

Nosocomial infections associated to COVID-19 in the Intensive Care Unit. Clinical characteristics and outcome

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Abstract

Background: Bacterial and fungal co-infection has been reported in patients with COVID-19, but there is limited experience on these infections in critically ill patients.

Aim: To assess the characteristics and outcome of ICU-acquired infections in COVID-19 patients.

Methods: In this retrospective single-centre, case-control study, we included 140 patients with severe COVID-19 admitted to the ICU between March and May 2020. We evaluated the epidemiological, clinical and microbiological features, and outcome of ICU-acquired infections.

Results: Fifty seven patients (40.7%), developed a bacterial or fungal nosocomial infection during ICU stay. Infection occurred after a median of 9 days (IQR 5-11) of admission, and was significantly associated with the APACHE II score ($p=0.02$). There were 91 episodes of infection: primary (31%) and catheter-related (25%) bloodstream infections were the most frequent, followed by pneumonia (23%), tracheobronchitis (10%) and urinary tract infection (8%), that were produced by a wide spectrum of Gram positive (55%) and Gram negative bacteria (30%) as well as fungi (15%). In 60% of cases, infection was associated with septic shock, and a significant increase in SOFA score. Overall ICU mortality was 36% (51/140). Infection was significantly associated with death (OR 2.7, 95% CI 1.2-5.9, $p=0.015$), and a longer ICU stay ($p<0.001$).

Conclusions: Bacterial and fungal nosocomial infection is a common complication of ICU admission in patients with COVID-19. It usually presents as a severe form of infection and it is associated with a high mortality and longer course of ICU stay.

Introduction

The pandemic of SARS-CoV-2 infection at the beginning of 2020 has heavily hit most countries in the world, and one of the major challenges imposed by this infection has been the large numbers of patients in need for intensive care [1-3]. Bacterial and fungal superinfection during Intensive Care Unit (ICU) stay has been reported in other outbreaks of severe acute respiratory syndrome (SARS), but there is limited data available regarding COVID-19 patients. Many authors recognize the importance of superinfection but definitive data is still lacking [4,5]. Reported incidence varies between 3,6% to 43% [6], and no study thus far, has focused specifically on the subpopulation of ICU patients.

Moreover the role of the host response to infection by SARS-CoV-2 in COVID-19 disease has been used as a potential target for therapy, and a number of immunomodulatory treatments have been proposed throughout the outbreak. Steroid therapy, with varying doses and regimens, specific biologic drugs such as tocilizumab, and a number of other repurposed drugs such as hydroxychloroquine and azithromycin are all examples of attempts at immunomodulation to fight the devastating effects of COVID-19.

Evidence on the efficacy and on the possible side effects of these drugs is only starting to emerge now, after a widespread use of these therapies has been done during the peak of the outbreak. This specific aspect of COVID-19 therapy represents a new challenge for most physicians involved in Intensive Care Medicine (ICM). In particular there is scarce evidence regarding the possible involvement and interaction of SARS-CoV-2 and its specific therapeutic regimens in the development of hospital acquired infections.

In this study, we investigated the clinical features of bacterial and fungal infections associated with COVID-19 in ICU patients, their microbiological characteristics, their impact on the course of critical illness, and the possible relation with risk factors.

Materials And Methods

Study design and setting

We conducted a retrospective study of all patients hospitalized in the Intensive Care Units at a tertiary university hospital in the city of Madrid, with a confirmed diagnosis of COVID-19, during the months of March, April and May 2020. The study was approved by the hospital ethics committee and complies with the principles of the Helsinki Declaration, and its later amendments.

Study population

We included in the study all adult patients with a positive SARS-CoV-2 polymerase chain reaction (PCR) in nasal or respiratory tract samples, who were hospitalized in the ICU between the 1st of March and the 30th of May 2020. We excluded from the analysis patients who were transferred from other centers and already had a confirmed diagnosis of nosocomial infection at the time of transfer.

Data collection and definitions

We collected the following data from the electronic medical records: demographic characteristics, medical comorbidities, SOFA score, APACHE II score, source of infection, bacterial and fungal species, severity of systemic inflammatory response and clinical outcome. We only included in the study cases with confirmed infection, defined by the presence of a positive culture of a significant clinical sample, associated with clinical signs of infection and/or worsening organ failure. Conventional microbiological testing (tracheal aspirate, blood and urine cultures) was requested by the treating physician when infection was suspected, and was not protocolized. Cases were reviewed by an Infectious Diseases specialist and an Anesthesia specialist to determine the presence of true clinical co-infection and its source. All infections were defined according to the Centers for Disease Control and Prevention criteria [7]. If diagnosis of co-infection was made during, or within the first 48h, of COVID-19 hospital admission, these infections were defined as community-acquired. If diagnosis occurred ≥ 48 h from admission for COVID-19, these infections were defined as hospital-acquired superinfections. All patients were treated according to the institution COVID-19 protocol and all the revisions published throughout the outbreak following the appearance of new scientific evidence regarding treatment drugs. Microorganisms were

defined as multidrug resistant (MDR) if they were resistant to ≥ 1 drug in at least 3 classes of antibiotics [8]. Outcome variables were ICU mortality, and mortality at hospital discharge, which was recorded for all patients.

STATISTICAL ANALYSIS

Data are presented as median and interquartile range (IQR) for continuous variables, and categorical data are represented as numbers (%). Chi-squared tests were used for categorical variables and T-test for continuous variables. Univariate logistic regression analyses were performed using the occurrence of infection in the ICU as dependent variable and the candidate risk factors as independent variables, variables with a $p < 0,1$ were included in a multivariate model built with a stepwise removal of the less significant variable. A second logistic regression was performed using death as a response variable with the same stepwise strategy. Statistical significance was defined as a p -value ≤ 0.05 . Statistical analysis was performed with STATA (version 16.1)

Results

We analyzed the records of 140 patients who fulfilled inclusion criteria for the study. Clinical characteristics of the patients are shown in table 1 which compares patients who developed a nosocomial infection with patients who did not.

Demographic and epidemiological data

The median age was 61 years (IQR, 57-67) and the majority were male (77%). Hypertension (42%) and diabetes (20%) were the most frequent underlying diseases. Severe pneumonia was the main cause of ICU admission in most patients, which was complicated with severe acute respiratory distress syndrome (ARDS) in 83 (59%) of them. Six patients (4.3%) had a previous episode of bacterial co-infection at the time of ICU admission.

During their stay in the ICU 57 patients (40.7%) developed at least one confirmed nosocomial infection. We excluded from the study 133 cases of positive cultures (42 blood cultures, 28 urine cultures, 33 tracheal aspirates, and 28 catheter tip cultures) that were considered as contaminations.

Source of infection and microbiology

We recorded a total of 91 episodes of confirmed nosocomial infection occurring in 57 patients during ICU stay (15 patients had 2 different episodes of infection, three patients had 3, three patients had 4 and one patient had 5). The median time from ICU admission to the onset of the first nosocomial infection was 9 days (IQR 5-11).

Data regarding the clinical features and type of infection are shown in the supplementary table 1. We observed 30 episodes of lower respiratory tract infection (LRTI), of which 21 were ventilator associated pneumonia (VAP), 28 episodes of primary bloodstream infections (BSI), 24 episodes of catheter-related

bloodstream infections (CRBSI), 7 urinary tract infections (UTI) and 2 soft tissue infections. The first episode of infection in the ICU was bacteremia in 35 patients (19 primary BSI and 16 CRBSI), LRTI in 17 patients (11 VAP), and UTI in 6 cases. The median SOFA score at the diagnosis of infection was 6 (IQR 5-8). Fifty-five episodes of infection (60.4%) occurring in 38 patients were complicated by septic shock.

The microbiology of the infections is described in Table 2. The most frequent bacteria among patients with primary BSI was *Enterococcus faecium* (43%), followed by *Enterococcus faecalis* (21%) and coagulase negative negative staphylococci (CNS) (11%). Gram positive bacteria also were the most common cause of CRBSI (CNS 54%, *E. faecium* 17%, *E. faecalis* 8%), followed by *Candida albicans* (17%). Gram negative microorganisms were the most frequent cause of LRTI, being *Pseudomonas aeruginosa* the most common isolated bacteria among patients with VAP (38%) and tracheobronchitis (33%). *Staphylococcus aureus* was also frequently isolated in patients with VAP (24%) and tracheobronchitis (33%), most of whom (87%) were resistant to methicillin (7/8). *Aspergillus* spp. were isolated in 3 cases of LRTI. As in the case of BSI, *E. faecium* (44%) and *E. faecalis* (28%) were the most common cause of UTI. *Enterobacterales* and nonfermenting gram negative bacilli such as *Acinetobacter baumannii* and *Stenotrophomonas maltophilia* were occasionally isolated as a cause of bacteremia, LRTI, UTI, and soft tissue infections (Table 2). A total of 28 (31%) episodes of infection, occurring in 22 patients were sustained by MDR microorganisms and 3 episodes of infection by XDR microorganisms. The most frequent resistant microorganisms were MRSA (n=9, 29%), *Enterococcus Faecium* (n=8, 25%), *Pseudomonas Aeruginosa* (n=5, 16%) .

Risk factors for the development of infection

Table 1 describes the main risk factors potentially associated with the development of nosocomial infection among COVID-19 patients. Most patients were treated with a course of ceftriaxone following admission (n=120, 86%) and/or azithromycin (n=118, 84%). Moreover, 105 patients (75%) were given a course of another antibiotic treatment for a duration of at least 3 days. In addition, a high proportion of patients received therapy with corticosteroids (90%) and/or tocilizumab (68%) The development of infection was significantly associated with the APACHE II score at ICU admission, diabetes and the use of corticosteroids (Table 1). In the multivariate analysis (including APACHE II, diabetes and the use of steroids) only the APACHE II score was independently associated with the development of infection (Odds Ratio 1.09, 95% Confidence Interval 1.02-1.17, p=0.013).

Mortality and outcome

Fiftyone (36%) patients died in the ICU. All patients who were discharged alive from the ICU survived to hospital discharge. Table 3 presents the characteristics of patients who died compared with those who survived.

Mortality correlated significantly (p<0.05) with a higher APACHE II score, the presence of severe ARDS at ICU admission, and the development of nosocomial infection at the ICU. Among the patients who had a nosocomial infection, 38 developed septic shock (27%) during the course of their disease, which was

significantly associated with a higher mortality ($p < 0.001$). In the multivariate analysis (including all the variables significantly associated with the mortality in the univariate analysis) the presence of severe ARDS at admission (OR 4.9, 95% CI 2-12.2; $p = 0.001$), the development of a nosocomial infection (OR 2.7, 95% CI 1.2-5.9, $p = 0.015$), and the APACHE II score (OR 1.1, CI 95% 1.01-1.19; $p = 0.017$), were all significantly associated with ICU mortality.

Infection was the main cause of death in 17 (33%) of the 51 patients who died in the ICU, representing the second cause of death, after refractory respiratory failure (Table 3). ICU stay was significantly longer in patients with ICU infection ($p < 0.001$).

Discussion

We analyzed nosocomial infections acquired in the ICU in critically ill COVID-19 patients, during the main outbreak of the disease which hit Spain at the beginning of 2020. To our knowledge it is the first series to specifically characterize the epidemiology, clinical presentation and outcome of this cohort of ICU patients. We recorded a high incidence of nosocomial infections, which had a significant impact on hospital mortality, representing the main cause of death in 33% of the patients who died in the ICU.

The general characteristics of our population are similar to those described in other reports of COVID-19 in the ICU published so far [9–11]. Co-infections in COVID-19 have been described in previous studies (often within larger studies including all hospitalized COVID-19 patients), and reported incidence varies greatly, according to definition criteria, the heterogeneity of patients included and the diagnostic methods used. We observed a higher incidence of nosocomial infections compared to those reported in some recent meta-analysis [5,6,12]. However, when we compared our results with those of studies that only included COVID-19 patients hospitalized in the ICU, we observed more similar results [11,13–16]. The occurrence of a nosocomial infection was a late complication, occurring after a median of more than one week of ICU stay.

We have observed a wide spectrum of nosocomial infections typically described in ICU patients such as VAP and tracheobronchitis, CRBSI, or catheter-related UTI. However, it is noteworthy the high proportion of patients with primary BSI and CRBSI, that represented the 31% and 25% of the infections, respectively. The high incidence of CRBSI could be explained by the strain put on the ICU and the whole hospital by the COVID-19 outbreak, in fact during the peak of the COVID-19 outbreak the ICU capacity of the hospital had to be increased by 350% in order to accommodate all patients in need of critical care. This entailed a high number of relocated healthcare personnel which often had to be employed in “non conventional” temporary ICUs, such as the operating theatres. Moreover, infection control measures were strongly directed at avoiding the spread of airborne viral pathogens, and, during the peak of the pandemic, less attention could have been paid to ordinary infection control practices, and care bundles when handling IV lines or tracheal tubes [4]. The vast majority of our cohort received empiric antibiotic treatment with ceftriaxone at hospital admission, as was advocated by the early literature and guidelines [17–19]. However our data show that co-infection at presentation or during ICU early stay was rare in our cohort.

Our data show that the only factor significantly associated with the development of nosocomial infection during ICU stay is the APACHE II score at admission. Immunomodulatory therapies have been used for the treatment of COVID-19, despite not being included in most treatment guidelines to this date for lack of convincing evidence [22]. In our sample the most widely used immunomodulatory therapies were tocilizumab and glucocorticoids. Tocilizumab has been found to be associated with a significant increase in co-infections in cohorts of COVID-19 patients [23], but this finding was not confirmed in our study. The use of corticosteroids in COVID-19 is being largely investigated and is showing promising results. The cohort of patients receiving mechanical ventilation seems to be the one who benefits the most from the use of corticosteroids [24]. In our sample corticoids were the only pharmacological treatment who was associated with the development of nosocomial infection (although not statistically significant in the multivariate analysis), and their use did not show any effect on mortality. The Recovery Trial which has shown the most promising data regarding the use of glucocorticoids in COVID-19, has not published results regarding the occurrence of nosocomial infection and their association with steroid treatment [24].

There are few data in the literature regarding the microbiology of bacterial/fungal co-infection in COVID-19. Some small studies have described the occurrence of infection sustained by MDR gram negative bacteria (*Enterobacteriales*, *A. baumannii*, *P. aeruginosa*) [5,12], others have found the commonest bacteria to be *Mycoplasma pneumoniae*, *P. aeruginosa*, *H. influenzae* and *Klebsiella* spp. [6]. A recent single centre study from Barcelona reported a similar microbiological pattern to the one we observed, however this study included all hospitalized patients and did not differentiate between infections acquired in the ICU and in hospital wards [25].

It is noteworthy in our series the high incidence of BSI due to enterococci, with a remarkable predominance of *E. faecium* over *E. faecalis*, which may have been selected by the use of ceftriaxone as early antimicrobial treatment [26]. Moreover *Enterococcus* spp. is not a major pathogen involved in nosocomial infections in spanish ICUs [27]. The elevated prevalence of *Enterococcus* spp. has been highlighted by another study investigating BSI in ICU patients with COVID-19, it is noteworthy that a high percentage of that cohort of patients also received cephalosporins as empirical treatment [28]. The majority of our patients have also received courses of broad spectrum antibiotics, in several cases without a confirmed diagnosis of nosocomial infection, and despite this large antimicrobial coverage we recorded a high incidence of infections. Severe COVID-19 can easily mimic bacterial sepsis [14,29] and this has certainly led many physicians to prescribing antibiotic treatment which then has proven not to be justified. This result shows that, during the peak of the outbreak, the principles of antimicrobial stewardship were implemented less strictly, a problem which has been highlighted in the literature [20,21]. Our data do not support the use of antimicrobials in COVID-19 unless a bacterial/fungal superinfection is suspected. This is now in accordance with more recent literature and updated guidelines for the treatment of COVID-19 [5,14,22]. Our data show a high incidence of VAP, with a strong predominance of gram negative bacteria, this is in accordance with previous reports of ICU patients with COVID-19 [15].

We observed a high incidence of MDR bacteria (31%). We recorded a high number of infections by fungi, and most importantly *Aspergillus* spp. A recent study [30] has shown an extremely high incidence of infection by *Aspergillus* spp. in COVID-19 patients hospitalised in the ICU. The authors diagnosed *Aspergillus* spp. infections by a systematic screening process, and showed a significant association with patient clinical outcomes. Our results have not shown any association with clinical outcomes of *Aspergillus* SPP infection, however our sample may be too small, and no systematic screening for this specific infection was in place during the study period. The overall mortality in our study was 36%, which is similar to the largest series of ICU patients published thus far [9-11]. APACHE II score and severity of ARDS were strongly associated with mortality, which is in line with what previous studies have shown in COVID-19 [10]. In our study, the development of a nosocomial infection during ICU stay was independently associated with mortality and it is noteworthy that septic shock was the main cause of the death in a third of the patients who died (17 of 51 cases). Few studies thus far have published data regarding the causes of death in the ICU, therefore it is hard to compare these results with the literature.

Study limitations

We should acknowledge some limitations to this study. The sample size was small and the retrospective design reduces control over multiple confounders and data collection. We only included infections that were documented by culture and, therefore, some episodes may be missing. Finally, this study was limited to a single institution, with its own local epidemiology on antimicrobial resistance, which may limit the generalisability of the findings.

Conclusions

The role of COVID19 in favouring bacterial superinfection is still a matter of debate. Our data show that patients who require ICU and advanced organ support tend to develop superinfection frequently and are at a significantly increased risk of death. Infection appears after more than one week of ICU stay and significantly prolongs the duration of ICU hospitalization. Bloodstream infections are a common occurrence and are frequently sustained by enterococci. In this context, measures aiming at reducing bacterial infection are fundamental in order to provide appropriate critical care, and the implementation of antimicrobial stewardship programmes are of paramount importance.

Declarations

Conflict of interest: the authors have no conflict of interest to declare

Funding: this work did not receive funding

Data availability: the data of this study are available by contacting the corresponding author upon reasonable request.

Ethics approval: this study was approved by the hospital ethics committee

Authors contributions: Tommaso Bardi and Vicente Pintando ideated the study analyzed the data and wrote the manuscript. Maria Gomez-Rojo, Rosa Escudero-Sanchez, Amal Azzam Lopez, Yolanda Diez-Remesal, Nilda Martinez Castro, Patricia Ruiz-Garbajosa, David Pestaña collected the data and reviewed the manuscript.

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Tables

Table 1: Clinical characteristics of the study population and comparison between infected and non-infected patients.

	PATIENTS (N = 140)	NOSOCOMIAL INFECTION DURING ICU (N=57)	NO INFECTION DURING ICU (N=83)	p-value
Age - yr (IQR)	61 (57 - 67)	63 (60-68)	61 (54- 66)	0.03
sex - male	108 (77%)	47 (82%)	61 (73%)	0.21
BMI (IQR)	30.4 (26-32)	30.7 (26-32)	30 (26-31)	0.56
APACHE II (IQR)	14 (10 - 17)	15 (12-19)	13 (9-16)	0.02
Comorbidities				
Hypertension	60 (42%)	26 (45%)	38 (46%)	0.9
Chronic ischemic heart disease	20 (14%)	11 (19%)	9 (11%)	0.16
Chronic kidney disease	8 (6%)	5 (9%)	3 (4%)	0.2
COPD	10 (7%)	7 (12%)	6 (7%)	0.31
Diabetes	28 (20%)	16 (28%)	12 (14%)	0.048
PaO2/FIO2 ratio on first day of MV (IQR)	124 (69 -156)	115 (60-143)	134 (71-210)	0.35
Time from hospital to ICU admission - days (IQR)	4 (1-6)	4 (1-4)	4 (1-6)	0.8
ICU length of hospitalization - days (IQR)	14 (8-17)	20 (11-24)	11 (7-15)	<0.001
Severe ARDS at ICU admission	83 (59%)	39 (68%)	44 (53%)	0.068
Ceftriaxone	120 (85%)	53 (92%)	67 (80%)	0.042
Azithromycin	118 (84%)	53 (92%)	65 (76%)	0.019
Other antibiotics	105 (75%)	47 (82%)	58 (60%)	0.091
Steroids	127 (90%)	56 (98%)	71 (85%)	0.01
Tocilizumab	96 (68%)	40 (70%)	56 (67%)	0.73
Mortality and causes of death				
ICU mortality	51 (36%)	31 (54%)	20 (24%)	<0.001
Refractory Respiratory Failure	19 (37%)	9 (29%)	10 (50%)	0.52
Septic Shock	17 (33%)	17 (55%)	0	<0.001
Multi Organ Failure	7 (14%)	1 (14%)	6 (86%)	0.14
Cardiac arrest	6 (12%)	3 (10%)	3 (15%)	0.63
Other causes	2 (4%)	1 (3%)	1 (5%)	0.78

Data are presented as number and %, unless otherwise indicated.

IQR, interquartile range; COPD, chronic obstructive pulmonary disease; ARDS, acute respiratory distress syndrome; ICU, intensive care unit.

Table 2: Microbiological isolates by type of infection.

BACTERIAL/FUNGAL CO-INFECTIONS	N=91
PRIMARY BLOODSTREAM INFECTION	N= 28 (31%)
<i>Enterococcus faecium</i>	12 (43%)
<i>Enterococcus faecalis</i>	6 (21%)
Coagulase-negative staphylococci	3 (11%)
<i>Pseudomonas aeruginosa</i>	2 (7%)
<i>Staphylococcus aureus</i> (methicillin-resistant)	1 (3,5%)
<i>Klebsiella oxytoca</i>	1 (3,5%)
<i>Serratia marcescens</i>	1 (3,5%)
<i>Bacteroides spp.</i>	1 (3,5%)
<i>Candida glabrata</i>	1 (3,5%)
CATHETER RELATED BLOODSTREAM INFECTION	N=24 (25%)
Coagulase-negative staphylococci	13 (54%)
<i>Enterococcus faecium</i>	4 (17%)
<i>Candida albicans</i>	4 (17%)
<i>Enterococcus faecalis</i>	2 (8%)
<i>Staphylococcus aureus</i> (Methicillin Resistant)	1 (4%)
VENTILATOR ASSOCIATED PNEUMONIA	N=21 (23%)
<i>Pseudomonas aeruginosa</i>	8 (38%)
<i>Staphylococcus aureus</i> (methicillin-resistant)	5 (24%)
<i>Aspergillus fumigatus</i>	2 (9%)
<i>Stenotrophomonas maltophilia</i>	2 (9%)
<i>Acinetobacter baumannii</i>	1 (5%)
<i>Aspergillus terreus</i>	1 (5%)
<i>Enterobacter cloacae</i>	1 (5%)
<i>Hafnia alvei</i>	1 (5%)
HOSPITAL ACQUIRED PNEUMONIA/TRACHEOBRONQUITIS	N=9 (10%)
<i>Pseudomonas aeruginosa</i>	3 (33%)
<i>Staphylococcus aureus</i> (methicillin-resistant)	2 (21%)
<i>Aspergillus fumigatus</i>	1 (9%)
<i>Haemophilus Influenzae</i>	1 (9%)
<i>Staphylococcus aureus</i> (methicillin-susceptible)	1 (9%)
<i>Stenotrophomonas maltophilia</i>	1 (9%)
URINARY TRACT INFECTION	N=7 (8%)
<i>Enterococcus faecalis</i>	3 (44%)
<i>Enterococcus faecium</i>	2 (28%)
<i>Pseudomonas aeruginosa</i>	1 (14%)
<i>Acinetobacter baumannii</i>	1 (14%)
SOFT TISSUE INFECTION	N=2 (2%)
<i>Klebsiella pneumoniae</i>	1 (50%)
<i>Enterobacter cloacae</i>	1 (50%)

Table 3: Clinical characteristics and comparison between survivors and non survivors

	PATIENTS (N = 140)	NON SURVIVORS (N = 51)	SURVIVORS (N = 89)	p-value
Age - yr (IQR)	61 (57 - 67)	64 (58-70)	60 (55-65)	0.006
sex - male	108 (77%)	41 (80%)	67 (75%)	0.48
BMI (IQR)	30.4 (26-32)	29.8 (26-32)	30.7 (26-32)	0.52
APACHE II (IQR)	14 (10 - 17)	15.9 (13-19)	12.9 (9-16)	0.001
Hypertension	60 (42%)	25 (49%)	39 (43%)	0.9
Chronic ischemic heart disease	20 (14%)	9 (17%)	11 (12%)	0.39
COPD	10 (7%)	5 (10%)	8 (9%)	0.9
Diabetes	28 (20%)	9 (17%)	19 (21%)	0.59
ICU length of hospitalization - median (IQR) days	14 (8-17)	18 (11-21)	13 (7-16)	<0.001
Severe ARDS at ICU admission	83 (59%)	40 (78%)	43 (48%)	< 0.001
Steroids	127 (90%)	49 (95%)	78 (87%)	0.09
Tocilizumab	96 (68%)	38 (74%)	58 (65%)	0.25
Nosocomial infection in the ICU	57 (40.7%)	31 (60%)	26 (29%)	< 0.001
Septic shock	38 (27%)	23 (45%)	15 (17%)	< 0.001

Data are presented as number and %, unless otherwise indicated. IQR = Interquartile range, COPD = Chronic Obstructive Pulmonary Disease, ARDS = acute respiratory distress syndrome, ICU = intensive care unit, MDR = Multi-drug resistant