COVID-19 association with multidrug-resistant bacteria superinfections: Lessons for future challenges

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Abstract: The future waves of COVID 19 infections will continue to raise serious problems in patients with severe forms of the disease. Bacterial infections associated with SARS-CoV-2 disease may complicate the progress of hospitalized patients with COVID-19. The present study aimed to evaluate the etiological spectrum of superinfection in adult patients with COVID-19 and to investigate the correlation between superinfection with multidrug-resistant (MDR) bacteria and serum procalcitonin (PCT). A total of 82 COVID-19 hospitalized patients with COVID-19 and bacterial superinfection were included. The superinfections were classified into early infections (3-7 days from admission) and late infections (>7 days from admission). Bacterial superinfection etiological spectrum, MDR bacteria profile and levels of serum PCT were studied. The most frequently isolated bacteria were *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *Enterococcus spp*. MDR bacteria were involved in 73.17% of COVID-19 patients with bacterial superinfections. Most MDR bacteria superinfections (73.52%) occurred in the late infection period. *Klebsiella pneumoniae*, *Enterococcus spp*. and *Methicillin-resistant Staphylococcus aureus* were the most common MDR bacteria identified in late infections after hospitalization in 20.43, 4.30 and 4.30% of all infections, respectively. Serum PCT values were significantly higher in patients with MDR bacteria superinfection compared with patients with sensitive bacteria superinfection (P=0.009). The principal findings of the present study were the high prevalence of superinfection with MDR bacteria among the COVID-19 patients with bacterial superinfections and the presence of a statistically significant association between serum PCT levels and the presence of superinfection with MDR bacteria. The most effective way to fight against microbial resistance to antibiotics, whether it occurs independently or overlaps with viral infections, is to pursue a national policy for the rational use of antibiotics.

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Abbreviations: ICU, intensive care unit; IQR, interquartile range; MDR, multidrug-resistant; MRSA, Methicillin-resistant *Staphylococcus aureus*; MSSA, Methicillin-susceptible *Staphylococcus aureus*; PCT, serum procalcitonin; RT-PCR, reverse transcription-polymerase-chain-reaction; SB, sensitive bacteria

Key words: COVID-19, bacterial superinfection, multidrug-resistant bacteria, serum procalcitonin

Introduction

The COVID-19 pandemic continues to challenge current medical practice and scientific research. Bacterial infections with antimicrobial-resistant pathogens had caused therapeutic challenges long before the current pandemic broke out. Empirical overprescription of antibiotics worldwide at the beginning of the COVID-19 pandemic has increased the

burden of this issue, increasing the risk of bacterial superinfection during hospitalization and the risk of antimicrobial resistance (1,2).

The future waves of COVID 19 infections will probably not overload health systems, but will continue to raise serious problems in patients with severe forms of the disease. The previous experience in managing superinfections with MDR bacteria in COVID-19 patients will be valuable for outcomes in patients.

Patients vulnerable to viral lung infections are at significant risk of developing multidrug-resistant (MDR) bacterial infections (3). Bacterial superinfections in COVID 19 patients have not been well studied yet and are considered a significant risk factor for COVID 19 mortality (4,5).

A recent Italian study suggests that pulmonary superinfections with MDR bacteria might negatively impact the outcome in COVID 19 patients (6).

Bacterial superinfections occur at least 48 h after hospital admission and are most often caused by hospital-acquired MDR bacteria (7). Patients with severe COVID-19 require extended hospitalization in intensive care units and are frequently treated with empiric, broad-spectrum antibiotics, which increases the risk of MDR bacteria selection (8). COVID-19 patients have a broad spectrum of clinical manifestations, which may change with emerging strains. Consequently, biological parameters are critical predictors of adverse outcomes, having a significant role in selecting the cases to be closely monitored. A real challenge for the clinician is to discern between COVID-19 severe inflammatory reaction and bacterial secondary infection (9).

Procalcitonin (PCT) is a glycoprotein synthesized in the C cells of the thyroid gland. In case of a microbial invasion, PCT is released from all parenchymal tissues (10). Serum PCT has normal values in patients with non-complicated COVID-19. A significant increase in the PCT serum levels suggests a non-viral coinfection or a development of a severe form of COVID-19 disease (11). It is unclear whether PCT can be used as a marker of bacterial coinfection for COVID-19 patients in the same way it has been used in other respiratory diseases (12).

The present study aimed to evaluate the etiological spectrum of bacterial superinfection in adult patients with COVID-19 and to investigate the correlation between superinfection with MDR bacteria and serum PCT.

Materials and methods

Data source. This retrospective observational study of bacterial superinfection in adult patients with confirmed COVID-19 was conducted in the Clinical Analysis Laboratory of the Arad County Hospital in Romania.

Definitions. A COVID-19 confirmed case was defined by a positive result for SARS-CoV-2 virus at admission, based on a reverse transcription-polymerase-chain-reaction (RT-PCR) test on a nasopharyngeal swab.

The cases with superinfection were carefully selected according to the following definition: The identification of a likely pathogen 48 h after admission (≥48 h) in a clinical sample taken for a diagnostic purpose. Coinfection was defined as identifying a pathogen within the first 24 h of hospital admission (7).

MDR bacteria are non-susceptible to at least one antimicrobial agent in three or more different antibiotic classes, except for intrinsic resistance.

The definition of a severe case was meeting one of the two criteria: The need for intensive care admission or assisted respiration (invasive ventilation or non-invasive oxygen support) in an intensive care unit (ICU). The non-severe cases were the patients admitted in non-ICUs, with oxygen saturation ≥94% on room air and no need for oxygen support.

Study design and population. The present single-center retrospective study included adult patients aged >18 years, diagnosed with COVID-19 and association bacterial infection hospitalized in Arad County Hospital between 01.04.2020 and 01.06.2021. Arad County Hospital serves ~470,000 individuals, which is a representative sample of the Romanian population. The period from which the cases were studied included the entire second pandemic wave in Romania and an optimal number of COVID-19 patients was provided in a short time.

Eligible patients presented COVID-19 infection at admission, an associated bacterial infection and available serum PCT within 24 h before and after the patients suspected of bacterial infection were taken samples for cultures.

Exclusion criteria were: Serum PCT determined outside the pre-set range of time, *Clostridium difficile* infection during hospitalization, surgical patients and presence of coinfections. Patients diagnosed with *Clostridium difficile* infection were excluded due to their particular progression and need for specific antibiotic treatment.

The present study evaluated the etiological spectrum of superinfection and observed the relation between superinfection with MDR bacteria and serum PCT. Also, an analysis was performed to identify the time from hospital admission to the diagnosis of superinfection. Based on these, the present study classified infections into early (3-7 days) and late (>7 days) infections.

Data collection. Electronic medical records of all SARS-CoV-2 positive patients (including both sexes and all age groups) were searched between 01.04.2020 and 01.06.2021. Personal data was removed. Patients who met the criteria of bacterial coinfection or superinfection were carefully selected. Fields collected were: Demographics (age, sex); hospital admission details (date of admission, number of days to the bacterial superinfection diagnosis); microbiological results; inflammatory biomarkers; the presence of underlying medical conditions; and COVID 19 vaccination status.

The present study reviewed the microbiological results (bacteria identified in cultures and antibiogram), time (days) from admission to superinfection and serum PCT as an inflammatory biomarker.

Microbiological results were: Standard positive culture from sputum, urine, tracheal aspirate, bronchoalveolar lavage and surgical wounds. Culture results were excluded if they were considered to represent colonization or contamination. The cultures were performed on VITEK 2C (bioMérieux), an automatic analyzer for bacterial identification and antibiogram. The present study used Vitek 2 GP

cards (cat. no. 21342 (bioMérieux) and Vitek 2 AST P592 cards cat. no. 22287; bioMérieux) to identify Gram-positive cocci, respectively, for their antibiograms. Gram-negative bacilli were identified with Vitek 2 GN cards (cat. no. 21341; bioMérieux). The present study tested the susceptibility of the bacilli to antibiotics using Vitek 2 AST N233 cards (cat. no. 413117; bioMérieux) and Vitek 2 AST XN05 (cat. no. 413230; bioMérieux).

At admission, the RT-PCR specimen was collected for all patients on a nasopharyngeal swab using SARS-CoV-2 automated analysis on the DLITE System (cat. no CTSC820001PCn; Certest Biotec) according to the manufacturer's protocol.

Serum PCT was measured by Electro-Chemiluminescence immunoassay kits (cat. no. 09318712190; Roche Diagnostics GmbH) on the Cobas e 601 analyzer (Roche Diagnostics GmbH) using the manufacturer's recommendations. The results were expressed as nanogram of PCT per microliter of serum (ng/ml). The normal ranges were considered to be between 0-0.5 ng/ml. Serum PCT values were analyzed in all studied patients within 24 h before and after taking samples for cultures. Patients with serum PCT determined outside this time range were excluded from the study.

Statistical analysis. Statistical analyses were performed using MedCalc v20.015 (MedCalc Software Ltd). The proportion of bacterial pathogens was recorded. The association between categorical data was performed by Chi-square with Fisher's exact test. The distribution of numerical results was calculated using the Shapiro-Wilk normality test. Normally distributed data were presented as mean ± standard deviation. Data following a nonparametric distribution were presented as the median and interquartile range (IQR) and the comparisons between two independent groups were performed with the Mann-Whitney U test. $P<0.05$ was considered to indicate a statistically significant difference.

Ethics. The study was carried out in accordance with the declaration of Helsinki. It was approved by the Ethics Commission for Clinical Trials of Arad County Hospital (approval no. 37/25.02.2021) and of Scientific Research Ethics Commission of Vasile Goldis, University of Arad (approval no. 10/29.03.2021).

Results

Superinfection profile. Overall, during the present study research period, 165 eligible patients hospitalized for COVID-19 with bacterial infection association were documented. Of these patients, 52 infections were identified in surgical patients, which were excluded due to the specificity of the germs related to the surgical wounds.

Another 113 infections were found in non-surgical patients, with 31 (27.4%) cases of coinfections and 82 cases of superinfection. Former patients met inclusion criteria and represented the study population (n=82 cases).

In these included patients, 66 (80.49%) superinfections occurred in severe cases, patients admitted in ICUs and 16 (19.51%) superinfections occurred in non-severe cases, patients admitted in non-ICUs-COVID-19 medical departments (Fig. 1).

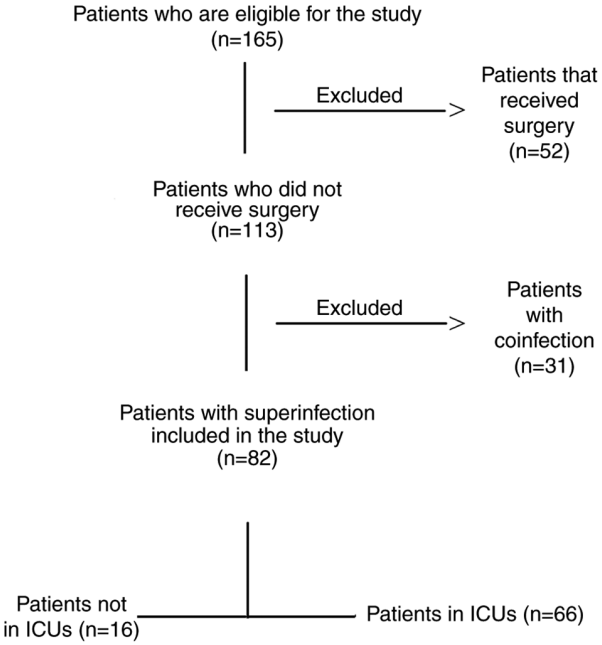

Figure 1. Flowchart of the study population. ICU, intensive care unit.

The mean age of the study population was 65.51±11.23 years. A total of 49 (59.75%) patients were male. Of the 82 patients included, only five were COVID-19 vaccinated, three with Pfizer BioNTech COVID-19 vaccine and two with AstraZeneca COVID-19 vaccine.

The main underlying medical conditions found were hypertension (63.4% of patients), obesity (48.8% of patients), diabetes mellitus (39% of patients, chronic lung disease (36.6% of patients) and cardiovascular disease (32.9% of patients).

In the period after 48 h from hospital admission to discharge, 93 bacterial infections were identified in the study population (n=82 patients), 32 (34.40%) potential pathogens from days 3-7 and 61 (65.59%) potential pathogens from day eight onwards. Polymicrobial infections were found in 11 patients (13.41%).

The median time from hospital admission to the diagnosis of superinfection was 11 days (IQR 6-17).

A total of 18 types of bacterial pathogens were identified. The most frequently isolated microorganisms were *Klebsiella pneumoniae* (29.03% of superinfections), *Acinetobacter baumannii* (9.68% of superinfections) and *Enterococcus spp*. (9.68% of superinfections). *Klebsiella pneumoniae* was detected early (days 3-7) in four (4.30%) superinfections and late (>7 days) in 23 (24.73%) superinfections. *Enterobacter aerogenes* and *Enterococcus faecalis* were detected only on days 3-7 (early detection). *Escherichia coli*, *Escherichia fergusonii*, *Acinetobacter calcoaceticus*, *Staphylococcus capitis*, *Staphylococcus cohnii*, *Staphylococcus haemolyticus*, *Staphylococcus lugdunensis*, *Staphylococcus hominis* and *Serratia marcescens* were detected only after 7 days (late detection). *Methicillin-resistant Staphylococcus aureus* (MRSA), *Methicillin-susceptible Staphylococcus aureus* (MSSA), *Pseudomonas aeruginosa* and *Enterococcus faecium* were identified both in early and late detection period.

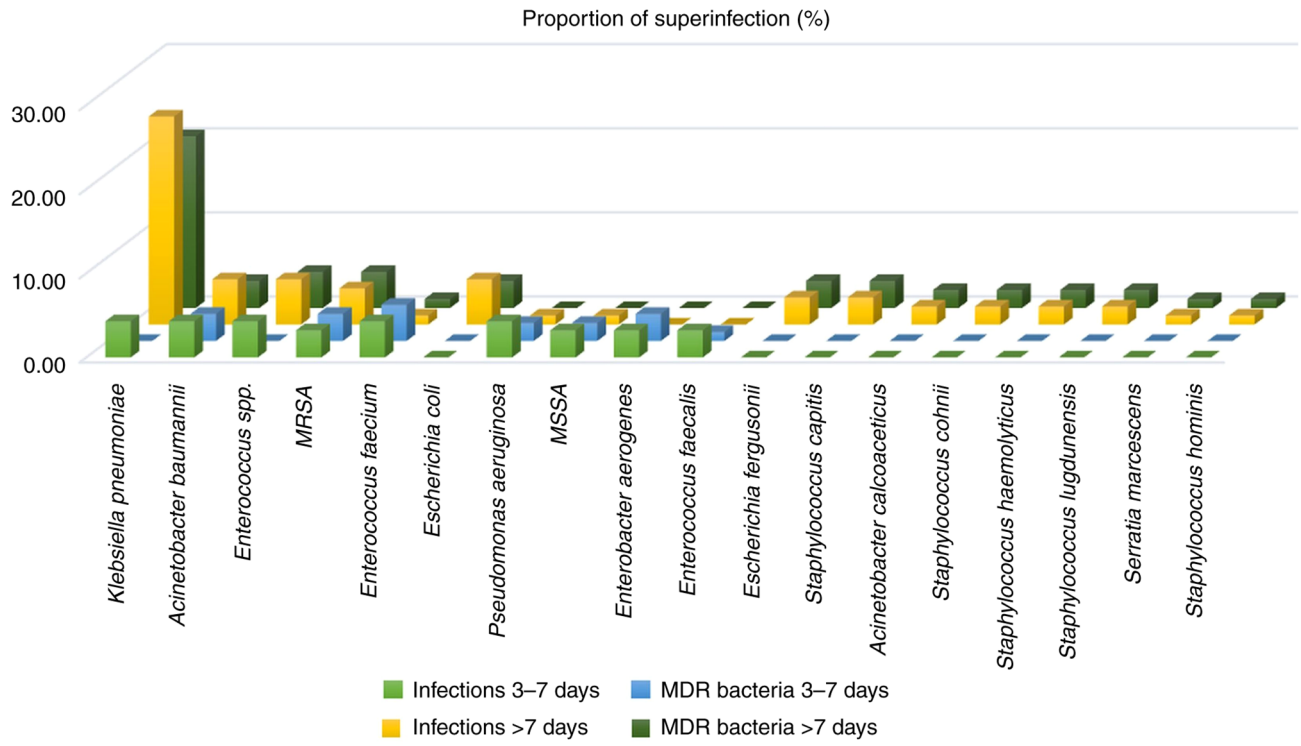

Figure 2. The proportion of superinfection. MRSA, Methicillin-resistant *Staphylococcus aureus*; MSSA, Methicillin-susceptible *Staphylococcus aureus*; MDR, multidrug-resistant bacteria.

MDR bacteria profile. Documented MDR bacteria superinfections were found in 60 (73.17%) patients (Fig. 2). Of MDR bacteria superinfections, 73.52% occurred in the late infection period. The most frequently identified MDR bacteria on days 3-7 were *Enterococcus faecium*, MRSA, *Acinetobacter baumannii* and *Enterobacter aerogenes* in a proportion between 3.22 and 4.30%. *Klebsiella pneumoniae*, *Enterococcus spp*. and MRSA were the most common MDR bacteria identified in late infections after hospitalization in 20.43, 4.30 and 4.30% of all infections, respectively. *Klebsiella pneumoniae* and *Enterococcus spp*. were associated with antibiotic resistance only in late infections.

No antibiotic resistance was observed in late infections with MSSA, *Pseudomonas aeruginosa*, *Enterobacter aerogenes* and *Enterococcus faecalis*.

There were no significant differences between sex and the presence of MDR bacteria (P=0.448). No association was found between MDR bacteria superinfections and age (P=0.565).

Site of infections. The site of infections according to the etiology is reported in Table I; there were 41 (44.09%) hospital-acquired pneumonia, 29 (31.18%) ventilator-associated pneumonia, nine bacteremia (9.68%), eight (8.60%) urinary tract infection and six (6.45%) acute bacterial skin and skin structure infection.

PCT-MDR bacteria association. The values of serum PCT (median, IQR) were significantly higher in patients with MDR bacteria superinfection than in patients with sensitive bacteria (SB) superinfections (5.665, 3.08-8.12 ng/ml vs. 3.150 ng/ml, 2.48-4.6 ng/ml, P=0.009).

Discussion

Superinfection in COVID-19 patients. There are differences in microbial resistance to antibiotics in urban compared with rural areas and from one geographical area to another. Microbial resistance to antibiotics differs even more from one country to another, depending on therapeutic protocols, specific indications and occasionally on the clinical experience of the prescribing physician.

On the other hand, it is difficult to estimate how the COVID-19 pandemic will change the MDR bacteria spectrum. Therefore, a comparative synthesis of several studies from different regions and countries would help to fight against microbial resistance to antibiotics.

Bacterial coinfection within 48 h of hospital admission for COVID-19 infection in adults was uncommon: 1.6% at admission and 5.5% within 48 h (13). In a study that evaluated *Streptococcus pneumoniae* coinfection in hospitalized patients with COVID-19, the most frequent pathogens identified within the first 48 h of hospital admission were *Staphylococcus aureus* and *Streptococcus pneumoniae* (14). In the present study, 27.4% of the total number of bacterial associations were coinfections, being diagnosed within the first 48 h from admission. This significantly higher proportion of already superinfected patients was probably due to a particularity, well known by the medical professionals working in the studied population, the late presentation of patients in the emergency room, often with clinically manifest respiratory failure and oxygen desaturation.

Most studies performed on COVID-19 patients show no clear distinction between early and late superinfections (15,16).

Table I. Etiology by the site of superinfections.

Site of superinfections	Bacteria	Total
HAP		41 (44.09%)
	Klebsiella pneumoniae	13
	Acinetobacter baumannii	7
	Enterococcus spp.	6
	Escherichia coli	5
	Enterobacter aerogenes	2
	MRSA	2
	Serratia marcescens	2
	Staphylococcus capitis	2
	Staphylococcus lugdunensis	2
VAP		29 (31.18)
	Klebsiella pneumoniae	9
	Pseudomonas aeruginosa	5
	Acinetobacter calcoaceticus	2
	Enterococcus faecalis	2
	Enterococcus faecium	2
	Enterococcus spp.	2
	MRSA	2
	Staphylococcus cohnii	2
	Staphylococcus haemolyticus	2
	Escherichia fergusonii	1
Bacteremia		9 (9.68%)
	Enterococcus faecium	3
	Enterococcus faecalis	2
	Klebsiella pneumoniae	2
	MSSA	1
	Staphylococcus hominis	1
UTI		8 (8.60%)
	Klebsiella pneumoniae	3
	Escherichia fergusonii	2
	MSSA	2
	Enterococcus spp.	1
ABSSSI		6 (6.45%)
	MRSA	3
	Acinetobacter baumannii	2
	MSSA	1

HAP, hospital-acquired pneumonia; VAP, ventilator-associated pneumonia; UTI, urinary tract infection; ABSSSI, acute bacterial skin and skin structure infection; MRSA, Methicillin-resistant *Staphylococcus aureus*; MSSA, Methicillin-susceptible *Staphylococcus aureus*.

By contrast, the high case fatality of COVID-19 in a relatively short time may exclude the development of a possible late superinfection, which may lead to an underestimation of the risk of superinfection (17).

In the present study, the number of superinfections was higher in severe compared with non-severe cases (80.49% vs. 19.1% of all diagnosed superinfections).

The results of the present study are superposable with the available literature data. In a study published by Baskaran *et al* (9) in 2021, 30.3% of bacterial infections in ICU patients represented hospital-acquired infections. The most frequently identified bacteria were *Klebsiella pneumoniae* (commonly associated with hospital and ventilator-acquired pneumonia) and *Escherichia coli*. The median time to superinfection was 9 days in the same study compared with 11 days in the present study.

In the vast majority of studies, the proportion of pathogens detected increased with the duration of ICU stay. It mainly consisted of Gram-negative bacteria, especially *Klebsiella pneumoniae* and *Escherichia coli*.

The present study found mostly *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *Enterococcus* spp. in the early infection period (3 to 7 days from admission). In the late infection period (after 7 days from admission), the same bacteria occurred, to which *Escherichia coli* was added in the same proportion as *Acinetobacter baumannii* and *Enterococcus spp*. *Klebsiella pneumoniae* was predominant after 7 days from admission.

According to a recent meta-analysis, the prevalence of bacterial superinfection was estimated to be ~14% in ICU patients (15). An observational cohort study from England (2021) reported a higher prevalence of superinfection (27.2%) in critically ill patients with COVID-19, with the majority of superinfection involving Gram-negative bacteria (*Klebsiella pneumoniae* and *Escherichia coli*) (10). A high prevalence of superinfection reported in a study on ICU patients was 45% (18). This significant variability is probably due to the vast diversity of patients, diagnostic and therapeutic procedures and environment-specific factors (19).

Superinfections are frequently caused by hospital-acquired MDR bacteria (7). A prolonged stay in an ICU associated with broad-spectrum antibiotic therapy significantly increases the risk of MDR bacteria selection (8).

In a study of 315 patients, conducted in 2020 by Falcone, which evaluated superinfection in hospitalized COVID-19 patients, MDR bacteria caused 61.5% of all superinfections (20). The present study identified MDR bacteria in 73.17% of all patients with bacterial superinfection. This high proportion of MDR bacteria raises significant concern about the future efficiency of antibiotics in treating bacterial infections.

Serum PCT levels. Serum PCT is widely used in the management of COVID-19 patients and its role in disease diagnosis, prognosis and clinical decision-making was reassessed in the current pandemic. According to a meta-analysis by Stegeman *et al* in 2020 (21), PCT has low sensitivity ranging (0-48%) and specificity from 26-95% in diagnosing COVID-19. By contrast, a number of studies show that PCT levels are significantly associated with the severity and potential complications of the disease (22-24).

Serum PCT levels increase markedly between the first 6 to 12 h after the onset of sepsis, systemic infection and severe inflammation (25). Serum PCT kinetics in infections with SB is well-known (26). However, there are insufficient data

about serum PCT kinetics and its practical utility in critically ill patients with infections caused by MDR bacteria. In this regard, a previous study showed that catheter-related bloodstream infections caused by MDR bacteria are associated with higher PCT levels and slower decline of its levels compared with those caused by SB, probably due to a more robust and prolonged inflammatory response (26).

To the best of the authors' knowledge, there is a lack of data in the literature regarding PCT levels in COVID-19 critically ill patients suffering from superinfection with MDR bacteria.

In critically ill COVID-19 patients, the release of PCT from extrathyroidal parenchymal tissues is increased by infectious insults and accelerated by the inflammatory cytokines storm (27). It is complicated to differentiate between the increase in PCT levels caused by the cytokine storm and that caused by a possible superinfection. Therefore, it appears crucial to corroborate serum PCT with other biomarkers, cultures and clinical data if superinfection is suspected.

The results of the present study demonstrate that serum PCT obtained within 24 h before and after the patients were suspected of superinfection and were taken samples for cultures are significantly higher (P=0.009) in patients with infection caused by MDR bacteria compared with those with infection caused by SB, suggesting that the increase in serum PCT levels is caused by superinfection rather than by de progression of COVID-19.

Strengths and limitations of the present study. The present study provided novel data on bacterial superinfection, including MDR bacteria superinfections and the association between MDR bacteria superinfections and serum PCT levels in hospitalized COVID-19 adult patients.

The principal findings were that the high prevalence of superinfection with MDR bacteria among the COVID-19 patients with bacterial superinfections and the presence of a statistically significant correlation between serum PCT levels and the presence of superinfection with MDR bacteria.

A notable limitation of the present study was its retrospective observational design, which mainly reported on the selection of cases. The fact that severe and non-severe patients were studied together resulted in a heterogeneity of the study population regarding the severity of the viral disease. The number of included patients was relatively small. Serial measurements of PCT were not performed to report its kinetics in dynamics. There is a possibility of empirical antibiotic treatment before admission, which could affect the studied laboratory parameters; unfortunately, no such details were found in the data records of the included patients.

Although COVID 19 has become a significantly less severe disease, patients with severe forms are still exposed to bacterial superinfections, especially during prolonged ICU hospitalizations. The MDR bacteria superinfection spectrum found in the present study and its correlation with PCT values may be helpful in future clinical judgment.

The principal findings of the present study were the high prevalence of superinfection with MDR bacteria among the COVID-19 patients with bacterial superinfections and the presence of a statistically significant correlation between serum procalcitonin levels and the presence of superinfection with MDR bacteria.

MDR bacteria were involved in almost three-quarters of COVID 19 patients with bacterial superinfections. Most MDR bacteria superinfections appeared in the late infection period.

Serum PCT values were significantly higher in patients with MDR bacteria superinfection compared with patients with SB superinfection. Serum PCT is a possible biomarker for individualizing antibiotic treatment in COVID-19 patients with MDR bacteria superinfection. More prospective studies are needed to establish the serum PCT role in monitoring these patients.

Corroboration of laboratory biomarkers in dynamics with clinical data is essential and COVID-19 patients with bacterial superinfection need to be monitored not only by hematological, biochemical and immunological markers, but also from the microbiological point of view.

An improved understanding of superinfection mechanisms, its favoring and precipitating factors and the variety of pathogens involved in COVID-19 patients with bacterial superinfection reinforces the need for more reviews and prospective clinical studies with standardized protocols.

The most effective way to fight against microbial resistance to antibiotics and subsequently preserve the antibiotics' effectiveness in the treatment of infectious diseases is to pursue a national policy for the rational use of antibiotics.

As pandemics have no borders, several countries must find common paths to fight against MDR bacterial infections, whether they occur independently or overlap with viral infections, as in the case of COVID 19.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

MS and DM together designed the study and were responsible for data analysis and writing the paper. RS, RB, AlI and AnI searched the literature and were responsible for data analysis and interpretation. CD and DL interpreted the data and critically revised the manuscript. VL, IB and AM were responsible for data collection, obtaining ethics approval and confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was performed in accordance with the declaration of Helsinki. It was approved by the Ethics Commission for Clinical Trials of Arad County Hospital (approval no. 37/25.02.2021) and of Scientific Research Ethics

Commission of 'Vasile Goldis' Western University of Arad (approval no. 10/29.03.2021).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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