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The impact of bacterial superinfections on the outcome of critically ill patients with COVID-19 associated acute respiratory distress syndrome (ARDS) – a single-centre, observational cohort study

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Abstract

Background: Bacterial superinfections are common in severely ill COVID-19 patients and could be associated with a significant increase in morbidity and mortality.

Methods: We assessed 29 critically ill patients treated in a university hospital's intensive care unit (ICU). Each patient required mechanical ventilation due to COVID-19-induced acute respiratory distress syndrome (ARDS). Fifteen patients who required venovenous extracorporeal membrane oxygenation (VV-ECMO) support (ECMO group) were compared to a control group (CON group) of 14 individuals without ECMO. This study aimed to assess the prevalence of superinfection in both studied groups. Moreover, we evaluated mortality, length of stay in the ICU, positive culture results, antibiotics used during treatment, and the impact of immunomodulatory drugs on secondary infections.

Results: We did not find a difference in the number of superinfections between the ECMO and CON groups (11 vs. 10, $P = 1.0$). The mortality rate was 67% in the ECMO group and 64% in the CON group ($P = 1.0$). The patients in both groups had similar numbers of positive culture results and days in the ICU prior to the detection of a positive culture. Antibiotics were administered to ten patients in the ECMO and eight patients in the CON group. The mortality rate was 81% in patients with superinfection versus 25% in those without co-infection ($P = 0.009$). We found a negative impact of urea concentration on mortality in our cohort, with an odds ratio of 0.942 (0.891–0.996, $P = 0.034$).

Conclusions: Our results suggest that bacterial superinfection in COVID-19 patients negatively impacted survival in the ICU. VV-ECMO support in COVID-19 patients does not seem to improve the outcomes of patients with severe ARDS.

Key words: superinfection, COVID-19, ECMO, ARDS.

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Bacterial co-pathogens are common in viral respiratory tract infections and are associated with a significant increase in morbidity and mortality [1]. This phenomenon has also been found in patients with severe influenza, where bacterial co-infection is as high as 20–30%, as well as in patients diagnosed with Middle East respiratory syndrome coronavirus [2, 3]. Such bacterial co-infections may have detrimental impacts on patient outcomes, mainly due to the greater severity of illness, resulting in an increased risk of death [4]. Furthermore, studies on patients with viral infections requiring venovenous extracorporeal membrane oxygenation (VV-ECMO) support have demonstrated an increased risk of bacterial superinfections. These superinfections result in prolonged VV-ECMO support, increased duration of mechanical ventilation, delayed lung recovery and increased risk of in-hospital mortality [5].

Initial findings in patients with SARS-CoV-2 infection showed a significantly lower incidence of bacterial superinfections than had been found in previous influenza pandemics, with only 4% of COVID-19 patients in mixed inpatient settings experiencing a bacterial co-infection, with a higher prevalence of superinfections in the ICU (14%) [6].

During the pandemic, the introduction of immunosuppressant/immunomodulatory drugs, including steroids and interleukin receptor antagonists, improved outcomes in critically ill patients with COVID-19. However, these drugs also resulted in an increased risk of superinfections and hindered diagnostics by affecting biomarkers, including leucocytes, C-reactive protein, and procalcitonin [7, 8].

Furthermore, the incidence of nosocomial infections increased with invasive ventilatory support, indicated by the fact that the lowest infection rates were observed in spontaneously breathing patients. In contrast, the patients on VV-ECMO were shown to be at the most significant risk (60.5%) for co-infections [9]. These findings were also confirmed by Shih *et al*., who reported a very high incidence of bacterial co-infections in patients on VV ECMO support (68.2%) [10].

Since patients with severe COVID-19-associated ARDS are likely to develop nosocomial superinfections during their ICU stay, which may result in significant morbidity and mortality, it is necessary to acquire more data on possible risk factors and their effects on outcomes.

The main aim of this observational study was to investigate the prevalence of superinfections and their impact on outcomes in a cohort of critically ill patients with COVID-19-associated ARDS who required invasive mechanical ventilation and VV-ECMO support.

METHODS

This retrospective cohort study was approved by the Bioethics Committee of the Medical University of Lublin (KE-0254/160/06/2022). It analyses patient data previously gathered by Piwowarczyk *et al*. [11] for their study concerning the pharmacokinetics of nadroparin in critically ill patients with COVID-19. The main aims of that study were to assess concentrations of nadroparin and determine the possibility of achieving a target appointment of this low-molecular-weight heparin using a single or double injection regime. The patients were evaluated during the first three days following ICU admission. In the present study, we assessed the risk of superinfection in this cohort of patients from ICU admission to ICU discharge.

The inclusion criteria included adult patients with COVID-19 infection and ARDS who required ICU therapy. We divided participants into ECMO and control (CON) groups. Patients in both groups were mechanically ventilated. Consecutive patients were included in the ECMO group, and patients with similar severity of disease were included in the CON group.

The study's main aim was to assess the prevalence of superinfection in the ECMO and CON groups. Superinfections were defined as the appearance of another, new infection. They were categorised as bacteraemia, ventilator-associated pneumonia (VAP), and urine tract infection. It also sought to evaluate the following factors in both groups: mortality in the ICU, length of stay in the ICU, positive culture results, antibiotics used during treatment and the impact of immunomodulatory drugs on secondary infections.

Our department's antibiotic policy states that antimicrobial prophylaxis should not be administered during mechanical ventilation and VV-ECMO. Based on clinical conditions and laboratory test results, antibiotic treatment was initiated following bacterial or fungal infection diagnosis. On admission to the ICU, patients were screened with cultures of the nasopharynx, urine, and anus. Cultures of blood, bronchioalveolar lavage (BAL) or urine were taken if signs of infection had appeared.

Statistical analysis

We analysed continuous variables with the Mann-Whitney *U* test and qualitative parameters with Fisher's exact test. We used medians (interquartile ranges) and numbers (percentages) to present the data. Logistic regression was applied to detect parameters affecting the risk of superinfection, and the odds ratio (OR) was used to describe predictors included in the model. The receiver operating characteristic (ROC) curve was calculated for the best model. All measurements were performed using Statistica 13.1 software (Stat Soft. Inc., Tulsa, OK, United States).

RESULTS

We analysed 29 patients hospitalised in 2021, 15 in the ECMO group and 14 in the CON group. We included consecutive patients on VV ECMO therapy and a similar number of participants in the CON group. Each patient had moderate or severe ARDS according to the Berlin definition [12]. Patient demographics are presented in Table 1. We found a significant difference in patients' ages. Participants in the ECMO group were younger than those in the CON group. Moreover, we detected discrepancies between groups in C-reactive protein and procalcitonin concentrations.

We did not find a difference in the number of superinfections between the ECMO and CON groups (Table 2). Mortality was also similar in both groups. Moreover, the patients had similar numbers of positive culture results and days in the ICU prior to the detection of positive cultures (Table 2). Blood culture results and the antibiotics administered are presented in Tables 3 and 4.

In our further analysis, we compared patients with superinfections to participants without secondary infections. The recognition of superinfection was based on clinical judgment, including fever, blood pressure drop requiring extra fluids and/or support with vasopressors, increased fraction of inspired oxygen and/or positive end-expiratory pressure, purulent airway secretion or pyuria, a rele-

vant shift in laboratory tests and a combination of above-mentioned features. We found lower mortality among patients without secondary infections. Of twenty-one patients with superinfections, only four patients survived ICU treatment (19%). Among the eight individuals without co-infection, six were alive at ICU discharge. Thus, the mortality rate was 81% in patients with superinfection versus 25% in those without co-infection ($P = 0.009$).

After the progressive input of eight variables with a *P*-value below 0.1, only urea concentration was left in the final model with OR = 0.942 (0.891–0.996, $P = 0.034$), showing the negative impact of this parameter on the risk of superinfection. The area under the receiver operating characteristic curve for this model was 0.857.

DISCUSSION

In our cohort of 29 patients with COVID-19-associated ARDS who required invasive mechanical ventilation, we found that 72% developed bacterial superinfection during their ICU stay (Table 2). We did not find a significant difference in the frequency of superinfection occurrence between patients on VV-ECMO support and those without (73% vs. 71%). Moreover, in both groups, we found a similar number of positive culture results and days from ICU admission to detection of superinfection. We did not observe a difference between the analysed groups in terms of length of stay in the ICU and mortality (Tables 1 and 2). All studied patients, regardless of whether they were in the ECMO or CON group, received dexamethasone, which made it impossible to determine the association of superinfections with immunosuppressive therapy in our population.

We compared patients with superinfections and those without secondary infective features during their ICU stay. We found lower mortality among patients without superinfection (25% vs. 81%). In their single-centre study, Iacovelli *et al*. [13] also found a positive association between superinfection and in-hospital mortality among COVID-19 patients, with 42.6% of non-survivors and only 14% of survivors experiencing superinfections. Iacovelli et al. observed lower mortality (30%) than we found in our cohort (66%). However, they did not assess patients as severely ill as we did in our current study; indeed, out of Iacovelli *et al.*'s 201 participants, only 12 required ICU admission. In our previous study on the risk factors of acute respiratory failure (ARF) development in COVID-19 patients, we observed similar mortality as Iacovelli *et al*. [14], reaching 32% among individuals with ARF. Yoon *et al*. [15] assessed the impact of superinfection on the clinical outcomes of critically ill patients with COVID-19 in Korea. Compared to our cohort, the patients in that study had a lower rate of superinfection (32 of 106 patients). Moreover, Yoon *et al*. did not present higher mortality among patients with secondary bacterial infection (13% vs. 7%, $P = 0.446$). One of the reasons for this discrepancy between our results and those obtained by Yoon *et al*. could be the less severe condition of the patients in the latter study. The median Sequential Organ Failure Assessment result was five in the research of Yoon *et al*. and eight in ours. Nonetheless, Yoon *et al*. found longer ICU stays and days of mechanical ventilation in patients with superinfection.

TABLE 1. Patient demographics and parameters at admission to the ICU

Factor	ECMO	CON	*P*-value
Female (%)	7 (46.7)	4 (28.6)	0.45
Age (years)	40 [31–56]	56 [45–64]	0.02
Weight (kg)	100 [80–120]	97 [90–110]	0.79
Height (cm)	180 [163–185]	175 [170–180]	0.72
BMI	33.2 [28.9–37.7]	32.0 [31.2–36.0]	0.90
WBC (10^3/μL)	15.1 [8.2–19.9]	11.1 [10.0–18.5]	0.81
HCT (10^3/μL)	35.0 [32.7–35.5]	35.3 [34.5–37.7]	0.16
PLT (10^3/μL)	256 [180–335]	185 [166–314]	0.35
Mean temperature (°C)	36.5 [36.3–36.8]	37.0 [36.3–37.0]	0.16
Albumin (g dL^{-1})	2.7 [2.3–3.0]	2.8 [2.5–3.0]	0.73
PaO_2/FiO_2	145 [112–200]	152 [122–230]	0.62
Urea (mg dL^{-1})	49 [37–80]	61 [41–106]	0.18
Creatinine (mg dL^{-1})	0.8 [0.6–1.1]	0.9 [0.7–1.3]	0.60
PT (seconds)	14.1 [12.7–14.4]	12.4 [12.0–13.8]	0.14
APTT (seconds)	32 [29–35]	28 [27–32]	0.12
D-dimers	3604 [2355–6171]	4112 [1635–19909]	0.48
Bilirubin (mg dL^{-1})	1.4 [0.5–2.3]	0.7 [0.4–0.9]	0.30
PCT (ng mL^{-1})	0.43 [0.28–0.59]	0.17 [0.09–0.27]	0.02
CRP (mg L^{-1})	125 [59–214]	33 [12–98]	0.03
HCO_3 (mmHg)	29.7 [27.3–31.4]	32 [27–35]	0.25
pCO_2 (mmHg)	42 [38–49]	50 [45–67]	0.07
pO2 (mmHg)	87 [67–114]	94 [73–115]	0.84
Lactates (mmol L^{-1})	1.1 [0.8–1.8]	1.4 [1.1–2.0]	0.42
SOFA	9 [8–10]	7 [6–9]	0.13
Diuresis (mL kg^{-1} h^{-1})	0.79 [0.53–1.42]	0.52 [0.39–0.93]	0.11
CCI (L min^{-1} m^{-2})	2.9 [2.7–3.7]	3.1 [2.6–3.9]	0.91
SVRI (dyn s cm^{-5} m^{-2})	2018 [1796–2754]	2026 [1587–2650]	0.91
ELWI (mL kg^{-1})	19.3 [13.7–29.4]	18.4 [16.5–21.6]	0.88
Norepinephrine (μg kg^{-1} h^{-1})	3 [1–8]	0.5 [0–8]	0.31
Dobutamine (μg kg^{-1} h^{-1})	0 [0–0]	0 [0–2]	0.014
Length of stay (days)	14 [11–19]	12.5 [11–24]	1.0

APTT – activated partial thromboplastin clotting time, BMI – body mass index, CCI – continuous cardiac index, CRP – C-reactive protein, ELWI – extravascular lung water index, FiO_2 – fraction of inspired oxygen, HCT – haematocrit, PaO_2 – partial pressure of oxygen, PCT – procalcitonin, PLT – platelets, PT – prothrombin time, SOFA – Sequential Organ Failure Assessment, SVRI – systemic vascular resistance index, WBC – white blood count.
Categorical variables are presented as numbers (percentage) and continuous variables as medians [interquartile ranges].

TABLE 2. Outcomes in patients from CON and ECMO groups

Factor	ECMO	CON	*P*-value
Superinfection (%)	11 (73)	10 (71)	1.0
Death (%)	10 (67)	9 (64)	1.0
Tocilizumab (%)	0 (0)	5 (36)	0.017
Remdesivir (%)	5 (33)	4 (29)	1.0
Positive blood cultures (%)	6 (40)	7 (50)	0.72
Positive urine cultures (%)	3 (20)	3 (21)	1.0
Positive BAL cultures (%)	5 (33)	3 (210)	0.68
Days to positive blood culture	10 [8–10]	9 [7–10]	0.57
Days to positive urine culture	6 [0–10]	0 [0–6]	0.51
Days to positive BAL culture	2.5 [0.5–5.5]	6 [5–9]	0.22
Patients on antibiotics (%)	10 (67)	8 (57)	0.71
Days to start antibiotics in ICU	6 [3–9]	6.5 [4.5–9]	0.56

Categorical variables are presented as numbers (percentage) and continuous variables as medians [interquartile ranges]. BAL – bronchoalveolar lavage, ICU – intensive care unit

TABLE 3. Microorganisms detected in blood samples, bronchioalveolar lavage (BAL) and urine from patients in ECMO and CON groups

	ECMO	CON	Total
Blood	10	9	19
Staphylococcus aureus MSSA	2	1	3
Staphylococcus aureus MRSA	0	1	1
Staphylococcus epidermidis	0	1	1
Streptococcus anginosus	1	0	1
Acinetobacter baumannii	2	2	4
Klebsiella pneumoniae ESBL+, MBL+	0	2	2
Enterococcus faecium HLAR	2	0	2
Enterococcus faecalis	2	0	2
Serratia marcescens AmpC	1	2	3
BAL	6	8	14
Staphylococcus aureus MRSA	2	2	4
Acinetobacter baumannii	3	3	6
Klebsiella pneumoniae ESBL+ MBL+	0	2	2
Escherichia coli ESBL–	0	1	1
Pseudomonas aeruginosa	1	0	1
Urine	5	1	6
Escherichia coli	2	0	2
Acinetobacter baumannii	2	0	2
Klebsiella pneumoniae ESBL+	0	1	1
Enterococcus faecalis HLAR	1	0	1

ESBL – extended spectrum beta-lactamase, HLAR – high-level aminoglycoside resistance, MBL – metallo-beta-lactamase, MRSA – methicillin-resistant *S. aureus*, MSSA – methicillin-susceptible *S. aureus*

TABLE 4. Antibiotic usage during the ICU stay in ECMO and CON groups

Antibiotic	ECMO	CON	Total
Piperacillin with tazobactam	1	3	4
Ampicillin with sulbactam	0	1	1
Cefuroxime	1	0	1
Ceftazidime	2	3	5
Meropenem	8	1	9
Vancomycin	2	2	4
Teicoplanin	1	0	1
Tigecycline	3	2	5
Linezolid	6	1	7
Gentamycin	6	2	8
Amikacin	6	5	11
Trimethoprim/sulfamethoxazole	4	4	8
Clindamycin	1	2	3
Metronidazole	5	4	11
Colistin	3	0	3
Fidaxomicin	1	1	2
Fluconazole	1	0	1
Micafungin	0	1	1
TOTAL	51	32	83

Of 50 patients treated with VV ECMO in the study of Andersen *et al*. [16], bacteraemia and VAP affected 19 and 21 people, respectively. The authors of this study did not find that VAP and bloodstream infections impacted survival. However, co-infection with cytomegalovirus was associated with higher mortality, with an OR of 12.9 [1.9–257]. Overall, the mortality rate of 58% at hospital discharge reported by Andersen et al. was in line with our results (66%). Rivosecchi *et al*. [17] noted a higher superinfection rate in their 43 COVID-19 patients on VV-ECMO support than we found in our cohort (86% vs. 72% in our study). As in our data, however, Rivosecchi *et al*. detected a higher mortality rate among patients with secondary bacterial infection (67%) than in the group without co-infection (33%, $P = 0.02$).

In logistic regression analysis, we found an association between baseline urea concentration and survival rate, with an OR of 0.942 (0.891–0.996). In other studies on COVID-19, acute kidney injury (AKI) was similarly an independent risk factor of in-hospital mortality. Paek *et al*. [18] reported a 12.2 (4.2–35.1) hazard ratio for mortality in patients who developed severe AKI. According to Ghosn *et al*. [19], AKI was an independent risk factor of ICU mortality, with an OR of 29.7 (4.1–215.8).

Our study has some limitations. It was a retrospective study covering a relatively small number of patients. We used the same population as we did in a previous study [11]. Some differences were present in the baseline characteristics of the ECMO and CON groups. We used many combinations of antibiotics, caused by empirical therapy and then their modification according to the obtained result of cultures.

CONCLUSIONS

Our results suggest that bacterial superinfection in COVID-19 patients negatively impacted survival in the ICU. We did not find that VV-ECMO support improved the outcomes of patients with severe ARDS. Our data confirmed that AKI was associated with poor survival in critically ill COVID-19 patients.

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