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Original article

COMPARATIVE ANALYSIS OF PROCALCITONIN KINETICS BETWEEN THE FIRST AND SECOND INFECTIOUS EVENTS IN THE INTENSIVE CARE UNIT

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Abstract

Introduction: Sepsis arises from a dysregulated host response to infection. After the initial hyperinflammatory phase, some patients may develop sepsis-induced immunosuppression, predisposing them to new infectious episodes whose immunological behavior remains poorly understood. Procalcitonin (PCT) is a widely used biomarker in sepsis management, but its kinetics during recurrent infections have not been systematically evaluated.

Materials and methods: Retrospective cohort study at a tertiary university hospital in Argentina, including adult intensive care unit patients who experienced two infectious events separated by 7 to 30 days. PCT levels and SOFA scores were analyzed using mixed-effects models, adjusting for infection source, bacterial isolation, and renal function.

Results: 55 patients met inclusion criteria. During the first infectious event, PCT levels were significantly higher: 42.13 pg/mL (95% CI 33.59–50.67) and showed a rapid daily decline of 5 pg/mL (95% CI –5.9 to –4; p<0.01). In contrast, the second event showed lower PCT peaks: 32.47 pg/mL (–9.66 pg/mL difference; p<0.01) and a slower decline (interaction coefficient 1.45; p=0.04). Organ dysfunction was greater during the first event, with higher delta SOFA scores compared to the second median 5 vs. 2 (coefficient –2.53; p<0.01).

Conclusion: These findings show distinct PCT kinetics between initial and subsequent infectious episodes, suggesting attenuated inflammatory responses and reduced organ dysfunction during the second event. The observed alteration in PCT values could reflect a change in the dynamics of the immune response secondary to the first infectious event.

Key words: sepsis, procalcitonin, organ dysfunction scores, intensive care units, kinetics

Resumen

Análisis comparativo de la cinética de la procalcitonina entre el primer y segundo evento infeccioso en la unidad de cuidados intensivos

Introducción: La sepsis se caracteriza por una respuesta desregulada frente a una infección. Tras una fase inicial hiperinflamatoria, los pacientes pueden desarrollar inmunosupresión inducida por sepsis, lo que los predispone a nuevos episodios infecciosos. La procalcitonina (PCT) es un biomarcador ampliamente utilizado en el manejo de la sepsis, aunque su cinética durante infecciones recurrentes no ha sido evaluada sistemáticamente.

Materiales y métodos: Estudio de cohorte retrospectivo en un hospital universitario de alta complejidad en Argentina, que incluyó pacientes adultos de terapia intensiva con dos episodios infecciosos separados entre 7 y 30 días. Se analizaron los valores de PCT y las puntuaciones de SOFA mediante modelos mixtos, ajustando.

Resultados: Se incluyeron 55 pacientes. Durante el primer evento infeccioso, los niveles de PCT fueron significativamente más altos 42.13 pg/mL (IC95% 33.59–50.67) y mostraron un descenso diario más rápido de 5 pg/mL (IC95% –5.9 a –4; p<0.01). En el segundo evento, los valores pico fueron menores 32.47 pg/mL (–9.66; p<0.01) y el descenso más lento (coeficiente de interacción 1.45; p=0.04). La disfunción orgánica, medida por delta SOFA, fue más grave en el primer evento, mediana de 5 vs. 2 (coeficiente -2.53 [IC95% -2.75/-2.3]; p<0.01).

Conclusión: Las cinéticas de PCT son diferentes entre el primero y el segundo episodio infeccioso, con menor respuesta inflamatoria y menor disfunción orgánica en el segundo.

Palabras clave: sepsis, procalcitonina, disfunción orgánica, unidades de cuidados intensivos, cinética

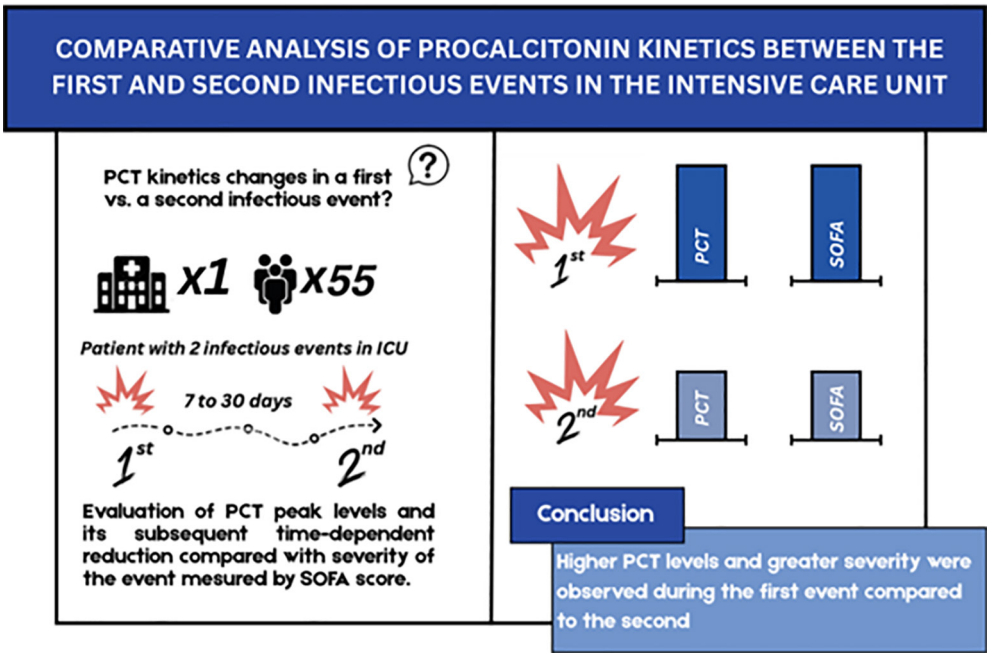
KEY POINTS
Current knowledge

- Procalcitonin (PCT) is a widely used biomarker for infection diagnosis, prognosis, and, most importantly, for guiding antibiotic discontinuation. However, its kinetics during subsequent infectious episodes has not yet been investigated.

Contribution of the article to current knowledge

- This study describes a distinct PCT kinetic pattern between the first and second infectious episodes. The second event was characterized by lower serum PCT levels and a slower daily decline, findings that may challenge current assumptions about PCT behavior reported in the literature, especially during subsequent infectious episodes.

Graphical abstract



PCT: procalcitonin; ICU: intensive care unit; SOFA: Sequential Organ Failure Assessment

Sepsis is a life-threatening syndrome characterized by organ dysfunction resulting from a dysregulated host response to infection[1]. In its early stages, sepsis is dominated by an exaggerated pro-inflammatory reaction that frequently culminates in multiorgan dysfunction and septic shock. This hyperinflammatory phase is subsequently followed by a compensatory but dysregulated anti-inflammatory state. When persistent, this immunological imbalance predisposes patients to a second stage, in which new infectious episodes further aggravate the clinical course and increase the risk of mortality[2-4].

The mechanisms underlying this phenomenon, known as sepsis-induced immunosuppression, involve profound alterations in both innate and adaptive immunity. Key mechanisms include the excessive release of anti-inflammatory cytokines such as IL-10 and TGF-β, severe lymphopenia with loss of immune effector cells, decreased expression of HLA-DR on monocytes, and upregulation of inhibitory costimulatory molecules[5-7]. Collectively, these processes impair the host's ability to mount effective immune responses against secondary pathogens, generating a predominantly anti-inflammatory environment.

This observation suggests that immune responses differ significantly between the first and subsequent infectious insults, potentially modifying the kinetics and diagnostic performance of biomarkers currently employed for clinical decision-making. Among these, procalcitonin (PCT) has emerged as one of the most extensively studied and clinically applied. PCT is strongly associated with the severity of systemic inflammation, with elevated concentrations correlating with severe sepsis and multiorgan dysfunction[8-10]. Furthermore, declining PCT levels have been linked to infection resolution, making it a valuable tool not only for diagnosis but also for prognostication and therapeutic monitoring[11,12].

Despite its broad clinical use, the role of PCT in the context of recurrent infections remains poorly defined. To date, no study has systematically evaluated its performance in subsequent infectious events. Addressing this knowledge gap is of particular relevance, given the increasing recognition that immune and inflammatory responses during a second infectious hit may differ substantially from those observed during the initial episode.

Accordingly, the present study aims to retrospectively analyze a cohort of intensive care unit patients who experienced two infectious episodes. Specifically, we seek to describe and compare the kinetics of PCT between the first and second events, with the goal of determining whether its behavior differs across episodes and whether these differences hold potential implications for diagnosis, prognosis, and patient monitoring in sepsis.

Materials and methods

Design and setting

We conducted a retrospective cohort study at a high-complexity university hospital in Argentina, specifically at the *Hospital Italiano de Buenos Aires* (HIBA). Data were collected using the Electronic Health Record (EHR). HIBA is a third-level university hospital located in the *Ciudad Autónoma de Buenos Aires*, Argentina, equipped with 750 beds and 38 critical care beds dedicated to adult patients.

Institutional Review Board approval (Ethics Committee of the Hospital Italiano de Buenos Aires # 4009) was obtained, and the requirement for informed consent was waived. Data were collected retrospectively for any events that occurred before obtaining this approval. This manuscript adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Participants

We evaluated patients hospitalized in the Intensive Care Unit (ICU) from January 1st, 2016 to October 1st, 2019. We included adult patients (18 years and older) who suffered two infectious events separated by a time interval of at least one week and a maximum of 30 days were included. Sepsis and septic shock were defined according to current guidelines[1]. Patients with less than 3 PCT determinations in a period of 7 days, chronic infections due to abscesses, endocarditis or tuberculosis were excluded.

Variables

Variables analyzed were age, APACHE II and Charlson score, condition at hospital discharge, Length of Stay (LOS) in ICU and Hospital. The higher PCT value recorded during sepsis onset was selected and successive PCT values were collected up to a maximum of 10 days. Sequential Organ Failure Assessment (SOFA) baseline[1] was calculat-

ed 24 hours before the septic event with the last laboratory recorded in the EHR. Subsequently, the SOFA score$_1$ at the time of the septic event was calculated, as well as the maximum dose of vasopressors reached in that 24-hour period. Subsequently, the SOFA$_2$ prior to the second infectious event and at the time of the septic episode was calculated following the same characteristics described for the first septic event, as well as the maximum dose of vasopressors reached.

Also the potential confounders in the kinetic of procalcitonine were recorded, such as bacterial isolation (categorized as Gram-positive bacteria, Gram-negative bacteria, and without isolation), creatinine clearance was calculated using the Cockroft-Gault formule, and also source of infection (categorized in: lung, abdominal, intravascular, urinarium, skin and soft-tissue and other)[13-15].

Statistical methods

Categorical variables were presented as proportions and absolute numbers, while numerical variables were reported as either median and Interquartile Range (IQR) or mean and Standard Deviation (SD) depending on their distribution.

To assess the relationship between PCT and delta SOFA in the first vs. second hit within the same patient, a linear mixed model was employed. Mixed models are particularly well-suited for accounting for within-cluster dependencies among patients[16]. These models are also capable of accommodating dependencies between repeated measurements. Consequently, the initial model to evaluate PCT kinetics incorporated random effects for (a) variability between individuals in terms of repeated measures, and (b) variability among individuals within the first and second hits. The second model to evaluate delta SOFA as continuous variable only incorporates random effects for variability among individuals within the first and second hits. The correlation matrix structure utilized in the model was unstructured[17].

Variables evaluated as potential confounders were bacterial isolation, source of infection, and creatinine clearance. A significance level of $\alpha = 0.05$ was applied to all models and tests. The statistical analysis was conducted using STATA V. 16.

Results

We included 55 patients who experienced two distinct infectious episodes during their intensive care unit (ICU) stay. Among them, 60% were male, with a mean age of 60.5 years. The median time from ICU admission to the first infectious event was 4.0 days [interquartile range (IQR) 0.0–8.0], and the interval between the first and second episodes was 11.0 days [IQR 8.0–15.0]. The primary reason for admission to the ICU was non-surgical in 50.9% of cases (n=28). The median hospital length of stay was 30 days [IQR 20.5;58.5], with an in-hospital mortality rate of 43.6% (n=24) (Table 1).

When analyzing the sources of infection during both the first and second infectious events, abdominal infections were the most frequent, accounting for 49.1% (n=27) and 32.7% (n=18) of cases, respectively. Respiratory infections followed closely, with a prevalence of 25.5% (n=14)

Table 1 | Baseline demographic and clinical characteristics of the study population

Variables	All (N=55)
Gender male[1]	33 (60.0)
Age[2]	60.5 (17.3)
Charlson score[3]	5.00 [2.00;7.00]
APACHE score[2]	19.0 (7.43)
Non surgical ICU admission[1]	28 (50.9)
Days to the first infectious event[3]	4.00 [0.00;8.00]
Days between first and second infectious events[3]	11.00 [8.00;15.00]
ICU LOS[3]	30.0 [20.5;58.5]
Hospital LOS[3]	42.0 [30.0;78.5]
In-hospital mortality[1]	24 (43.6)

ICU: intensive care unit; LOS: length of stay
[1]*Continuous variable - n (%)*
[2]*Continuous variables with normal distribution are expressed as mean ± standard deviation (SD)*
[3]*Non-normally distributed continuous variables are expressed as median [interquartile range (IQR)]*

in the first event and 29.1% (n=16) in the second. Gram-negative bacteria were the most commonly isolated pathogens in both infectious events, accounting for 40% (n=22) and 49.1% (n=27) of cases, respectively (Table 2).

Regarding initial PCT levels, the median concentration during the first infectious episode was 24.2 ng/mL (IQR 8.71-52.6), compared with 12.0 ng/mL (IQR 3.47-20.8) during the second episode (p = 0.005) (Table 2). The median number of PCT determinations was 5 [IQR 4-6] during the first infectious event and 4 [IQR 3–5.5] during the second event, The proportion of missing data in daily procalcitonin measurements is presented in Table S1 (Supplementary Material). PCT kinetics are shown in Figure 1.

In the mixed effects model, which was adjusted for sources of infection, bacterial isolation, and creatinine clearance, the first hit exhibited a PCT coefficient of 42.13 pg/mL (IC95% 33.59 - 50.67), presented by the constant in the model. However, in the second hit, the peak PCT value was significantly lower, 32.47 pg/mL (coefficient -9.66 [-15 / -4] pg/mL; p<0.01). Additionally, the time coefficient indicated a daily decrease in PCT was 5 pg/mL (95% CI -5.9/-4; p<0.01) pg/mL during the first hit. Notably, this decline was significantly less pronounced during the second hit (coefficient interaction term second hit* days 1.45 [95% CI 0.3 / 2.8]; p=0.04) (Table 3).

Regarding delta SOFA, the median value during the first infectious episode was 5 (IQR 3.50–7.50), whereas during the second episode it was 2 (IQR 1.00-4.00). In the mixed-effects model, after adjusting for infection source and bacterial isolation, the second hit was associated with a significantly lower delta SOFA compared with the first hit (coefficient for second hit: –2.53 [95% CI –2.75 to –2.30]; p < 0.01) (Fig. 2).

Table 2 | Differences between first and second hit

	First hit (N=55)	Second hit (N=55)
Source of infection		
Abdominal[1]	27 (49.1)	18 (32.7)
Endovascular[1]	4 (7.3)	5 (9.1)
Respiratory[1]	14 (25.5)	16 (29.1)
Unknown[1]	4 (7.3)	11 (20.0)
Urinary[1]	4 (7.3)	5 (9.1)
Other[1]	2 (3.6)	0 (0.0)
Isolation:		
Gram-negative bacteria[1]	22 (40.0)	27 (49.1)
Gram-positive bacteria[1]	13 (23.6)	1 (1.8)
Negative cultures[1]	20 (36.4)	27 (49.1)
Creatinine Clearance[2]	57.3 (35.2)	61.9 (37.5)
Hemodialysis[1]	10 (18.2)	12 (21.8)
PCT peak (pg/dL)[3]	24.2 [8.7;52.6]	12.0 [3.5;20.8]
Number of total PCT determinations[3]	5 [4–6]	4 [3–5.5]
SOFA score[3]	7.0 [5.0;9.5]	5.0 [3.0;8.0]
Basal SOFA score[3]	1.0 [0.0;3.0]	3.0 [1.0;5.0]
Delta SOFA score[3]	5.0 [3.5;7.5]	2.0 [1.0;4.0]

PCT: procalcitonin
PCT peak (The median value of PCT during the infectious event; SOFA score (Secuential Organ Failurre Assessment) represents the median value during the infectious event; Basal SOFA score represents the median value during the 24 hours preceding the infectious event. Delta SOFA score represents the change in SOFA score from baseline to the time of the infectious event
[1]*Continuous variable - n (%)*
[2]*Continuous variables with normal distribution are expressed as mean ± standard deviation (SD)*
[3]*Non-normally distributed continuous variables are expressed as median [interquartile range (IQR)]*

Figure 1 | Procalcitonin *median [interquartile range (IQR)]* during first and second septic hit

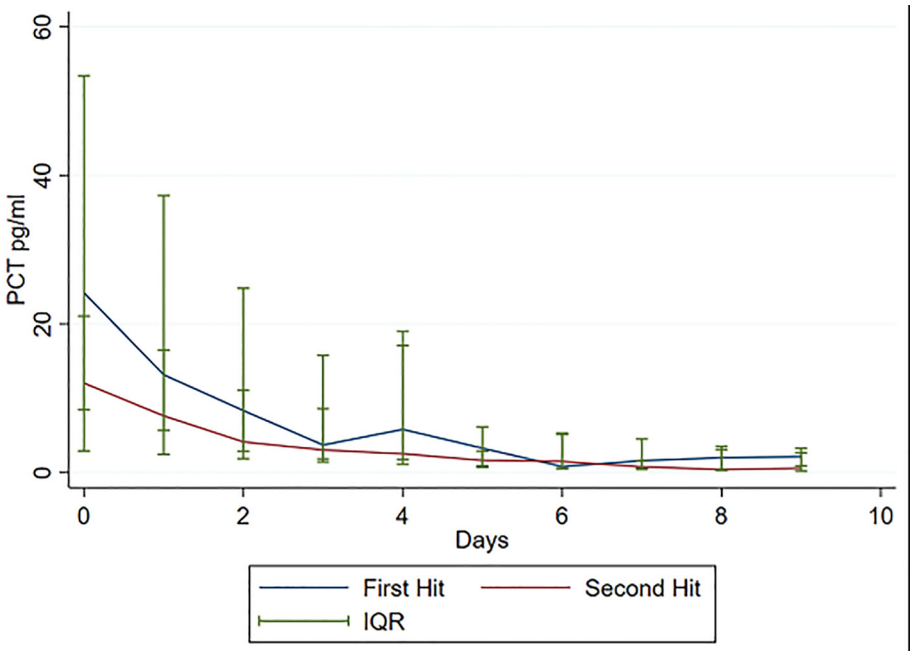
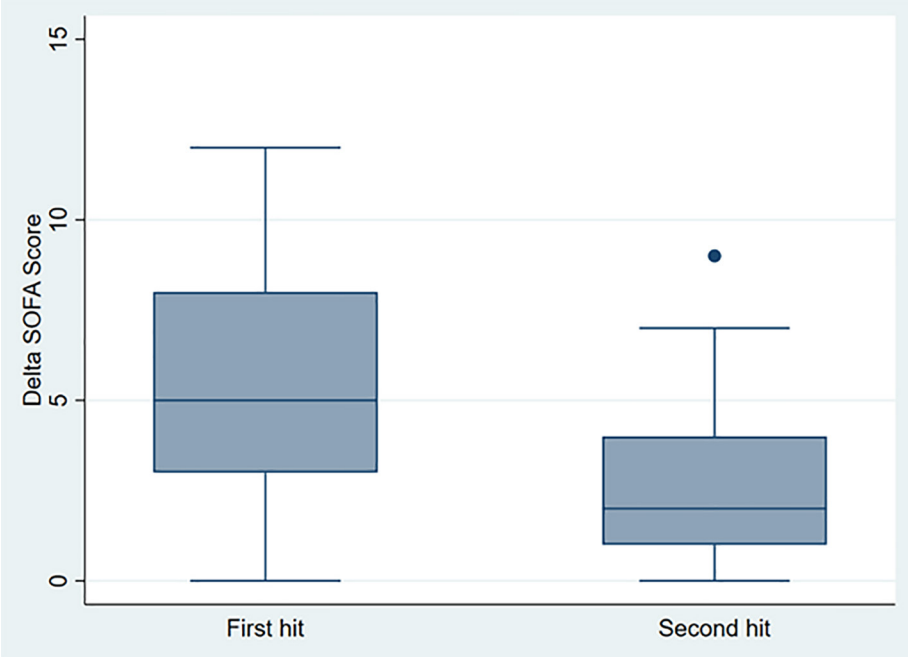


Tabla 3 | Coefficients of procalcitonin levels over days and SOFA score in the first and second hit in the unadjusted and adjusted mixed effect model

Variable	Coefficient	p value
	PCT over time unadjusted model	
Constant	33.8 (95%CI 27.9 - 39.6)	<0.001
Second hit	-11.8 (95%CI -17.4 - -6.1)	<0.001
Days	-4.9 (95%CI -5.8 - -3.9)	<0.001
Interaction term second hit* days	1.2 (95%CI -0.2 - 2.6)	0.101
	PCT over time adjusted model	
Constant	42.1 (95%CI 33.6 - 50.7)	0.001
Second Hit	-9.7 (95%CI -15.4 - -3.9)	0.001
Days	-5.0 (95%CI -5.95 - -4.1)	0.001
Interaction term second hit* days	1.5 (95%CI 0.04 - 2.9)	0.045
	SOFA unadjusted model	
Constant	5.4 (95%CI 4.9 - 5.9)	<0.001
Second hit	-3 (95%CI -3.2 - -2.8)	<0.001
	SOFA adjusted model	
Constant	5.6 (95%CI 4.9 - 6.2)	<0.001
Second hit	-2.5 (95%CI -2.8 - -2.3)	<0.001

PCT: procalcitonin
The constant in this table represents the peak value of PCT during the first hit, while the coefficient for the second hit signifies the difference in peak PCT values between the first and second hits. The coefficient for days represents the rate of reduction in PCT values per day during the first hit. Additionally, the interaction term (second hit days) represents the variance in daily PCT reduction between the first hit and the second hit. Models were adjusted for bacterial isolation, source of infection, and creatinine clearance at the time of the infectious event*

Figure 2 | Delta SOFA score during first and second septic hit



Discussion

In our study we evaluated a specific population of critically ill patients who survived an initial septic episode and subsequently developed a second infectious event during their ICU stay. The complexity of this subgroup is reflected in their prolonged length of stay and high mortality, which exceed those reported in general sepsis cohorts that do not distinguish patients with recurrent infections. Their elevated burden of comorbidities likely contributes further to this increased mortality risk.

Regarding the primary objective of the study, we observed distinct patterns in the kinetics of PCT between the first and second infectious events. During the initial episode, patients exhibited markedly higher PCT peak levels and a more rapid decline over time, whereas the second event was characterized by significantly lower peaks and a slower rate of decrease. In parallel, greater organ dysfunction reflected by higher SOFA was observed during the first event.

Our observations are consistent with the existing research that links elevated PCT levels with increased organ dysfunction. The study conducted by Shigeto Ishikawa et al. described PCT prognostic value for organic failure among critically ill patients. Similar results were described by Takashi Shimazui et al and Michael Meisner et al.[10,18,19]. This association might be attributed to the fact that escalated PCT levels are indicative of more inflammatory burden, consequently contributing to augmented organ dysfunction. F. Bozza et al. also delved into this correlation, revealing a positive link between elevated levels of proinflammatory cytokines including IL-1B, IL-6, IL-8, IL-10, MCP-1, and G-CSF, and higher SOFA score[20].

On the other hand, second infectious events define a different scenario, characterized by diminished PCT levels aligned with lower increase in SOFA score. This phenomenon might reflect -to some extent- an underlying immunosuppressive state induced by sepsis, together with possible mechanisms of immune tolerance. Although our results do not allow definitive conclusions, several mechanisms described in the literature might provide a possible explanation for the findings observed: the attenuated expression of proinflammatory cytokines, partic-

ularly TNF, IL-1β, IL-6, and IL-12, alongside the reduction in HLA-DR expression in monocytes, produces an "anergic" state and, consequently, immunosuppression[6]. In addition, anti-inflammatory cytokines, such as IL-4, IL-10 and IL-37, dominate the environment while second infectious events take place[5]. IL-4 is a cytokine that promotes autocrine signaling through positive feed- back to produce other anti-inflammatory cytokines and inhibiting the release of proinflammatory cytokines. Similarly, IL-10 also decreases proinflammatory cytokines, including IL-2 and interferon-γ (IFN-γ) and promotes the proliferation of immunosuppressive cells, such as Tregs and MDSCs. Additionally, IL-37 in patients with sepsis is significantly upregulated, which could hinder the proliferation and release of proinflammatory cytokines and is closely related to the severity of sepsis-induced immunosuppression[5]. Although our study was retrospective in nature and measurements of proinflammatory and anti-inflammatory cytokines are not routinely performed in infected patients, our findings might provide a hypothetical explanation for the observed behavior of PCT. These results open the possibility for future studies aimed at correlating PCT dynamics with the balance of cytokine responses, potentially offering new insights into the immunological mechanisms underlying sepsis-induced immune dysregulation.

One of the strengths of this study relies on the fact that we analyzed patients with serial PCT determinations thanks to the strict inclusion criteria, also we consider that the data provided by this study is of great value, because there are few studies that have correlated PCT levels with the impact on organic dysfunction measured by the SOFA score, but this is the first study that analyzes the kinetics and behavior of PCT in a second infectious event in comparison to a first one in the same patient. Nevertheless, this rigorous criteria for inclusion, turned out to be restrictive and determined a relatively small population of study of 55 patients. The small number of patients, the single-center design of our study as well as its retrospective character are main weaknesses of this research. At the same time, a limitation is that we did not include cytokine measurements, which could have provided greater support to our hypothesis.

On the other hand, we believe that this study opens the door to further investigation of PCT kinetics in parallel with analysis of different cytokines, in order to strengthen the hypothesis regarding why this phenomenon occurs, as proposed in our discussion.

These novel findings not only expand our understanding of PCT's role but also open up promising avenues for further research and important clinical implications.

In conclusion, the initial infectious event triggers a robust inflammatory response, resulting in elevated levels of PCT and substantial organ damage, in contrast to a subsequent infectious event (second hit). The authors propose that intricate immunological processes come into play (Sepsis-induced immunosuppression), leading to reduced inflammation levels, consequent lower PCT levels, and diminished impact on organ function.

Conflict of interest: None to declare

Declaration of Generative AI and AI- assisted technologies in the writing process:

During the preparation of this work the authors used *chat.openai* in order to improve language and readability. After using this tool, the author reviewed and edited the content as needed and takes full responsibility for the content of the publication.

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Supplementary material

Tabla S1 | Proportion of missing data in the procalcitionine daily measurements

	Number missing	Percent missing (%)
PCT first hit day 0	0	0
PCT first hit day 1	18	32.7
PCT first hit day 2	17	30.9
PCT first hit day 3	23	41.8
PCT first hit day 4	24	43.6
PCT first hit day 5	24	43.6
PCT first hit day 6	35	63.6
PCT first hit day 7	35	63.6
PCT first hit day 8	43	78.2
PCT first hit day 9	40	72.7
PCT second hit day 0	0	0
PCT second hit day 1	13	23.6
PCT second hit day 2	20	36.4
PCT second hit day 3	27	49.1
PCT second hit day 4	37	67.3
PCT second hit day 5	35	63.6
PCT second hit day 6	39	70.9
PCT second hit day 7	44	80
PCT second hit day 8	45	81.8
PCT second hit day 9	48	87.3

PCT: procalcitonin