Ann Ig 2023 Jan-Feb; 35(1): 49-60 doi: 10.7416/ai.2022.2515. Epub 2022 Feb 24.

Co-infections among COVID-19 adult patients admitted to intensive care units: results from a retrospective study

V. Damico[1], L. Murano[2], V. Margosio[1], C. Ripamonti[1]

Key words: Infection, Healthcare Associated Infections, HAI, Intensive Care, ICU, COVID-19, SARS-CoV-2, Surveillance
Parole chiave: Infezioni, Terapia Intensiva, COVID-19, SARS-CoV-2, Sorveglianza

Abstract

Background. *Co-infection rates increase in patients admitted to the Intensive Care Units. The aim of this study was to examine the Healthcare Associated Infections in critically ill adult patients infected with SARS-CoV-2.*
Methods. *A retrospective observational study in adults with confirmed SARS-CoV-2 infection requiring intensive care unit admission was performed. From February 2020 to September 2021, healthcare records from a total of 118 patients were evaluated.*
Results. *In the study period, 39 patients were diagnosed with at least 1 Healthcare Associated Infection (33.1%). The co-infection/co-colonisation rate >48 hours after admission was 29.0 per 1,000 person/ days (95% CI 19.1–33.9). A total of 94 isolates were identified, the most common being Klebsiella spp, Clostridium difficile, Acinetobacter baumanii and Enterococcus spp. Associated outcomes for Healthcare Associated Infections have been identified: age >64 years (p= .003), length of Intensive Care Unit stay> 7 days (p= .002), Type 2 Diabetes mellitus (p= .019), cardiovascular disease (p= .021), inserted central venous catheter (p= .014), intubation (p< .001), APACHE II score >25 (p< .001), mechanical ventilation >48 hours (p= .003), and inserted urinary catheter (p= .002). The overall fatality rate of patients included in the study was 41.5% (n= 49), and it was found to be significantly higher in patients who acquired a Healthcare Associated Infection (n=26/39, 66.7%) compared to those who did not acquire it (n= 23/79, 29.1%) (OR= 4.87; 95% CI = 2.14-11.10; p< .001).*
Conclusions. *Our study showed high rates of Healthcare Associated Infections in critically ill adults with COVID-19. Associated factors for Healthcare Associated Infections acquisition and fatality in Intensive Care Units patients were identified as a good reason for a revision of existing infection control policies.*

[1] *Local Health and Social Authority, Province of Lecco, Italy*
[2] *Sanitary Assistance Residency "Madonna della Neve" Onlus, Premana, LC, Italy*

Annali di Igiene : Medicina Preventiva e di Comunità (Ann Ig)
ISSN 1120-9135 https://www.annali-igiene.it

Introduction

Since December 2019, when the first case of human transmission of the severe acute respiratory syndrome due to Coronavirus 2 (SARS-CoV-2) was reported in Wuhan (China), more than a hundred million confirmed cases of Coronavirus disease 2019 (COVID-19) have been described worldwide (1).

The clinical spectrum of SARS-CoV-2 infection ranges from asymptomatic to severe disease requiring hospitalization and admission to the Intensive Care Unit (ICU) (1). Confirmation of acute infection is reliant on a positive SARS-CoV-2 polymerase chain reaction (PCR) test result. The immune response to SARS-CoV2 infection includes a rise in IL-6 and C-reactive protein (CRP), with higher levels associated with more severe disease (2, 3).

The symptoms associated with the SARS-CoV-2 infection are relatively non-specific. Fever and lower respiratory tract symptoms, such as a cough or breathlessness, and radiological changes consistent with pneumonia are evident in up to 97 % of these patients (4) but are common with pneumonia patients who require hospital care. Several multicenter studies showed that 5–32% of hospitalized patients with COVID-19 need ICU admission (4-6). In a recent Italian study (6), the patients infected with SARS-CoV-2 admitted to ICUs were represented mostly by males (82%) and older individuals. The median age of the patients admitted to the ICUs is 63 years, which is the same as the median age of all the positive Italian cases with COVID-19, suggesting that, to date, older age alone is not a risk factor for admission to the ICUs. In this cohort of patients, 68% had at least 1 comorbidity. Hypertension was the most common comorbidity, followed by cardiovascular disorders, hypercholesterolemia, and diabetes (6).

According to the available published data, the death-to-case rate of critically ill COVID-19 patients ranges from 16 to 78% (5, 7-8). In a recent study (8), the fatality rate was higher in patients older, immunocompromised, extremely obese, diabetic, and those with a shorter delay between first symptoms and ICU admission, and those with extra-pulmonary organ dysfunction at ICU admission.

Data regarding secondary respiratory infections in the severe disease caused by the SARS-CoV-2 are still limited, in spite of the still ongoing spread of the disease worldwide. However, some reports showed that secondary infections significantly decreased survival of COVID-19 patients, particularly when they were admitted to the ICUs (9). In the studies of Huang and Zhou et al. (2, 5) secondary infection was reported in 50% of non-survivors and only in 1% of COVID-19 survivors. In another study, Zhang et al (10) reported that in 221 COVID-19 patients in Wuhan, those with severe illness were 14.2, 18.2 and 2.9 times more likely to have co-infections with bacteria, fungi and other viruses, respectively, than those not severely ill. Furthermore, deaths associated with co-infections by bacteria, fungi and other viruses occurred in 55.6, 44.4 and 44.4%, respectively, of patients in the ICUs, and in 26.1, 13.0 and 8.7%, respectively, of patients transferred from ICU to the general wards (10).

A recent review of the literature showed that the incidence of co-infections (i.e., infections detected at admission) in patients with COVID-19 is lower than in previous pandemics (9). However, co-infection rates increase in patients admitted to the ICUs. Super-infections by antibiotic-resistant bacteria occur in 1.3% of patients in ICU and 0% in non-ICU care (9). Currently, data on secondary infections (i.e., infections acquired during the course of ICU stay) in COVID-19 patients are scarce.

In the hypothesis that the 2020 outbreak has increased mortality also because of associated co-infections, the aim of this study was to examine the Healthcare Associated Infections (HAIs) in critically ill adult patients infected with SARS-CoV-2. The secondary goal was to investigate associated outcomes and predictors of fatality in patients who acquired a HAI during ICU stay.

Methods

Design and Setting

A retrospective observational study of co-infection in adults with confirmed COVID-19 requiring ICU admission was performed. The study was conducted in an Italian adult ICU in a 850 bed second line hospital. Common conditions that were treated within the ICU included acute respiratory distress syndrome (ARDS), post-operative surgical, trauma, multiple organ failure and sepsis. During the COVID-19 outbreak, the ICU (grown from 24 to 48 beds) was staffed with dedicated full-time intensivists (registered nurses and medical doctors) trained in adult multidisciplinary medicine; 56 registered nurses and 20 medical anesthesiologist doctors working full-time in the department (11 registered nurses on each shift, 5 medical doctors morning-afternoon and 3 medical doctors on night shift). The study protocol was in line with the Declaration of Helsinki, as revised in 2013 and was approved by the Institutional Review Board (IRB) of the "Azienda Socio-Sanitaria Territoriale" (Local Social & Health Assistance Authority) of Lecco. In addition, data were collected anonymously and the authorization to access the data was given by the director and the manager of the ICU involved in the study.

Selection of participants

Case inclusion criteria were adults aged > 18 years with completed ICU admissions (discharged from or died whilst in ICU) for COVID-19. From February 2020 to September 2021, healthcare records from a total of 118 admitted patients were evaluated. SARS-CoV-2 infection was confirmed using reverse transcriptase-polymerase chain reaction (RT-PCR) from a respiratory specimen. Exclusion criteria were defined as SARS-CoV-2 infection diagnosed >48 h after hospital admission and patients transferred into the ICU from a different hospital. Only the first admission to ICU was included. In addition, exclusion criteria were length of stay <48 hours (n = 4) and incomplete patient record data (n = 12).

Data collection

Data were obtained from the electronic medical records (Margherita 3 2010 form) stored in the ICU. Basic demographic and clinical characteristics (gender, age, diagnosis, comorbidities, associated outcomes, and antimicrobial use within 48 hours upon admission) were collected and extracted from patient medical records, including onset of HAIs, clinical course, and outcome.

Data analysis

Basic epidemiologic indicators (incidence and case-fatality rate) were calculated. The Statistical Package for Social Sciences (SPSS) software version 21 (IBM Corp Released 2015. IBM SPSS Statistics, Version 23.0. Armonk, NY: IBM Corp.) was used for analysis of patient data. For normally distributed data, mean and SD were applied, while median and interquartile range were used for data that did not exhibit normal distribution. Kolmogorov-Smirnov test was used for data normality assessed. The crude incidence rate per 1,000 patient/day of ICU

stay and relative 95% CIs were calculated. The incidence rate was measured for 1,000 days and expressed in patient/day. The incidence rate (Fine and Gray method) was calculated as the ratio between number of patients developing HAI (numerator) and total time experienced by population at risk (denominator). All the infectious episodes, including multiple infectious episodes for each patient, were considered. The analysis time scale was the time since ICU admission until the date of ICU discharge. Time at risk was from ICU admission to HAIs appearance, fatality, or discharge from ICU. Fine and Gray competing risk regression models were used to assess independent risk factors for HAIs. Univariate and multivariate logistic regression analysis was used for investigation of possible associated outcomes and predictors of HAI acquisition, and also for evaluation of possible risk factors and predictors of death in patients who acquired a HAI. In both instances, a confidence interval (CI) of 95% and a significance of $p < .05$ were used. A stepwise regression for retaining the predictors in the model was used.

Results

Socio-demographic presentation of the analyzed sample

A total of 118 patients were included in the study; 69 (58.5%) of them were male and 49 (41.5%) female. The mean age was 61.7 years (SD = 15.4). The median time from onset of symptoms to admission was 7 days (Inter Quartile Range: 4–10). The median time from hospital admission to ICU admission was 1 day (Inter Quartile Range: 0–1). The overall median length of stay (LOS) in ICU was 15 days (Inter Quartile Range: 4–23); 16 days (Inter Quartile Range: 2–22) for survivors and 14 days (Inter Quartile Range: 3–21) for non-survivors.

Main diagnoses for admission were ARDS (79.7%), surgical and trauma (16.1% and 4.2% respectively). Other patients' characteristics are shown in Table 1.

Incidence and nature of HAI in critically ill patients infected with SARS-CoV-2

In the study period, 39 patients were diagnosed with at least 1 HAI. An incidence rate of 33.1% was observed. The co-infection/co-colonisation rate >48 hours after admission was 29.0/1,000 person-day (95% CI 19.1–33.9).

A total of 68 episodes of HAI were recorded. The principal HAIs were urinary tract infection (UTI) (25/68 episodes, 36.8%), bloodstream infections (14/68 episodes, 20.6%), healthcare-associated *C. difficile* infection (13/68 episodes, 19.1%), and pneumonia (non-COVID-19 viral pneumonia) (9/68 episodes, 13.2%). Skin infection (4/68 episodes, 5.9%), device associated (2/68 episodes, 2.9%) and central nervous system infection (1/68 episodes, 1.5%) were the remaining types of HAIs. More than 1 distinct HAI was identified in 18 patients (46.1%).

A total of 94 isolates were identified, the most common being *Klebsiella* (ESBL), *Clostridium difficile, Acinetobacter baumanii* and *Enterococcus* spp (Table 2). Polymicrobial infections accounted for 22.3% of all HAIs. Antimicrobial resistance rates were investigated for all pathogens and stratified for the 2 most frequent isolates. Resistance rates <20% were only seen for tigecycline (14.9%), colistin (11.7%), and linezolid (1.0%). Resistance rates exceeded 50% for all other antimicrobials and antimicrobial groups. High rates of Multi-drug resistant (MDR) *Klebsiella* (n= 13, 86.7%) and *Pseudomonas aeruginosa* (n= 8, 80.0%) were identified. 69.2% of *Enterococcu*s spp isolates (n=9) were MDR.

Table 1 - Characteristics of patients with COVID-19 admitted to the ICU

Characteristics (n= 118)	Total	%	HAI (n= 39)	No HAI (n=79)
Diagnosis				
ARDS	94	79.7	28	66
Surgical	19	16.1	8	11
Trauma	5	4.2	3	2
Invasive procedures				
Urinary catheter	116	98.3	38	78
Intubation	113	95.7	23	90
Mechanical ventilation	111	94.1	19	92
Nasogastric tube	99	83.9	22	77
Presence of CVC	97	82.2	5	92
AB use 48 h upon admission	113	95.8	38	75
Penicillinis	20	16.9	10	10
Cephalosporins	83	70.3	27	56
Aminoglycosides	5	4.2	2	3
Carbapenems	21	17.8	6	15
Metronidazole	17	14.4	5	12
Vancomycin	58	49.1	28	30
Comorbidities				
Immunosuppression	19	16.1	5	14
Cardiovascular disease	64	54.2	24	40
Type 2 Diabetes mellitus	38	32.2	16	22
Urinary tract pathology	13	11.0	5	8
Respiratory disease	11	9.3	5	6

ARDS= acute respiratory distress syndrome; CVC,=central venous catheter; HAI=Healthcare-associated infection, AB,=antibiotic.

The risk curves of contracting a co-infection during the ICU stay were reported (Figure 1). The risk of HAI reached 80% after 10 days of ICU stay. The risk reached 97% if the patient remained in ICU for at least 20 days. The curves were interrupted at 20 days of ICU stay, as the subsequent estimates, based on the few patients staying longer than 20 days, would have been unstable. The dotted lines outlined the 95% confidence interval of the estimates. The calculated statistics excluded ward readmissions.

Associated outcomes for co-infection in critically ill patients infected with SARS-CoV-2

In the univariate regression model, the following associated outcomes for infection acquisition have been identified: age> 64 years (OR = 1.0; 95% CI = 0.49-1.08; p= .003), length of ICU stay> 7 days (OR = 2.6; 95% CI = 1.19-3.54; p= .002), Type 2 Diabetes mellitus (OR = 1.8; 95% CI = 1.07-2.29; p= .019), cardiovascular disease (OR = 1.4; 95% CI = 1.05-2.29; p= .021), inserted central venous catheter (OR = 4.9; 95% CI = 1.56-11.52; p= .014), intubation (OR = 2.4; 95% CI = 1.26-3.12; p< .001), APACHE II score> 25 (OR = 2.5; 95% CI = 1.31-3.28; p< .001), mechanical ventilation> 48 hours (OR = 4.2; 95% CI = 1.49-11.51; p= .003) and inserted urinary catheter (OR = 2.5; 95% CI = 1.26-3.28; p< .001) (Table 3). In the multivariate regression model, 4 predictors for HAI acquisition were identified: length of ICU stay> 7 days (OR = 2.4; 95% CI =

Table 2 - Etiology of HAIs in COVID-19 patients in the ICU

Isolate (n= 94)	n	%
Klebsiella (ESBL)	15	15.9
Clostridium difficile	14	14.9
Acinetobacter baumanii	13	13.8
Enterococcus spp	13	13.8
Pseudomonas aeruginosa	10	10.6
Candida spp	10	10.6
Proteus mirabilis	5	5.3
Staphilococcus. coagulasi negativo	4	4.3
Staphylococcus aureus	2	2.1
Stenotrophomonas	2	2.1
Haemophilus influentiae	1	1.1
Stenotrophomonas maltophila	1	1.1
Staphylococcus haemolyticus	1	1.1
Escherichia coli	1	1.1
Enterobacter cloacae	1	1.1
Staphylococcus epidermidis	1	1.1
Total	94	100

1.18-3.14; p= .004), intubation (OR = 3.9; 95% CI = 1.36-11.08; p= .011), mechanical ventilation> 48 hours (OR = 2.8; 95% CI = 1.01-8.21; p= .03) and inserted urinary catheter (OR = 2.2; 95% CI = 1.38-3.41; p= .002).

Case-fatality rate among patients who acquired co-infections during ICU stay

The case-fatality rate of patients included in the study was 41.5% (n= 49), and it was found to be significantly higher in patients who had acquired a HAI (n=26/39, 66.7%) compared to those who hadn't (n= 23/79, 29.1%) (OR= 4.87; 95%CI = 2.14-11.10; p< .001). In addition, a logistic regression model was used to investigate which factors could contribute to an increased risk of fatality among patients who caught HAI during ICU stay (Table 4).

In the univariate analysis, the following associated outcomes for fatality have been identified: increased age (OR = 1.0; 95%CI = 0.52-1.11; p= .032), Type II Diabetes mellitus (OR = 6.42; 95%CI = 1.18-34.86; p= .021), length of ICU stay> 7 days (OR = 8.80; 95%CI = 1.88-41.21; p= .003), mechanical ventilation> 48 hours (OR = 6.42; 95%CI = 1.40-29.47; p< .001), and APACHE II score> 25 (OR = 4.90; 95%CI = 1.13-21.16; p= .027). When the multivariate regression analysis was performed, Type II Diabetes mellitus (OR = 2.43; 95%CI = 1.01-6.29; p= .032) and length of ICU stay> 7 days (OR =

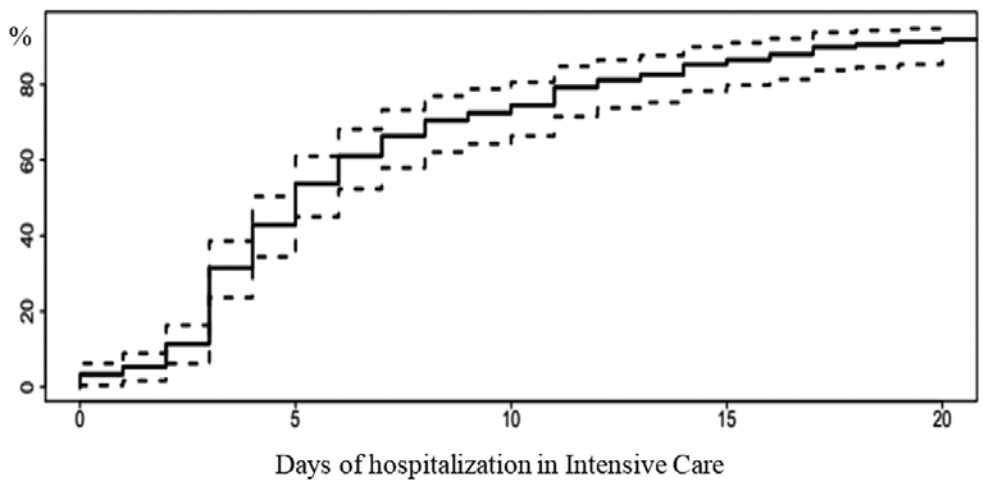

Figure 1 - Risk of acquiring a co-infection in the critically ill adults with CoVD-19

Table 3 - Risk of acquiring a co-infection during ICU stay. Results of univariate and multivariate regression.

Outcomes	Univariate regression			Multivariate regression		
	OR	CI 95%	p	OR	CI 95%	p
Gender (male)	0.7	0.51-1.29	.459			
Age (years)	1.0	0.49-1.08	.003			
Antibiotic use (48h prior to admission)	1.5	0.37-5.32	.713			
Length of ICU stay> 7 days						
Sepsis	2.6	1.19-3.54	.002	2.4	1.18-3.14	.004
Immunosuppression	1.0	0.50-2.95	.972			
Type 2 Diabetes mellitus	0.8	0.38-1.56	.329			
Cardiovascular Disease	1.8	1.07-2.29	1.05- .019			
Inserted CVC	1.4	2.29	.021			
Intubation	4.9	1.56-11.52	1.26- .014			
APACHE II score > 25	2.5	3.12	.001	3.9	1.36-11.08	.011
Mechanical ventilation (>48h)	2.5	1.31-3.28	.001			
Inserted urinary catheter	4.2	1.49-11.51	1.26- .003	2.8	1.01-8.21	.003
Inserted nasogastric tube	2.5	3.28	<.001	2.2	1.38-3.41	.002
	0.9	0.37-3.14	.234			

Bold values are statistically significant p< .05.
CVC= central venous catheter; OR= odds ratio; APACHE II= Acute Physiology and Chronic Health Evaluation II, it is applied within 24 hours of admission of a patient to the ICU

Table 4 - Univariate and multivariate analysis of factors that contribute to co- infections fatality.

Risk Factors	Univariate regression					Multivariate regression		
	Deceased (n=26)	Survived (n=13)	OR	CI 95%	p	OR	CI 95%	p
Gender (male)	12	9	0.38	0.09-1.56	.173			
Age (years)	69.6	64.2	1.0	0.52-1.11	.032			
Intubation	15	8	0.85	0.22-3.33	.817			
MDR infection	18	9	1.0	0.24-4.23	1.00			
>1 infection	8	5	0.71	0.18-2.87	.631			
Type II Diabetes mellitus	14	2	6.42	1.18-34.86	.021	2.43	1.01-6.29	.032
Cardiovascular Disease	17	7	1.62	0.42-6.29	.485			
Urinary Catheter	26	12	1.08	0.93-1.27	.151			
Inserted CVC	3	2	0.72	0.10-4.93	.734			
Length of ICU stay >7 days	22	5	8.80	1.88-41.21	.003	8.1	3.54-18.37	<.001
Mechanical ventilation (>48h)	22	6	6.42	1.40-29.47	.011			
APACHE II score >25	21	6	4.90	1.13-21.16	.027			

Bold values are statistically significant p< .05.
CVC= central venous catheter; MDR= multidrug-resistant; OR= odds ratio; APACHE II= Acute Physiology And Chronic Health Evaluation II, it is applied within 24 hours of admission of a patient to an ICU.

8.1; 95%CI = 3.54-18.37; p< .001) were isolated as predictors of increased fatality in patients who caught a HAI (Table 4). Neither infections with MDR pathogens nor additional infections were isolated as associated outcomes or predictors for increased fatality.

Discussion and Conclusions

The primary aim of our study was to obtain a deeper insight into the epidemiology of HAIs in COVID-19 ICUs and determine what could contribute to both acquisition and increased fatality in patients who suffered from a COVID-19.

As one of the rare studies looking at incidence rates and profiles of HAIs in critically ill adult patients infected wih SARS-CoV-2, the rate of 33.1% was in agreement with isolated European studies from Serbia (32.7%) (11), Slovenia (35.7%) (12), and Poland (27.6%) (13) but still much higher than the overall European rates of 19.4% (14).

In a recent retrospective cohort study of adults with COVID-19 admitted to seven ICUs in England up to 18 May 2020, bacterial co-infections/co-colonization were identified within 48h of admission in 14 (5.5%) patients (15). The co-infection/co-colonization rate >48h after admission was 27/1,000 person/days. This result was similar to our data (28/1,000 person/day).

Our findings show that the proportion of pathogens detected increase with duration of ICU stay and consist largely of Gram-positive bacteria, particularly *Clostridium difficile* or *Enterococcus* spp and Gram-negative bacteria, particularly *Klebsiella pneumoniae* or *Acinetobacter baumanii*. This result is in line with Baskaran et al study (15), though they observed that the proportion of pathogens consisted largely of Gram-negative bacteria, particularly *Klebsiella pneumoniae* and *Escherichia coli* in critically ill patients with COVID-19 (15).

During the 2020 outbreak, until 88% of patients infected with SARS-CoV-2 were treated with broad-spectrum antibiotics, including third-generation cephalosporins, quinolones, carbapenems (9). The choice of empiric regimens should take into account possible side effects (e.g. QT prolongation, diarrhea), local epidemiology of drug resistance, and impact of drug resistance on the patient. In some countries, bacteria are resistant to at least one antibiotic class, therefore empiric broad-spectrum therapy could have limited effect, particularly in HAIs. In case of sepsis, inadequate antibiotic therapy may increase fatality (9).

Most significant associated outcomes for HAI acquisition in our study referred to procedures occuring during the hospital use of urinary catheters, CVCs, and nasogastric tubes, and are consistent with findings from other studies (11, 12, 16-18). Similarly to urinary tract infections (UTIs), the indication for use of invasive devices and stricter control of Safe Operating Procedures (SOPs) for their placement and maintenance should be re-evaluated. However, given that practically all invasive devices have been associated with an increased risk of HAI acquisition, SOPs about invasive devices in general must be revised (16).

When it came to associated outcomes for increased fatality in patients who acquired a HAI, Type II Diabetes mellitus (OR = 2.43; p= .032) and length of ICU stay > 7 days (OR = 8.1; p < .001) were identified as significant. Surprisingly, mechanical ventilation, which is often identified as an associated outcome for HAI fatality (19), was not identified together with intubation as a predictor in the multivariate analysis. However, ventilator-associated pneumonia infection (VAP) remains a high significant

cause of morbidity and fatality in critically ill cancer patients. In fact, neutropenia is an important risk factor for infection in cancer patients. Respiratory agents remain the leading cause of infection in cancer patients and in immunocompromised patients admitted to the ICU, with a severe impact on patient survival (20).

Another interesting finding was the absence of MDR pathogens among risk factors for HAI fatality in critically ill adults with COVID-19, since many studies have identified MDRs and extensively drug-resistant (XDR) strains to cause more severe infections with higher case-fatality rates (20), while incurring higher hospital costs.

Despite multiple reports of fatality rates exceeding 50% among critically ill adults with COVID-19, particularly among those requiring mechanical ventilation, our early experience indicates that many patients survive their critical illness (21). Our study demonstrates an important reduction in fatality of patients with severe COVID-19 who required ICU admission in comparison to previous observational reports and emphasizes the importance of standard of care measures in the management of COVID-19 (21, 22).

Our study does not support the previously reported overwhelmingly poor outcomes of mechanically ventilated patients with COVID-19 induced respiratory failure and ARDS (21, 22). In fact, it is reassuring that the application of well-established ARDS and mechanical ventilation strategies can be associated with fatality and outcomes comparable to non-COVID-19 induced sepsis or ARDS.

The initial Surviving Sepsis Campaign guidelines for the management of critically ill patients with COVID-19 suggested an empiric antibacterial agent in all mechanically ventilated patients (16). However, subsequent data have shown that, at ICU admission, patients infected with SARS-CoV-2 seldom have concomitant bacterial infection. For this reason, and because of the high incidence of infectious complications caused by MDR germs, most experts agree that prophylactic administration of an empiric antibiotic therapy in the absence of clear signs of a co-infection or of a secondary infection should be discouraged. Indeed, it has been demonstrated that inappropriate initial antimicrobial treatment is associated with increased fatality in VAP and with increased bacterial resistance (23).

Robust evidence exists nationally and internationally that links nurse staffing to patient outcomes (24). Recent meta-analyses have found that there was a 3-12% reduction in adverse outcomes and a 16% reduction in the risk of fatality in surgical patients with superior registered nurse staffing. Evidence confirms that improvements in nurse staffing is a cost-effective investment for the healthcare system but this is not fully appreciated by health policy advisors (24). We emphasize that there is a growing body of evidence that links registered nurse staffing and physicians to better patient outcomes. We suggest studying the correlation between the shortage of HCWs and the spread of HAIs during the COVID-19 outbreak.

Limitation

This study provides novel data on both community-acquired and nosocomial co-infection/co-colonization in patients infected by SARS-CoV-2 requiring ICU care.

A key limitation of the study is its retrospective observational design, subject specifically to case selection, ascertainment and sampling biases. Inclusion of consecutive eligible patients was not feasible due to pandemic workload constraints. Furthermore, apart from goodness-of-fit, we have not reported the analysis of residuals for the regression models.

A second key limitation is that reliance on culture-dependent techniques may have falsely decreased co-infection rates.

No data regarding the shortage of nurses and physicians was collected and no correlation between the shortage of Healthcare Workers and the spread of HAIs has been studied. In addition, no residual analysis was performed.

Conclusions

HAIs, frequently caused by MDR bacteria, are common in critically ill patients with COVID-19 admitted to the ICUs, as a result of a number of favoring conditions. Early and accurate diagnosis and adequate antimicrobial treatment are essential to improve patients' outcome.

Our study showed high rates of HAIs in critically ill adults with COVID-19. Associated factors for HAI acquisition and fatality in ICU patients were identified and ask for the revision of existing HAIs control policies.

Preliminary published data indicate that secondary infections are associated with increased duration of mechanical ventilation and of ICU stay, and that they may have an impact on patient survival. However, data from large, well-designed studies are needed to confirm these findings and to improve our knowledge of the epidemiology and treatment of infections complicating the clinical course of COVID-19.

Financial support and sponsorship: No support from commercial or not-for-profit organizations

Conflicts of interest: There are no conflicts of interest.

Acknowledgment: The Authors wish to thank the Head of the Anaesthesiology and Critical Care Service Operative Unit (M. Tavola), the Charge nurse and all the staff of the Anaesthesiology and Critical Care Service Operative Unit, Local Health and Social Authority, Province of Lecco, Italy

Riassunto

Le co-infezioni tra i pazienti adulti affetti da COVID-19 ricoverati in terapia intensiva: risultati di uno studio retrospettivo

Premessa. Le infezioni sono comuni tra i pazienti ricoverati in Terapia Intensiva. Lo scopo di questo studio era quello di esaminare l'incidenza di infezioni nosocomiali tra i pazienti critici con infezione da SARS-CoV-2.

Metodi. È stato condotto uno studio osservazionale retrospettivo che ha incluso tutti i pazienti adulti con infezione da SARS-CoV-2 ammessi in Terapia Intensivs. In totale 118 pazienti sono stati arruolati da Febbraio 2020 a Settembre 2021.

Risultati. Un totale di 39 pazienti ha avuto almeno una nuova infezione durante la degenza (33.1%). Il tasso di co-infezione/co-colonizzazione >48 ore dopo l'ammissione era di 29.0 per 1.000 persone/giorno (IC 95% 19.1-33.9). Sono stati identificati un totale di 94 isolati, i più comuni erano *Klebsiella*, *Clostridium difficile*, *Acinetobacter baumanii* ed *Enterococcus* spp. Le variabili associate alle co-infezioni sono state: età > 64 anni (p= .003), degenza in Terapia Intensiva > 7 giorni (p= .002), diabete mellito di tipo 2 (p= .019), malattie cardiovascolari (p= .021), posizionamento catetere venoso centrale (p= .014), intubazione (p< .001), punteggio APACHE II >25 (p<.001), ventilazione meccanica >48 ore (p= .003) e posizionamento di catetere vescicale (p= .002). Il tasso di letalità complessivo dei pazienti è stato del 41.5% (n= 49) ed è risultato essere significativamente più alto tra i pazienti che hanno presentato una co-infezione (n= 26/39, 66.7%) rispetto ai pazienti senza co-infezione (n = 23/79, 29.1%) (OR= 4.87; IC 95% = 2.14-11.10; p< .001).

Conclusioni. Il nostro studio ha mostrato un elevato numero di co-infezioni tra i pazienti con COVID-19 ricoverati in Terapia Intensiva. Sono stati identificati alcuni fattori associati alla letalità tra i pazienti critici e queste variabili necessitano di osservazioni e severi controlli in futuro.

References

1. Grasselli G, Pesenti A, Cecconi M. Critical care utilization for the COVID-19 outbreak in Lombardy, Italy. JAMA. 2020 Apr 28; **323**(16): 1545-6. doi: 10.1001/jama.2020.4031.
2. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020 Mar 28; **395**(10229): 1054-62. doi: 10.1016/S0140-6736(20)30566-3.

Epub 2020 Mar 11. Erratum in: Lancet. 2020 Mar 28; 395(10229): 1038.
3. Herold T, Jurinovic V, Arnreich C, et al. Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19. J Allergy Clin Immunol. 2020 Jul; **146**(1): 128-36.e4. doi: 10.1016/j.jaci.2020.05.008. Epub 2020 May 18.
4. Guan W, Ni Z, Hu Y et al; China Medical Treatment Expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020 Apr 30; **382**(18): 1708-20. doi: 10.1056/NEJMoa2002032. Epub 2020 Feb 28.
5. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020 Feb 15; **395**(10223): 497-506. doi: 10.1016/S0140-6736(20)30183-5. Epub 2020 Jan 24.
6. Grasselli G, Zangrillo A, Zanella A, et al; COVID-19 Lombardy ICU Network. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region, Italy. JAMA. 2020 Apr 28; **323**(16): 1574-81. doi: 10.1001/jama.2020.5394. Erratum in: JAMA. 2021 May 25; 325(20): 2120.
7. Weiss P, Murdoch DR. Clinical course and mortality risk of severe COVID-19. Lancet. 2020: Mar 28; **395**(10229): 1014-5. doi: 10.1016/S0140-6736(20)30633-4. Epub 2020 Mar 17.
8, Schmidt M, Hajage D, Demoule A, et al. Clinical characteristics and day-90 outcomes of 4244 critically ill adults with COVID-19: a prospective cohort study. Intensive Care Med. 2021 Jan; **47**(1): 60-73. doi: 10.1007/s00134-020-06294-x. Epub 2020 Oct 29.
9. Fattorini L, Creti R, Palma C, Pantosti A. Bacterial coinfections in COVID-19: an underestimated adversary. Ann Ist Super Sanita. 2020 Jul-Sep; **56**(3): 359-64. doi: 10.4415/ANN_20_03_14.
10. Zhang G, Hu C, Luo L, et al. Clinical features and short-term outcomes of 221 patients with COVID-19 in Wuhan, China. J Clin Virol. Jun 2020; **127**: 104364. doi: 10.1016/j.jcv.2020.104364. Epub 2020 Apr 9.
11, Despotovic A, Milosevic B, Milosevic I, et al. Hospital-acquired infections in the adult intensive care unit—Epidemiology, antimicrobial resistance patterns, and risk factors for acquisition and mortality. Am J Infect Control. 2020 Oct; **48**(10): 1211-5. doi: 10.1016/j.ajic.2020.01.009. Epub 2020 Feb 21.
12, Klavs I, Kolman J, Zupanc TL, Kevorkijan BK, Koroec A; SNHPS Network. The prevalence of and risk factors for healthcare-associated infections in Slovenia: results of the second national survey [Prevalenca in Dejavniki Tveganja Za Bolninine Okube V Sloveniji: rezultati druge Nacionalne Presene Raziskave]. Zdr Varst. 2016 Jul 28; **55**(4): 239-47. doi: 10.1515/sjph-2016-0033.
13. Kolpa M, Walaszek M, Gniadek A, Wolak Z, Dobros W. Incidence, microbiological profile and risk factors of healthcare-associated infections in intensive care units: a 10 year observation in a provincial hospital in southern Poland. Int Environ Res Public Health. 2018 Jan 11; **15**(1): 112. doi: 10.3390/ijerph15010112.
14. Suetens C, Latour K, Karki T, et al; The Healthcare-Associated Infections Prevalence Study Group. Prevalence of healthcare-associated infections, estimated incidence and composite antimicrobial resistance index in acute care hospitals and long-term care facilities: results from two european point prevalence surveys, 2016 to 2017. Euro Surveill. 2018 Nov; **23**(46): 1800516. doi: 10.2807/1560-7917.ES.2018.23.46.1800516. Erratum in: Euro Surveill. 2018 Nov; 23(47).
15, Baskaran V, Lawrence H, Lansbury LE, et al. Co-infection in critically ill patients with COVID-19: an observational cohort study from England. J Med Microbiol. 2021 Apr; **70**(4): 001350. doi: 10.1099/jmm.0.001350.
16. Alhazzani W, Møller MH, Arabi YM, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). Intensive Care Med. 2020 May; **46**: 854-87. doi: 10.1007/s00134-020-06022-5. Epub 2020 Mar 28.
17. Rodríguez-Acelas AL, de Abreu Almeida M, Engelman B, Cañon-Montañez W. Risk factors for health care-associated infection in hospitalized adults: systematic review and meta-analysis. Am Infect Control. 2017 Dec 1; **45**: e149-e156. doi: 10.1016/j.ajic.2017.08.016. Epub 2017 Oct 12.
18. Koch AM, Nilsen RM, Eriksen HM, Cox RJ, Harthug S. Mortality related to hospital associated infections in a tertiary hospital; repeated cross-sectional studies between 2004-2011. Antimicrob Resist Infect Control. 2015 Dec 29; **4**: 57. doi: 10.1186/s13756-015-0097-9.

19. Pouwels KB, Vansteelandt S, Batra R, Edgeworth D, Smieszek T, Robotham V. ICU acquired bacteraemia and ICU mortality and discharge: addressing time-varying confounding using appropriate methodology. J Hosp Infect. 2018 May; **99**(1): 42-7. doi: 10.1016/j.jhin.2017.11.011. Epub 2017 Nov 23.
20. Cornejo-Juárez P, Vilar-Compte D, Pérez-Jiménez C, Ñamendys-Silva SA, Sandoval Hernández S, Volkow-Fernáandez P. The impact of hospital-acquired infections with multidrug-resistant bacteria in an oncology intensive care unit. Int Infect Dis. 2015 Feb; **31**: 31-4. doi: 10.1016/j.ijid.2014.12.022. Epub 2014 Dec 17.
21. Auld SC, Caridi-Scheible M, Blum JM, et al; and the Emory COVID-19 Quality and Clinical Research Collaborative. ICU and Ventilator Mortality Among Critically Ill Adults With Coronavirus Disease 2019. Crit Care Med. 2020 Sep; **48**(9): e799-e804. doi: 10.1097/CCM.0000000000004457.
22. Oliveira E, Parikh A, Lopez-Ruiz A, et al. ICU outcomes and survival in patients with severe COVID-19 in the largest health care system in central Florida. PLoS One. 2021 Mar 25; **16**(3): e0249038. doi: 10.1371/journal.pone.0249038.
23. Iregui M, Ward S, Sherman G, Fraser VJ, Kollef MH. Clinical importance of delays in the initiation of appropriate antibiotic treatment for ventilator associated pneumonia. Chest. 2002 Jul; **122**(1): 262-8. doi: 10.1378/chest.122.1.262.
24. Twigg D, Duffield C, Thompson PL, Rapley P. The impact of nurses on patient morbidity and mortality - the need for a policy change in response to the nursing shortage. Aust Health Rev. 2010 Aug; **34**(3): 312-6. doi: 10.1071/AH08668.

Corresponding Author: Dott. Vincenzo Damico, Azienda Socio Sanitaria Territoriale di Lecco, Via dell'Eremo 9/11 23900 Lecco
e-mail: vi.damico@asst-lecco.it