Cogitare Enfermagem

ORIGINAL ARTICLE

PROCALCITONIN AS ANTIMICROBIAL MANAGEMENT TOOL IN COVID-19 PATIENTS

HIGHLIGHTS

1.The procalcitonin-guided therapy in COVID-19 reduces antimicrobial use.
2. The procalcitonin serum levels showed an association with mortality.
3. There was a relationship between the PCT serum levels and laboratory markers related to bacterial infection.

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ABSTRACT

Objective: to investigate the relationship between procalcitonin in the differential diagnosis of bacterial coinfection in COVID-19 patients. **Method:** a cross-sectional retrospective study conducted between February and March 2021 in the Intensive Care Unit of a public hospital from southern Brazil by filling in a form. Descriptive statistical analyses were performed, as well as of association between variables. **Results:** of the 231 patients, 28.14% presented infection (63.20% in the lungs), 25% had bacteria isolated, 77.49% used antimicrobials and, in 14.72% of the cases, procalcitonin > 2 ng/mL. There was a significant association between antimicrobial use and infection (p=0.001), isolation of bacteria (p<0.001), topography of the infection (p<0.001) and procalcitonin values (p<0.001). Procalcitonin use showed an association with bacterial infection (p<0.001), isolation of bacteria (p<0.001), antimicrobial use (p=0.001) and death (p<0.001). **Conclusion:** procalcitonin can reduce empirical antimicrobial use and stimulate detection and identification of pathogens, taking into account the clinical and epidemiological data.

DESCRIPTORS: Antimicrobial Management; COVID-19; Procalcitonin; In-hospital Infection Control Services; Intensive Care Unit.

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INTRODUCTION

The COVID-19 pandemic imposed a significant demand on health systems at the global level. There was an increase in the need for an emergency expansion of qualified personnel, supplies and, in addition to that, some courses of action were based on national and international guidelines, mostly empirical, imposing unforeseen costs on the health system[1].

In the COVID-19 pandemic context, in patients with initial clinical signs of fever, tachypnea, hypoxia, pulmonary infiltrates in chest imaging and increased biomarkers such as C-Reactive Protein (CRP)[2], rational antimicrobial use and exclusion of bacterial coinfection become a challenge. The bacterial coinfection rates are estimated at 7% to 14%[3-4]. Even so, at the beginning of the pandemic, 80% of the COVID-19 patients underwent treatment with antibiotics[5].

In March 2021, the *National Institute for Health and Care Excellence* instructed the performance of various tests that assist in decision-making referring to antibiotic use. The following stand out among the exams: complete blood count, chest images (X-ray, computed tomography or ultrasound), blood and urine samples, and nasal and oropharyngeal swabs for the respiratory viral polymerase chain reaction test (atypical pathogen), not indicating the Procalcitonin (PCT) dosage[4].

During the pandemic, PCT was initially used for the COVID-19 diagnosis[6-7], for evaluating severity of the infection[8-10] and for detecting bacterial coinfection. A Cochrane meta-analysis from November 2020, which evaluated routine laboratory tests for COVID-19, including PCT, evidenced low sensitivity (which varied from 0% to 48%) and specificity (from 26% to 95%) for the COVID-19 diagnosis[6]. Subsequently, an observational cohort study, conducted in the emergency sector of a tertiary-level hospital in Italy with 444 patients, considered the inclusion of PCT in the panel of pre-intervention tests as an intervention, including blood count, fibrinogen, prothrombin activity time, glucose, creatinine, sodium, potassium, alanine aminotransferase (ALT), total bilirubin, lactic dehydrogenase (LDH), CRP and interleukin-6. It was observed that PCT was not useful for the COVID-19 differential diagnosis in the emergency sector among patients who presented fever or respiratory symptoms[7].

PCT is widely used to assess the bacterial infection risk and progression to severe sepsis and septic shock, together with other laboratory findings and clinical evaluation. The variation in the PCT levels was proposed to differentiate systemic inflammation of a viral origin from the one of bacterial origin in community-acquired pneumonia and sepsis. The significant increase in the PCT serum levels would indicate bacterial infection[11].

PCT can emerge as a strategy in the identification of COVID-19 patients that do not present bacterial infection, with the purpose of reducing the prescription of antimicrobials[12]. Several studies report that high PCT levels are positively associated with COVID-19 severity[8-10]; in addition to that, serial measures can be useful in foreseeing the prognosis[13].

A meta-analysis, which aimed at investigating whether PCT would play a role in distinguishing patients with or without severe COVID-19, showed that increased PCT values are related to a five-fold increased risk of severe SARS-CoV-2 infection[14]. However, other studies suggest that PCT use might act as a guide for antibiotics de-escalation, reducing antibiotic use by two days in COVID-19 patients[15]. Severity and inflammation in the COVID-19 patients led to indiscriminate antimicrobial use, turning the bacterial coinfection diagnosis into a challenge.

Therefore, the pandemic reduced access to the United Kingdom *Antimicrobial Stewardship Programs*, with an increase in the consumption of antibiotics despite absence of bacterial infections[16]. Consequently, it becomes very important to implement and expand

the concept of antimicrobial use clinical management, specially prioritizing the activities performed by an interdisciplinary team.

Most of the studies that investigated the usefulness of the PCT-guided therapy in COVID-19 patients found reduced antibiotic use with no negative impact on the results[15,17-19]. The PCT cutoff point of 0.5 ng/mL was studied in the differential diagnosis between viral and bacterial infections[20]. PCT was investigated in a large number of studies with different populations and environments, with divergent results. These findings can be explained by several factors, including different cutoff values and strategies, routine implementation of the PCT-guided therapy, adherence to the protocol, or presence of antimicrobial management programs[21].

With the objective of improving patient management, the PCT test was included in the list of exams to be requested in a hospital providing exclusive care by the Unified Health System in a capital city from southern Brazil. Given the above, the objective of the current study was to investigate the relationship of procalcitonin in the differential diagnosis of bacterial coinfection in COVID-19 patients.

METHOD

This is a retrospective cross-sectional study developed at a public hospital in a capital city from southern Brazil, with secondary data extracted from the In-hospital Infection Control Service (*Serviço de Controle de Infecção Hospitalar*, SCIH) spreadsheet and the *Tasy*® electronic medical record. The population included was comprised by patients that evolved with the severe form of COVID-19 and Severe Acute Respiratory Syndrome (SARS) in all 84 ICU beds of the Institution.

The following inclusion criteria were established: being aged ≥ 18 years old and presenting a confirmed COVID-19 diagnosis by the Reverse Transcription Polymerase Chain Reaction test, ICU admission with indication of prone position, and PCT collection by the care team. The exclusion criteria were as follows: severe COVID-19 with no indication of invasive airway and prone position.

The data were collected in a two-month sampling period, which encompassed from February to March 2021. For data collection, a form consisting of the variables of interest was prepared: gender, presence of infection and topography, confirmation of healthcare-associated infection (HAI) as defined by the SCIH, culture result, hematological parameters (leukocytes, neutrophils, band cells), PCT, antimicrobial use and presence of intervention by an infectologist with or without suspension of the antimicrobial. The HAI diagnostic criteria took into account documents issued by the National Health Surveillance Agency (*Agência Nacional de Vigilância Sanitária*, ANVISA)[22].

The study was carried out with patients hospitalized in critical beds, given the majority availability of these beds to the population during this period. Regarding the profile of the population, it was defined as patients with SARS and need for prone position, as they presented a low PaO_2/FiO_2 ratio, configuring a more homogeneous group for comparison purposes. The data were collected by the researchers in SCIH spreadsheets, complemented by diverse information forwarded from the Curitiba Municipal Laboratory and from the electronic medical charts. A two-month follow-up period was chosen so that the data could be worked on rapidly by statisticians and to evaluate subsequent changes in the care practices. In this study, the PCT reference values and interpretation criteria were as follows: PCT < 0.5 ng/mL, normal test with low septicemia risk; PCT between 0.5 and 2 ng/mL, systemic inflammations; and PCT > 2 ng/mL, severe bacterial infections or septic shock[20].

The data were organized in *Excel*® spreadsheets and later analyzed in the R 4.0.4

environment[23]. Descriptive statistical analyses were performed, with distribution of simple and relative frequencies, confidence interval, and association between variables with Pearson's chi-square test and Fisher's exact test when n < five. The tests were considered significant when $p<0.05$.

The study received a favorable opinion from the Committee of Ethics in Research with Human Beings from the Health Sciences Sector: CEP/SD 5,250,857.

RESULTS

It was observed that, of all 231 patients selected for the sample, 126 (54.55%) were male, 146 (63.20%) presented pulmonary infections, and 159 (68.83%) evolved to death. There was suspicion of infection by the attending physician in 65 (28.14%) patients, with confirmation of the infections by an infectologist in 95 (41.13%), according to ANVISA criteria. The most commonly reported infection topography was pulmonary with 146 (63.20%), 179 (77.49%) used antibiotics, 58 (24.11%) with identification of bacteria, and 34 (14.72%) with probability of bacterial coinfection according to the PCT level (Table 1).

Table 1 – Frequency distribution of the variables of interest of the study. Curitiba, PR, Brazil, 2021

Variable		n†	%	CI‡ (95%)	
Gender	Female	105	45.45	39.16	51.9
	Male	126	54.55	48.1	60.84
Outcome	Not death	72	31.17	25.54	37.41
	Death	159	68.83	62.59	74.46
Healthcare-Associated Infection	No	166	71.86	65.74	77.27
	Yes	65	28.14	22.73	34.26
Confirmed infection by ANVISA§ criteria	No	136	58.87	52.43	65.02
	Yes	95	41.13	34.98	47.57
Topography	Bloodstream infection	7	3.03	1.48	6.12
	Unidentified infection site	69	29.87	24.34	36.06
	Skin - Soft parts	1	0.43	0.076	2.41
	Pulmonary	146	63.20	56.82	69.16
	Urine	8	3.46	1.77	6.68
Isolated bacterium	No	173	74.89	68.92	80.05
	Yes	58	25.11	19.95	31.08
Antibiotic use	No	52	22.51	17.6	28.32
	Yes	179	77.49	71.68	82.4

Procalcitonin	Normal	136	58.87	52.43	65.02
	Viral infection	61	26.41	21.14	32.44
	Probability of bacterial coinfection	34	14.72	10.73	19.86

Note: †n = Number of patients in the subgroup; ‡CI = Confidence Interval; §ANVISA = *Agência Nacional de Vigilância Sanitária* (National Health Surveillance Agency).
Source: The authors (2021).

Table 2 evidences that, of the patients with a probability of bacterial coinfection (PCT > 2 ng/mL), one (2.9%) did not use antimicrobials, nine (26.5%) used them and their use was suspended, and 24 (70.6%) used them and the attending physician did not suspend their use. On the other hand, in patients with normal tests (PCT < 0.5 ng/mL) it was observed that 41 (30.1%) did not use antibiotics, 53 (39%) used them and their use was interrupted, and 42 (30.9%) used them and the attending physician did not suspend their use after the PCT result was known. It is also observed that there was an association between antimicrobial use and infection as defined by the care team, SCIH infection diagnosis, topography of the infection and isolation of bacteria in the cultures (p<0.001).

Table 2 – Frequency distribution of the association between antimicrobial use and the variables of interest of the study. Curitiba, PR, Brazil, 2021

Variables	Covariates	Antibiotics						p-value
		Did not use		Used and suspended		Used and did not suspend		
		n†	%row‡	n†	%row‡	n†	%row‡	
Gender	Female	27	25.7	30	28.6	48	45.7	0.363
	Male	25	19.8	46	36.5	55	43.7	
Outcome	Not death	17	23.6	30	41.7	25	34.7	0.091
	Death	35	22	46	28.9	78	49.1	
HAI§	No	48	28.9	63	38	55	33.1	<0.001
	Yes	4	6.2	13	20	48	73.8	
IC††	No	39	28.7	28	20.6	69	50.7	<0.001
	Yes	13	13.7	48	50.5	34	35.8	
Topography	Bloodstream infection	0	0	2	28.6	5	71.4	<0.001
	No	33	47.8	14	20.3	22	31.9	
	Skin - Soft parts	0	0	1	100	0	0	
	Pulmonary	19	13	59	40.4	68	46.6	
	Urine	0	0	0	0	8	100	
Isolated bacterium	No	48	27.7	65	37.6	60	34.7	<0.001
	Yes	4	6.9	11	19	43	74.1	
PCT‡‡	Normal	41	30.1	53	39	42	30.9	<0.001
	Viral infection	10	16.4	14	23	37	60.7	
	Probability of bacterial coinfection	1	2.9	9	26.5	24	70.6	

Test used: Pearson's Chi-Square.
Note: †n = Number of patients in the subgroup; ‡%row = Value in each row as a percentage of the row total; §HAI = Healthcare-Associated Infection; ††IC = Infection confirmed by ANVISA criteria; ‡‡PCT = Serum procalcitonin.
Source: The authors (2021).

In Table 3, PCT is categorized into three subgroups according to its serum value: Subgroup A, PCT < 0.5 ng/mL; Subgroup B, PCT from 0.5 to 2 ng/mL; and Subgroup C, PCT > 2 ng/mL. A relationship is observed between the PCT serum values and the increase in the laboratory markers related to bacterial infections, such as total leukocytes, neutrophils, band cells and CRP. With a PCT result < 0.5 ng/mL, the following mean values were found: leukocytes, 12,405 (SD: 5,224); neutrophils, 10,884 (SD: 4,714); band cells 799 (SD: 715); and CRP, 130 (SD: 98). When PCT reaches levels between 0.5 and 2 ng/mL, the mean values rise as follows: leukocytes. 16,761 (SD: 7,787); neutrophils, 14,775 (SD: 6,643); band cells, 1,648 (SD: 1,822); and CRP, 169 (SD: 92). With PCT values > 2 ng/mL the mean values are increased as follows: leukocytes, 16,478 (SD: 8,609); neutrophils, 14,396 (SD: 8,128); band cells, 1,927 (SD: 1,629); and CRP, 192 (SD: 127).

Table 3 – Descriptive parameters of the laboratory test values related to bacterial infections and PCT† levels. Curitiba, PR, Brazil, 2021

	A (PCT† < 0.5 ng/mL)				B (PCT† from 0.5 to 2 ng/mL)				C (PCT† > 2 ng/mL)			
Variable	**M‡**	**MD§**	**SD††**	**IQR‡‡**	**M‡**	**MD§**	**SD††**	**IQR‡‡**	**M‡**	**MD§**	**SD††**	**IQR‡‡**
Total leukocytes	12,405	11,395	5,224	6,925	16,478	16,590	7,787	8,810	16,761	15,520	8,609	11,195
Neutrophils	10,884	10,029	4,714	6,115	14,775	14,988	6,643	8,112	14,396	12,400	8,128	9,507
Band cells	799	635	715	666	1,648	1,207	1,822	1,599	1,927	1,457	1,629	2,656
CRP§§	130	122	98	105	169	158	92	128	192	165	127	211

Test used: Fisher's test, Normality test (Shapiro-Wilk)
Note: †PCT = Serum Procalcitonin; ‡M = Mean; §MD = Median; ††SD = Standard Deviation; ‡‡IQR = Interquartile Range; §§CRP = C-Reactive Protein.
Source: The authors (2021).

Table 4 shows the frequency distribution and association of the variables of interest with the PCT values, according to the categorization proposed. There was statistical significance between the PCT serum levels and mortality. Of the total deaths, 80 (50.3%) were in patients that presented PCT serum levels ≤ 0.5 ng/mL, 49 (30.8%) in those with PCT between 0.5 and 2 ng/mL, and 30 (18.9%) in those with PCT ≥ 2 ng/mL. Considering the subgroup of 136 patients that presented PCT ≤ 0.5 ng/mL, mortality was observed in 80 (58.8%); of the 61 patients with PCT from 0.5 to 2 ng/mL, in 49 (80.3%); and, of the 34 with PCT > 2 ng/mL, in 30 (88.2%) (p<0.001).

There was statistical significance between healthcare-associated infection reported by the attending physician and the PCT levels, where PCT < 0.5 ng/mL was found in 26 (19.1%) of the patients with infection, in 27 (44.3%) with PCT from 0.5 to 2 ng/mL, and in 12 (35.3%) with PCT > 2 ng/mL (p<0.001). In the subgroup with PCT levels < 0.5 ng/mL, the bacterial agent was identified in 22 (16.2%) patients, in 23 (37.7%) with PCT from 0.5 to 2 ng/mL, and in 13 (38.2%) with PCT > 2 ng/mL (p<0.001); in addition, antimicrobials were used in 95 (69.9%) subjects from the PCT < 0.5 ng/mL subgroup, in 51 (83.6%) from the PCT from 0.5 to 2 ng/ml subgroup, and in 33 (97.1%) from the PCT > 2 ng/ml subgroup (p<0.001).

Table 4 - Frequency distribution and association of the variables of interest with the PCT† values, according to the categorization proposed. Curitiba, PR, Brazil, 2021

Variables/Covariates		A (PCT† < 0.5 ng/mL)			B (PCT† from 0.5 to 2 ng/mL)				C (PCT† > 2 ng/mL)				
	n‡	%row§	%col††	%total	n‡	%row§	%col††	%total	n‡	%row§	%col††	%total	p-value
Gender	Female	63	60	46.3	27.3	26	24.8	42.6	11.3	16	15.2	47.1	6.9	0.871
	Male	73	57.9	53.7	31.6	35	27.8	57.4	15.2	18	14.3	52.9	7.8	
Outcome	Not death	56	77.8	41.2	24.2	12	16.7	19.7	5.2	4	5.6	11.8	1.7	<0.001
	Death	80	50.3	58.8	34.6	49	30.8	80.3	21.2	30	18.9	88.2	13	
HAI‡‡	No	110	66.3	80.9	47.6	34	20.5	55.7	14.7	22	13.3	64.7	9.5	<0.001
	Yes	26	40	19.1	11.3	27	41.5	44.3	11.7	12	18.5	35.3	5.2	
IC§§	No	81	59.6	59.6	35.1	38	27.9	62.3	16.5	17	12.5	50	7.4	0.49
	Yes	55	57.9	40.4	23.8	23	24.2	37.7	10	17	17.9	50	7.4	
Topography	Bloodstream infection	2	28.6	1.5	0.9	3	42.9	4.9	1.3	2	28.6	5.9	0.9	0.036
	No	52	75.4	38.2	22.5	13	18.8	21.3	5.6	4	5.8	11.8	1.7	
	Skin - Soft parts	1	100	0.7	0.4	0	0	0	0	0	0	0	0	
	Pulmonary	78	53.4	57.4	33.8	41	28.1	67.2	17.7	27	18.5	79.4	11.7	
	Urine	3	37.5	2.2	1.3	4	50	6.6	1.7	1	12.5	2.9	0.4	
Isolated bacterium	No	114	65.9	83.8	49.4	38	22	62.3	16.5	21	12.1	61.8	9.1	<0.001
	Yes	22	37.9	16.2	9.5	23	39.7	37.7	10	13	22.4	38.2	5.6	
Antibiotic use	No	41	78.8	30.1	17.7	10	19.2	16.4	4.3	1	1.9	2.9	0.4	<0.001
	Yes	95	53.1	69.9	41.1	51	28.5	83.6	22.1	33	18.4	97.1	14.3	

Note: †PCT = Serum procalcitonin; ‡n = Number of patients in the subgroup; §%row = Value in each row as a percentage of the row total; ††%col = Percentages in the columns, that is, adding up to 100% in the column category; ‡‡HAI = Healthcare-Associated Infection; §§IC = Infection confirmed by ANVISA criteria.
Source: The authors (2021).

DISCUSSION

A cross-sectional study carried out with 93 patients from an ICU in southern Brazil, aimed at describing the profile of the patients hospitalized due to COVID-19 and evaluating which variables were related to mortality. 50.5% of the patients were male, with a mortality rate of 69.3%[24].

In March 2021, the *National Institute for Health and Care Excellence* pointed to the occurrence of bacterial coinfection in approximately eight percent (8%) of the people with COVID-19[4]. A meta-analysis, which aimed at assessing the proportion of patients with bacterial, fungal and/or viral coinfection, evidenced that seven percent (7%) of the hospitalized patients due to COVID-19 had a bacterial coinfection; this proportion increases to 14% in studies that only included patients admitted to the ICU[3].

A systematic review with meta-analysis was carried out with 14 studies and a total sample of 3,492 patients, with the objective of investigating the association between PCT and COVID-19. From the analyses of the studies, rates of secondary bacterial infections ranging from 4.7% to 19.5% were observed, which were associated with an increased risk of severe progression or fatal outcomes (OR: 20.8; 95% CI: from 11.6 to 37.4)[25].

The bacteria isolation procedure performed in the preliminary analysis of a prospective cohort study conducted in France[26] observed values below 40.6%, detected through a CRP panel (bacteria, viruses and antimicrobial resistance genes), in samples of the lower respiratory tract of 32 COVID-19 patients.

The *op. cit* French study aimed at investigating bacterial coinfection in patients critically affected by COVID-19, through rapid molecular testing and measurement of its impact on management of the antibiotic therapy. The authors conclude that the identification of bacteria is essential to evaluate coinfection in COVID-19 in ICUs. Use of molecular diagnostic tools and initiation of narrow-spectrum antibiotics are key elements of the antimicrobial management guidelines for COVID-19 in critically-ill patients[26].

Antibiotic use at the beginning of the pandemic exceeded 80% of the COVID-19 patients[5]. There are even studies in which these rates exceed 90%[8,10].

A cohort with a sample of 1,705 patients hospitalized due to COVID-19 from 38 hospitals in Michigan (USA), selected between March 13th and June 18th, 2020, observed 3.5% prevalence of infections, although 56.6% received early empirical antibacterial therapy. In all the hospitals, initial use of empiric antibacterials varied from 27% to 84%[27].

In a retrospective study conducted with 73 COVID-19 patients in two US emergency departments, the overall antimicrobial prescription rate was 37%. A possible explanation for the low prescription rates was the use of rapid PCT to guide the empirical antibiotic decision. Of the 32 patients who had their PCT result available before the antibiotic prescription was given, 25% received antibiotics when compared to 46.3% of those who did not undergo the PCT test or whose result was only available after the antibiotic request (-21.3%; 95% CI: from -42.74% to -0.06%, p=0.061)[18].

The prescription of antibiotics in relation to the PCT serum values was verified in the current study. In the patients diagnosed with infection, there was no prescription of antimicrobials in 6.2%, 20% used them and their use was suspended, and 73.8% used them and their use was not suspended. On the other hand, in the patients without an infection diagnosis, only 28.9% did not use antibiotics, 38% used them and their use was suspended, and 33.1% used them and their use was not suspended. Non-suspension of the antimicrobials, mainly in the group without infection, may have been due to therapeutic obstinacy of the care teams, in view of the severity of the cases.

A retrospective study, conducted in the United Kingdom with 118 patients with mild to moderate COVID-19 (non-ICU), aimed at suspending the antimicrobial with a PCT cutoff point < 0.25 ng/mL. The results showed that, in 72.5% of the cases, the antibiotic was not initiated and/or it was interrupted within 48 hours[17].

A retrospective study also conducted in the United Kingdom with a sample of 368 COVID-19 patients aimed at evaluating prescription of antimicrobials, mortality and ICU admission. In the analyses, using a PCT cutoff point of 0.25 ng/mL, the researchers observed that 33% (n=73) of the patients from the negative PCT group (PCT ≤ 0.25 ng/mL) were using antibiotics 48 hours after the COVID-19 diagnosis, when compared to 126 (84%) patients from the positive PCT group (PCT ≥ 0.25 ng/mL) (p≤0.001), which suggests good compliance with the guideline for reducing the prescription of antimicrobials, with no increase in mortality[19].

In the secondary analysis of a multicenter prospective observational study conducted at 148 ICUs in Spain, the presence of lower PCT levels proved to have a negative predictive value of 94% for bacterial coinfection in ICU patients with confirmed Influenza A (H1N1). According to the authors, this may demonstrate that low PCT serum levels can be a good tool to rule out the presence of bacterial coinfection[28].

In a study carried out in the Netherlands with data obtained from the *Good Clinical Practice - Compliant data management system Castor*, the PCT value to identify secondary infections was demonstrated in an analysis of 66 critically-ill patients. Although the CRP and PCT levels were high in many patients at the initial presentation, secondary increases were associated with superinfections exacerbating COVID-19. This effect was particularly different for PCT[29].

The *COVID-19 rapid guidelines recommendation* from *The National Institute for Health and Care Excellence* (NICE) suggest that elevated CRP levels do not necessarily indicate that pneumonia is caused by bacteria or SARS-CoV-2. However, lower C-Reactive Protein levels indicate that a secondary bacterial infection is less likely[4].

Serum procalcitonin levels can signal the extent of the bacterial infectious process, which, when not diagnosed and treated, can progress to major complications such as sepsis and/or death. This scenario represents the main cause of death in ICUs and the increase in the procalcitonin serum levels might predict deterioration of the clinical condition. PCT can be relevant in the diagnosis of coinfections and in de-escalation and discontinuation of antimicrobials, as well as in prognosis. Health professionals should work in a transdisciplinary way, seeking beneficial advances for patients affected by COVID-19.

The limitations of this study include the fact that it was carried out in a single center and with a retrospective cross-sectional design, not allowing generalizations or causal relationship between the variables of interest. Although the study showed an association between PCT and antimicrobial use, it was not possible to determine whether it was only the PCT result that directed the clinical practice in relation to the administration of antimicrobials since, in these cases, both the clinical condition and other infection markers may have affected the decision.

CONCLUSION

PCT can be a useful tool in detecting bacterial coinfection in patients with severe COVID-19. The results allow asserting that procalcitonin can reduce empirical antimicrobial use and stimulate detection and identification of pathogens, taking into account the clinical and epidemiological data.

It is indispensable to continuously analyze data and encourage research studies on procalcitonin, with the objective of optimizing the clinical management of individuals with viral infections such as COVID-19, in addition to dissemination of the use of this biomarker by health professionals.

PCT should be evaluated within a concept of antimicrobial use clinical management, especially prioritizing the activities carried out by an interdisciplinary team, duly trained and with a common language, thus contributing more safety to the care provided to hospitalized patients.

REFERENCES

1. Wright B, Anderson D, Whitaker R, Shrader P, Bettger JP, Wong C, *et al.* Comparing health care use and costs among new Medicaid enrollees before and during the COVID-19 pandemic. BMC Health Serv Res [Internet]. 2021 [cited on 2022 Apr. 28]; 21(1):1152. Available in: https://bmchealthservres.biomedcentral.com/articles/10.1186/s12913-021-07027-6.

2. Henry BM, Oliveira MHS de, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. Clin Chem Lab Med [Internet]. 2020 [cited on 2022 Apr. 28]; 58(7):1021–8. Available in: https://www.degruyter.com/document/doi/10.1515/cclm-2020-0369/html.

3. Lansbury L, Lim B, Baskaran V, Lim WS. Co-infections in people with COVID-19: a systematic review and meta-analysis. J Infect [Internet]. 2020 [cited on 2022 Apr. 28]; (2):266–75. Available in: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7255350/pdf/main.pdf.

4. Shah W, Hillman T, Playford ED, Hishmeh L. Managing the long term effects of covid-19: summary of NICE, SIGN, and RCGP rapid guideline. BMJ [Internet]. 2021 [cited on 2022 Apr. 28];136. Available in: https://www.bmj.com/content/bmj/372/bmj.n136.full.pdf.

5. Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, *et al*. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. BMJ [Internet]. 2020 [cited on 2022 Apr. 28];1985. Available in: https://www.bmj.com/content/bmj/369/bmj.m1985.full.pdf.

6. Stegeman I, Ochodo EA, Guleid F, Holtman GA, Yang B, Davenport C, *et al*. Routine laboratory testing to determine if a patient has COVID-19. Cochrane Database Syst Rev [Internet]. 2020 [cited on 2022 Apr. 28];(11). Available in: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013787/epdf/full.

7. Nazerian P, Gagliano M, Suardi LR, Fanelli A, Rossolini GM, Grifoni S. Procalcitonin for the differential diagnosis of COVID-19 in the emergency department. Prospective monocentric study. Intern Emerg Med [Internet]. 2021 [cited on 2022 Apr. 28]; 16(6):1733–5. Available in: https://link.springer.com/content/pdf/10.1007/s11739-021-02641-y.pdf.

8. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J. Clinical characteristics of 138 hospitalized patients Wwith 2019 novel Coronavirus–Infected pneumonia in Wuhan, China. JAMA [Internet]. 2020 [cited on 2022 Apr. 28]; 323(11):1061. Available in: https://jamanetwork.com/journals/jama/fullarticle/2761044.

9. Zhang J-J, Dong X, Cao Y-Y, Yuan Y-D, Yang Y-B, Yan Y-Q, *et al*. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy [Internet]. 2020 [cited on 2022 Apr. 28]; 75(7):1730–41. Available in: https://onlinelibrary.wiley.com/doi/10.1111/all.14238.

10. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, *et al*. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet [Internet]. 2020 [cited on 2022 Apr. 28]; 395(10223):497–506. Available in: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7159299/pdf/main.pdf.

11. Müller B, Harbarth S, Stolz D, Bingisser R, Mueller C, Leuppi J, *et al*. Diagnostic and prognostic accuracy of clinical and laboratory parameters in community-acquired pneumonia. BMC Infect Dis [Internet]. 2007 [cited on 2022 Apr. 28]; 7(1):10. Available in: https://bmcinfectdis.biomedcentral.com/track/pdf/10.1186/1471-2334-7-10.pdf.

12. Seaton RA, Gibbons CL, Cooper L, Malcolm W, McKinney R, Dundas S, *et al*. Survey of antibiotic and antifungal prescribing in patients with suspected and confirmed COVID-19 in Scottish hospitals. J Infect [Internet]. 2020 [cited on 2022 Apr. 28]; 81(6):952–60. Available in: https://www.journalofinfection.com/action/showPdf?pii=S0163-4453%2820%2930616-2.

13. Hu R, Han C, Pei S, Yin M, Chen X. Procalcitonin levels in COVID-19 patients. Int J Antimicrob Agents [Internet]. 2020 [cited on 2022 Apr. 28]; 56(2):106051. Available in: https://www.sciencedirect.com/science/article/pii/S0924857920302211.

14. Lippi G, Plebani M. Procalcitonin in patients with severe coronavirus disease 2019 (COVID-19): a meta-analysis. Clin Chim Acta [Internet]. 2020 [cited on 2022 Apr. 28]; 505:190–1. Available in: https://www.sciencedirect.com/science/article/pii/S0009898120301066.

15. Heesom L, Rehnberg L, Nasim-Mohi M, Jackson AIR, Celinski M, Dushianthan A, *et al.* Procalcitonin as an antibiotic stewardship tool in COVID-19 patients in the intensive care unit. J Glob Antimicrob Resist [Internet]. 2020 [cited on 2022 Apr. 28]; 22:782–4. Available in: https://www.sciencedirect.com/science/article/pii/S2213716520301922.

16. Ashiru-Oredope D, Kerr F, Hughes S, Urch J, Lanzman M, Yau T, *et al*. Assessing the impact of COVID-19 on antimicrobial stewardship activities/programs in the united Kingdom. Antibiotics [Internet]. 2021 [cited on 2022 Apr. 28]; 10(2):110. Available in: https://www.mdpi.com/2079-6382/10/2/110/htm.

17. Peters C, Williams K, Un EA, Little L, Saad A, Lendrum K, *et al.* Use of procalcitonin for antibiotic stewardship in patients with COVID-19: a quality improvement project in a district general hospital. Clin Med (Northfield Il) [Internet]. 2021 [cited on 2022 Apr. 28]; 21(1):e71–6. Available in: https://www.rcpjournals.org/

lookup/doi/10.7861/clinmed.2020-0614.

18. Pulia MS, Wolf I, Schwei RJ, Chen D, Lepak AJ, Schulz LT, *et al.* Antibiotic prescribing patterns for coronavirus disease 2019 (COVID-19) in two emergency departments with rapid procalcitonin. Infect Control Hosp Epidemiol [Internet]. 2021 [cited on 2022 Apr. 28]; 42(3):359–61. Available in: https://www.cambridge.org/core/product/identifier/S0899823X2001329X/type/journal_article.

19. Williams EJ, Mair L, Silva TI de, Green DJ, House P, Cawthron K, *et al.* Evaluation of procalcitonin as a contribution to antimicrobial stewardship in SARS-CoV-2 infection: a retrospective cohort study. J Hosp Infect [Internet]. 2021 [cited on 2022 Apr. 28]; 110:103–7. Available in: https://linkinghub.elsevier.com/retrieve/pii/S0195670121000232.

20. Kamat IS, Ramachandran V, Eswaran H, Guffey D, Musher DM. Procalcitonin to distinguish viral from bacterial pneumonia: a systematic review and meta-analysis. Clin Infect Dis [Internet]. 2020 [cited on 2022 Apr. 28]; 70(3):538–42. Available in: https://academic.oup.com/cid/article/70/3/538/5523199.

21. Wolfisberg S, Gregoriano C, Schuetz P. Procalcitonin for individualizing antibiotic treatment: an update with a focus on COVID-19. Crit Rev Clin Lab Sci [Internet]. 2022 [cited on 2022 Apr. 28]; 59(1):54–65. Available in: https://www.tandfonline.com/doi/full/10.1080/10408363.2021.1975637.

22. Agência Nacional de Vigilância Sanitária. Critérios diagnósticos de infecção relacionada à assistência à saúde [Internet]. 2. ed. Brasília-DF: Agência Nacional de Vigilância Sanitária; 2017 [cited on 2022 Apr. 28]. Available in: http://www.saude.mt.gov.br/upload/controle-infeccoes/pasta5/novo/novos_criterios_diagnosticos_nacionais_iras_2017.pdf.

23. R Core Team. The R project for statistical computing [Internet]. R project. 2021 [cited on 2022 Apr. 28]. Available in: https://www.R-project.org/.

24. Kruger AR, Vier C da V, Saute AABQ, Kreutz DNM, Kunst L, Miltersteiner D da R, *et al.* Perfil epidemiológico de pacientes com COVID-19 em UTI de hospital de referência do sul do Brasil: a idade como fator de risco para pior desfecho. Res Soc Dev [Internet]. 2022 [cited on 2022 Aug. 09];11(2):e57611225672. Available in: https://rsdjournal.org/index.php/rsd/article/view/25672.

25. Vazzana N, Dipaola F, Ognibene S. Procalcitonin and secondary bacterial infections in COVID-19: association with disease severity and outcomes. Acta Clin Belg [Internet]. 2022 [cited on 2022 Apr. 28]; 77(2):268–72. Available in: https://www.tandfonline.com/doi/full/10.1080/17843286.2020.1824749.

26. Verroken A, Scohy A, Gérard L, Wittebole X, Collienne C, Laterre P-F. Co-infections in COVID-19 critically ill and antibiotic management: a prospective cohort analysis. Crit Care [Internet]. 2020 [cited on 2022 Apr. 28]; 24(1):410. Available in: https://ccforum.biomedcentral.com/articles/10.1186/s13054-020-03135-7.

27. Vaughn VM, Gandhi TN, Petty LA, Patel PK, Prescott HC, Malani AN, *et al.* Empiric antibacterial therapy and community-onset bacterial coinfection in patients hospitalized with Coronavirus Disease 2019 (COVID-19): a multi-hospital cohort study. Clin Infect Dis [Internet]. 2021 [cited on 2022 Apr. 28]; 72(10):e533–41. Available in: https://academic.oup.com/cid/article/72/10/e533/5895253.

28. Rodríguez AH, Avilés-Jurado FX, Díaz E, Schuetz P, Trefler SI, Solé-Violán J, *et al.* Procalcitonin (PCT) levels for ruling-out bacterial coinfection in ICU patients with influenza: a CHAID decision-tree analysis. J Infect [Internet]. 2016 [cited on 2022 Apr. 28]; 72(2):143–51. Available in: https://linkinghub.elsevier.com/retrieve/pii/S0163445315003722.

29. Berkel van M, Kox M, Frenzel T, Pickkers P, Schouten J. Biomarkers for antimicrobial stewardship: a reappraisal in COVID-19 times? Crit Care [Internet]. 2020 [cited on 2022 Apr. 28]; 24(1):600. Available in: https://ccforum.biomedcentral.com/articles/10.1186/s13054-020-03291-w.

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