positive blood culture and 12.7% (n=23) for the patients with negative blood cultures with an odds ratio (OR) for mortality in patients with a positive blood culture of 0.87 [IQR 0.344 – 2.21] (p=0.75) (Figure 3).

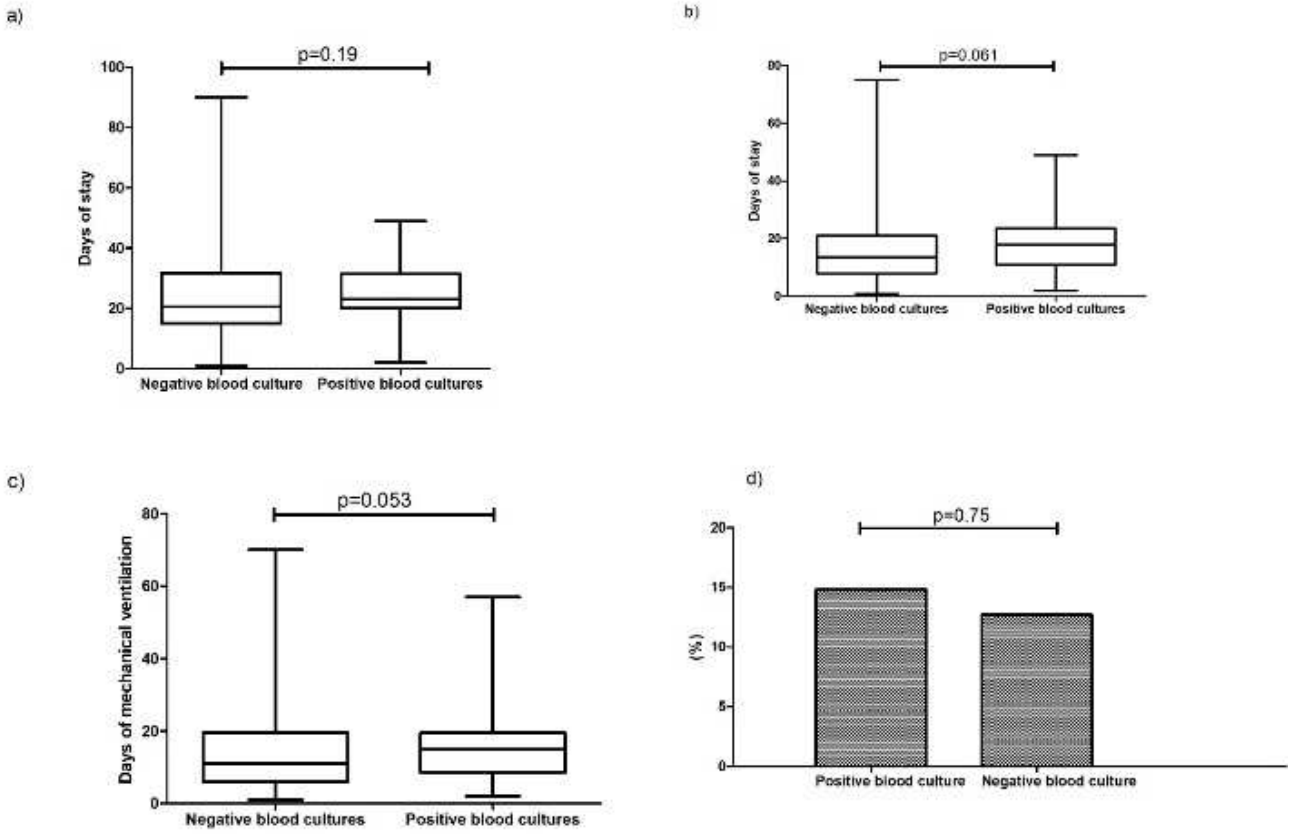

Figure 3. *Clinical outcomes in critically III COVID-19 patients with bacteremia. a) Median of hospital days of stay of patients with and without a bacteremia; b) Median of ICU days of stay of patients with and without a bacteremia; c) Median of days on IMV in patients with and without a bacteremia; d) Mortality of patients with and without a bacteremia.*

6. Discussion

We describe the clinical characteristics of COVID-19 patients hospitalized in ICU with or without a bacteremia and their clinical relevance. In the demographic data we can observe the presence of a middle age population with an elevated BMI and almost one third of them with hypertension and diabetes. The primary strength of this study is the population evaluated because there are no studies in Hispanic population with these comorbidities and in critically III COVID-19 patients that describe the pathogens and characteristics of bacteremia making an association with the hospital and ICU length of stay, days on IMV and mortality.

The presence of a positive blood culture was reported in 13.2% (n=17) of the patients, greater than other studies, like in Engsbro, et al., were the presence of blood stream infections was demonstrated in 5.3% of their critically III patients (n=12) [6]; in Yu and cols that reported the presence of a positive blood culture in 6.5% of their patients; and Martinez-Guerra and cols. [7] they observed the presence of a blood stream infections on 29.1% of their population (n=32) being a coagulase negative staphylococci the most frequent cause in 40%, followed by Enterobacter complex in 20% with a 14.3% of AmpC producers pathogens, 2.9% Extended spectrum beta lactamases and 2.9% Pseudomonas aeruginosa multidrug resistant, nevertheless this last studies does not make difference between mild, moderate or critically III patients [7, 8].

Bacteremia related to other sources was described by Sligl and colleagues where the most common source of bacteremia was an E. coli associated pneumonia in 33% [9]. However, the studies from Engsbro and Hughes the source of bacteremia was related to CLABSI [5, 6]. In our study secondary bacteremia was related to VAP in 72.7%, to CLABSI in 18.2% and, UTI 9.1% respectively. The most common pathogen isolated was P.

aeruginosa, followed by E. faecalis and S. aureus.

Giacobbe et al. observed an increased risk for CLABSI in 25% of the patients with an ICU stay greater than 15 days, and up to 50% of risk in prolonged stay (30 days) [10]. In the study by Cataldo et al. they observed an incidence of CLABSI in 49% of their population in the ICU and had a mean of ICU stay of 13 days prior the isolation [11]. In our study we reported the positivity of cultures in the first 14 days of ICU stay and an increased amount of positivity in blood samples, increasing the percentage of secondary bacteremia, but still a lower percentage in CLABSI compared to Cataldo study.

The presence of a primary bacteremia was reported in 35.3% of the patients where Chryseobacterium indologenes was the most common pathogen isolated, followed by E. coli, similar microorganisms' isolations were observed in other studies [12, 13]. Also, we observed an increased requirement of vasopressor during their stay on the ICU, with a tendency of increase ICU stay without changes in hospital length of stay or mortality (OR of 0.87) with no statistical significance (p=0.75); Similar to our findings Cataldo et al that did not reported changes in mortality with an overall ICU mortality of 32% [11]. However, it differs from Hughes that observed a relative risk for mortality of 1.5 on these patients [5].

Our study has several limitations. First, this is a single-center retrospective analysis with a relatively small sample size. Second, the follow-on time of 14 days, may generate an infra-estimation of positive cultures on patients with a prolonged length of stay. Third, several of the patients was already treated with antibiotics, prior to the ICU or hospital admission.

7. Conclusions

Critically ill patients with active SARS-CoV-2 infection and a bacteremia tend to increase the ICU length of stay, days on IMV and dosage of norepinephrine, which could end up in multiple hospital complication, such as, use of renal replacement therapy, ventilator-induced lung injury, requirement of a tracheostomy and other nosocomial infection. Nevertheless, the mortality has no change compared to patients without a bacteremia.

Disclosure Statement

The authors declare that they have no competing interests.

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