# ROLE OF THE BIOMARKERS PRESEPSIN AND PROCALCITONIN IN THE EARLY DETECTION OF SEPSIS AND RISK STRATIFICATION IN INTENSIVE CARE PATIENTS

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***ABSTRACT***

*Sepsis is one of the main realities in Intensive Care, in terms of frequency and significance. Therefore, an early detection is essential. The objective of this observational study, carried out within the multispecialty department of Anesthesia and Intensive Care of the "G. Rodolico" Polyclinic Hospital of Catania, is the evaluation of the diagnostic role that a marker of sepsis, such as Presepsin, also has with discriminating power and risk stratification, in comparison with the data of another biomarker of infection, such as Procalcitonin.*

*The study was conducted on 26 patients admitted in 4 months, from 28 May 2020 to 28 September 2020, at multispecialty department of Anesthesia and Intensive Care of the "G.Rodolico" Polyclinic Hospital of Catania. The clinical data for each patient were obtained from the daily assessment, supplemented by the data drawn from the consultation of individual clinical records. Patients transited to Intensive Care aged > 18 years and hospitalization period of at least 48 hours were included.*

*Our data seems to give higher predictive value for presepsin, despite the small number of patients tested. This also allows the evaluation on the possible evolution of the clinical picture, with prognosis prediction favorable for lower values and unfavourable for considerably high values.*

***Keywords:*** *Sepsis, Critical care, Biomarkers, Early diagnosis.*

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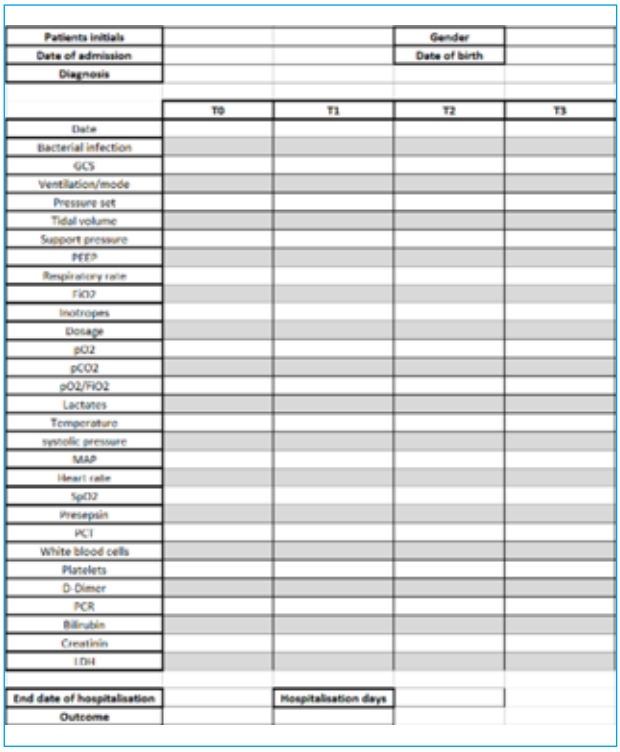
## Introduction

Sepsis is one of the main realities in Intensive Care, in terms of frequency and significance, with an incidence of about 25%. Despite the progress made in recent years on pathophysiological and therapeutic knowledge of this disease, mortality rates worldwide are still unacceptably high[(1)]. Sepsis is a time-dependent pathology therefore, among other things, an early diagnosis is essential, with the support of every means at our disposal, starting from biochemical markers, which, together with the appropriate treatment, can improve the outcome, insofar as evolution and survival are associated with early detection and treatment[(2)].

The objective of this observational study, carried out within multispecialty department of Anesthesia and Intensive Care of the "G.Rodolico" Polyclinic Hospital of Catania, is the evaluation of the diagnostic role that a sepsis marker, such as Presepsin[(3)], also has with discriminating power and risk stratification[(4)], in comparison with the data of another biomarker of infection, such as Procalcitonin. The study also pays attention, as from recent studies, also to the prognostic value that Presepsin and Procalcitonin have in the course of such clinical pictures, correlating the laboratory data to the clinical aspects of the patient, from hemodynamics to ventilation[(5)].

## Materials and methods

The study was conducted on 26 patients admitted in 4 months, from 28 May 2020 to 28 September 2020, at the multispecialty department of Anesthesia and Intensive Care of Anaesthesia and Intensive Care of the "G.Rodolico" Polyclinic Hospital of Catania. The clinical data for each patient were obtained from the daily assessment, supplemented by the data drawn from the consultation of individual clinical records. Patients transited to Intensive Care Unit with an age > 18 years and with a period of hospitalization of at least 48 hours were included, therefore excluding relatively short hospitalizations, such as protected awakenings not burdened by complications in the post-operative course. The data were collected on paper forms and integrated into a Microsoft Excel file, for subsequent analysis and processing. The data sheet used for data collection is shown in Figure 1.



| Patients initials | | | Gender | |
|---|---|---|---|---|
| Date of admission | | | Date of birth | |
| Diagnosis | | | | |
| | T0 | T1 | T2 | T3 |
| Date | | | | |
| Bacterial infection | | | | |
| GCS | | | | |
| Ventilation/mode | | | | |
| Pressure set | | | | |
| Tidal volume | | | | |
| Support pressure | | | | |
| PEEP | | | | |
| Respiratory rate | | | | |
| FiO2 | | | | |
| Inotropes | | | | |
| Dosage | | | | |
| pO2 | | | | |
| pCO2 | | | | |
| pO2/FiO2 | | | | |
| Lactates | | | | |
| Temperature | | | | |
| systolic pressure | | | | |
| MAP | | | | |
| Heart rate | | | | |
| SpO2 | | | | |
| Presepsin | | | | |
| PCT | | | | |
| White blood cells | | | | |
| Platelets | | | | |
| D-Dimer | | | | |
| PCR | | | | |
| Bilirubin | | | | |
| Creatinin | | | | |
| LDH | | | | |
| End date of hospitalisation | | Hospitalisation days | | |
| Outcome | | | | |

**Figure 1**: Patient data collection form.

At the beginning of the hospitalization, the personal data, the date of admission to the ward and the diagnosis, divided into categories by primary pathology that led to the hospitalization, were described. The collection of the other data covered, from biomarkers to the various clinical and laboratory parameters, was divided into 4 stages:

- T0 (on the admission of the patient in ICU),
- T1 (24 hours after admission),
- T2 (48 hours after admission),
- T3 (7 days after admission).

For each individual patient of the study, at each evaluation, data were collected to evaluate the topic in question, specifically the following clinical parameters: body temperature, systolic blood pressure and mean blood pressure (MAP), heart rate, pulse oximeter oxygen saturation, GCS (Glasgow Coma Scale), respiratory rate. The following laboratory data were integrated into the clinical parameters: white blood cell count, platelet number, D-Dimer, PCR, total bilirubin, serum creatinine, LDH. Microbiological research was carried out to assess the presence or absence of bacterial infection and reported as positive, suspect or negative as appropriate. General condition support aspects were also considered in the overall assessment: ventilation if automatic with description of the modality used and the pressure set/support pressure values, tidal volume, PEEP set, FiO2 and continuous pharmacological support with inotropes or vasopressors and infusion dosage. Finally, pO2, pCO2, P/F ratio and lactate measurement were extrapolated from the blood gas analysis.

The study was focused on the dosage of the two biomarkers under investigation: Procalcitonin PCT and Presepsin P-SEP. Presepsin analysis was performed using the immunoluminometric system, PATHFAST with whole blood samples with 51 volume required at least 100µL. The entire procedure is carried out automatically, taking approximately 15 minutes. PCT was analysed on a 200µL serum or plasma sample (centrifuged whole blood test tube) using the VIDAS system, an automated benchtop immunoassay using ELFA (Enzyme Linked Fluorescent Assay) technology. The collected data were integrated on the archive for two further evaluations: the presence or not of clinical picture by SIRS, SEPSIS, SEVERE SEPSIS and SEPTIC SHOCK, the SOFA and qSOFA scores extrapolated from the combination of the parameters under examination.

At the end of the hospitalization, the date of discharge was reported, indicating the number of days of the hospitalisation, and the outcome, stating if the patient was transferred or deceased.

## Results

The demographic features of the 26 enrolled patients are summarised in the following tables and graphs. The sample is predominantly represented by men (20 out of 26, 77%). Age varies from a minimum of 18 years to a maximum of 90 years with

a average value of 61 and a median of 64, with the following age distribution. The admission diagnoses were classified by primary aetiology or relevance, and clustered by disease category or group (as represented in the pie chart below); there were 3 exclusive diagnoses of sepsis, 12% of the cases under review. As can be seen from the following graph, however, the presence of bacterial infection, confirmed by laboratory investigations or clinically suspected, was found in approximately 65% of the enrolled patients. Medications to support haemodynamics, vasopressors and inotropes, were used in 43% of cases, with almost exclusive use of noradrenaline in continuous infusion, at dosages ranging from a minimum of 0.03 mcg/Kg/min to a maximum of 1.65 mcg/Kg/min (mean 0.31, median 0.19). P-SEP and PCT were found with the values presented in Table 1 and presented the variability shown in Table 2.

Hospitalizations varied from a minimum of 72 hours (as per the inclusion criteria of the study) to a maximum of 42 days, with mean and median values of 13. In 58% of the cases examined, patients were discharged and transferred to another ward, while in the remaining 42%, patients died: As a further clarification, it should be noted that only 58% of patients (15 out of 26) reached the complete assessment with the 4 moments of data collection, including also the T3 at 7 days after admission; for 42% of patients in fact it was not possible to integrate the last assessment because they had already been discharged or died.

**Discussion**

Despite the small number of the sample examined, probably not adequately representative of the usual target of patients admitted to the intensive care unit, also in the light of the limited period of observation and the variability due to the emergency condition of the Covid-19 pandemic in progress at the time of data collection, the information collected from the study nevertheless prompts various reflections, which could be the subject of further study and possible moments of comparison.

Analysing the three patients admitted for sepsis-related clinical pictures, it was highlighted that all three of them presented advanced severe conditions with septic shock on admission, obviously with documented infection, and SOFA and qSOFA values of 14/2, 12/2 and 15/0 respectively, corresponding to mortality rates > 95% as shown in the literature. Indeed, all three patients died, after 14, 3 and 6 days respectively. The SOFA score in the first patient was steady in the first 48 hours and dropped to 10 on day 7, in the second patient it rose from 12 to 15 on the day of death, and in the third patient it dropped from 15 to 13 in the first 48 hours of hospitalisation. As manifestations of severe and advanced sepsis, hemodynamics were always supported by variable-dose vasopressors, specifically norepinephrine, as in all overt pictures of septic shock. Less specific parameters such as white blood cell counts or lactates did not show significant changes, thus showing little correlation with either the severity of the clinical picture or the poor prognosis. PCR was found to be significantly high ( > 100 mg/dl), although this was not very specific as it was altered in all the patients examined and not only in patients with sepsis, regardless of diagnosis, severity and prognosis, with the exception of one polytrauma patient who was transferred to the inpatient ward after 48 hours and whose PCR was normal. In contrast to PCR, the two biomarkers in the study, PCT and presepsin, showed significant correlation with the clinical picture, both in the early detection of sepsis and in the predictive importance of outcome. Both in fact were found to be considerably elevated in the daily dosages; in particular, presepsin was always found to be > 2000 pg/ml, well above the threshold value of 600 pg/ml considered to be a cut-off point for confirmation of the infectious state and also higher than the 1000 pg/ml which represents, as described above, the limit for the high risk of systemic progression of the infectious pathology and the high risk of mortality (comparable to SOFA scores > or = 8). Indeed, presepsin on admission was found in the three septic patients with values of 7018, 3411 and 5534 respectively, with a daily variation, either increasing or decreasing depending on the case, leading to values of 4766, 2072 and 8548 on the last day of evaluation. As for PCT, the dosage revealed stable trends with slightly altered values in the second patient (between 0.32 and 0.57 mcg/L) and significantly elevated values which improved between the first and last measurements in the first and third patients examined, from 56.19 to 6.48 and from 13.78 to 7.65 respectively. It is thus clear that presepsin plays an excellent and even better role than PCT, in all three cases, in the threefold role of early diagnosis of sepsis, assessment of the severity of the clinical picture and predictive of evolution and prognosis. However, the fundamental role of PCT in supporting the recognition of infection and the management of associated antibiotic therapy is confirmed[6].

| *PT.1* | **T0** | **T1** | **T2** | **T3** |
|---|---|---|---|---|
| **PSEP** | 7018 | 9578 | 6655 | 4766 |
| **PCT** | 56,19 | 44,09 | 41,09 | 6,48 |
| *PT.2* | | | | |
| **PSEP** | 348 | 288 | 245 | 1045 |
| **PCT** | 0,3 | 4,35 | 1,86 | 0,28 |
| *PT.3* | | | | |
| **PSEP** | 1104 | 1412 | 1243 | 1165 |
| **PCT** | 0,57 | 0,54 | 1,32 | 0,23 |
| *PT.4* | | | | |
| **PSEP** | 172 | 256 | 245 | |
| **PCT** | 0,72 | 0,54 | 0,3 | |
| *PT.5* | | | | |
| **PSEP** | 1646 | 1101 | 1164 | 2689 |
| **PCT** | 7,4 | 8,42 | 4,21 | 0,89 |
| *PT.6* | | | | |
| **PSEP** | 1117 | 1250 | 1319 | 1988 |
| **PCT** | 1,28 | 1 | 1,12 | 1,38 |
| *PT.7* | | | | |
| **PSEP** | 655 | 763 | 674 | |
| **PCT** | 0,24 | 0,36 | 0,8 | |
| *PT.8* | | | | |
| **PSEP** | 216 | 258 | 167 | 354 |
| **PCT** | 0,41 | 1,06 | 0,67 | 0,57 |
| *PT.9* | | | | |
| **PSEP** | 3411 | 2127 | 2072 | |
| **PCT** | 0,44 | 0,57 | 0,32 | |
| *PT.10* | | | | |
| **PSEP** | 2728 | 3892 | 2833 | 1580 |
| **PCT** | 1,56 | 1,8 | 1,29 | 1,38 |
| *PT.11* | | | | |
| **PSEP** | 452 | 444 | 1601 | 1602 |
| **PCT** | 3,41 | 0,86 | 0,53 | 0,2 |
| *PT.12* | | | | |
| **PSEP** | 277 | 167 | 173 | |
| **PCT** | 0,89 | 0,46 | 0,34 | |
| *PT.13* | | | | |
| **PSEP** | 103 | 121 | 129 | |
| **PCT** | 0,06 | 0,07 | 0,09 | |

**PCT**

**PCT**

**PCT**

**PCT**

| *PT.14* | **T0** | **T1** | **T2** | **T3** |
|---|---|---|---|---|
| **PSEP** | 226 | 459 | 428 | |
| **PCT** | 3,41 | 1,08 | 1,12 | |
| *PT.15* | | | | |
| **PSEP** | 418 | 216 | 307 | |
| **PCT** | 16,05 | 11,17 | 5,1 | |
| *PT.16* | | | | |
| **PSEP** | 523 | 137 | 524 | 111 |
| **PCT** | <0,05 | 0,08 | 0,12 | 0,04 |
| *PT.17* | | | | |
| **PSEP** | 289 | 341 | 513 | 842 |
| 1,1 | 0,57 | 0,46 | 0,19 | |
| *PT.18* | | | | |
| **PSEP** | 412 | 712 | 1996 | |
| **PCT** | 0,43 | 3,71 | 8,06 | |
| *PT.19* | | | | |
| **PSEP** | 1357 | 1023 | 2055 | |
| **PCT** | 23,69 | 148,15 | 50,21 | |
| *PT.20* | | | | |
| **PSEP** | 17564 | >20000 | >20000 | |
| 2,46 | 4,71 | 4,85 | | |
| *PT.21* | | | | |
| **PSEP** | 8839 | 4256 | 3681 | 16435 |
| **PCT** | 56,65 | 58,9 | 40,22 | 8,13 |
| *PT.22* | | | | |
| **PSEP** | 451 | 566 | 1934 | 1519 |
| 41,6 | 25,81 | 33,41 | 5,57 | |
| *PT.23* | | | | |
| **PSEP** | 314 | 332 | 200 | 177 |
| **PCT** | 0,14 | 0,09 | 0,09 | 0,1 |
| *PT.24* | | | | |
| **PSEP** | 749 | 217 | 272 | 923 |
| **PCT** | 10,16 | 4,74 | 2,9 | 3,01 |
| *PT.25* | | | | |
| **PSEP** | 5534 | 6448 | 8548 | |
| 13,78 | 8,12 | 7,65 | | |
| *PT.26* | | | | |
| **PSEP** | 2761 | 2460 | 2339 | |
| 0,14 | 0,14 | 0,13 | | |

**Table 1**: P-SEP and PCT values per patient.

Specifically, it should be noted that PCT intervals, in addition to identifying possible septic status, provide a more or less marked reference for the introduction of broad-spectrum and subsequently targeted antibiotic treatment (Table 3). To underline also the importance of the evaluation at a distance after 7 days from admission, which contributes to a more complete information on the evolution and history of the individual patient, in the first case of sepsis the passage to relatively lower SOFA scores, with corresponding mortality rates nearly halved (from 95% for SOFA of 12 to 50% for SOFA 10), as

well as the decrease of about 32% in the presepsin values and of about 88% in the PCT, seems to imply a partial improvement of the clinical picture, even if in the seriousness of the situation. This was probably due to a gradual response to the therapies administered and to the pharmacological and mechanical support, even if it was not enough to modify the outcome of the patient who then died. This reaffirms the importance of close monitoring with biomarkers to highlight trends in evolution and management efficacy according to established treatments, as well as the role of the two parameters studied in early identification and risk stratification in patients with sepsis. Further considerations on the SOFA score concern the mortality rates of the entire sample represented in the study: mortality rates divided by SOFA score groups can be assimilated to those known from the literature and reported above.

| | MIN | MAX | MEAN | MEDIAN |
|---|---|---|---|---|
| **PSEP** | 103 | >20000 | 2326 | 88 |
| **PCT** | <0,05 | 148,5 | 8,82 | 1,11 |

**Table 2**: Analysis of the variability of the presented data.

| | | |
|---|---|---|
| **PCT < 0,05 mcg/L.** | Normal values | Antibiotic therapy not recommended |
| **PCT > 0,05 e < 0,5 mcg/l** | Improbable sepsis<br>Possible localised infection | Antibiotic therapy not recommended, only if patient is unstable |
| **PCT > 0,5 e < 2 mcg/1.** | Possible sepsis | Recommended antibiotic therapy |
| **PCT > 2 e < 10 mcg/L** | Probable sepsis | Strongly recommended antibiotic therapy |
| **PCT > 10 mcg/L** | Severe sepsis or septic shock | Strongly recommended antibiotic therapy |

**Table 3**: Correlation between PCT levels, diagnosis of sepsis and indication a ????

Specifically, for initial SOFA values < 9, mortality is about 37% (33.3% in literature), and for SOFA > 10, deaths reached about 60% of cases (higher than the 50% reported in literature). With the higher SOFA values during hospitalisation there was a good correlation with known evidence, as deaths with SOFA < 12 were 6 out of 17, about 35% (45.8% in literature), while significant discrepancy was found with the percentage of deaths among those with SOFA > 12, 55% in the study and 80% in literature. A final consideration regarding SOFA is the difference in scores between successive assessments, as described above, which is a likely prognostic index of the evolution of the clinical picture. Among those who died, 54% showed an increase in SOFA values during hospitalisation and among those who were discharged, a decrease in SOFA was seen in 60% of cases. As reported in some publications, the related meaning is the greater likelihood of a poor prognosis in the case of increasing SOFA and expectation of improvement in the case of decreasing SOFA[7].

In order to investigate the diagnostic significance of the biomarkers, the entire sample enrolled in the study was divided into two macroscopic groups, infected and non-infected; among the infected, both positives with documented infection and suspects were considered, resulting in a total of 17 patients against 9 negatives. Attention was drawn to the PCT and presepsin values in these two groups. For PCT, the maximum values found were 10.16 mcg/L for the non-infected and 148.15 mcg/L for the infected (almost 15-fold higher) and the mean values 1.33 mcg/L for the non-infected and 13.21 mcg/L for the infected (1:10 ratio). The same proportion for presepsin, with a maximum dosed value of 1988 pg/ml for negatives and > 20000 pg/ml for positives and suspects (a 10-fold increase) and mean values of 495 pg/ml for negatives versus 3400 pg/ml for positives and suspects (a ratio of approximately 1:7). It is therefore clear that high values of the two biomarkers are a reliable expression of an ongoing generalised infection with a progressive sepsis that varies in severity. It is precisely the value of the two markers that represents a high degree of assessment of the evolutionary state of sepsis itself, correlating with higher dosages to more serious clinical pictures, predominantly as concerns presepsin. The cut-off of 600 pg/ml known in literature as the limit for classifying an infectious subject with a potential history of complicated disease in the initial assessment is reflected in our study, as is evident from the mean values of the two macro-groups. The same reasoning applies to PCT, with average values of around 10 mcg/L for patients with an infectious state, a value which, according to the classification, identifies severe sepsis/septic shock, while the average value of 1.33 for non-infected patients is less significant and more controversial, and lies in the grey area of PCT parameters which still includes possible sepsis.

Analysing the issue of SIRS, among the 9 non-infected patients on admission, 4 (44%) showed clinical SIRS during hospitalisation. The average presepsinaemia in these uninfected patients with SIRS was 634pg/ml and the average PCT was 1.99 mcg/L, while the average presepsin value in the 5 (56%) uninfected patients without SIRS was 386 pg/ml and the average PCT was 0.81 mcg/L. Therefore, there is no significant difference in measured presepsinemia and PCT between uninfected patients with and without SIRS. Just as there is no significant difference in presepsin between patients with SIRS against patients who do not have SIRS, regardless of known or unknown infection; the values are 2368

pg/ml versus 2251 pg/ml. While for PCT the difference is more evident with an average of 13.15 mcg/L among patients with SIRS and 1.07 mcg/L among patients without SIRS. Regarding mortality, as reported in the descriptive paragraph on the study sample, there were 11 deaths out of 26 (42%).

When dividing the groups according to outcome and analysing the dosages of the markers, it becomes clear that there is no difference between the average presepsin values between the deceased and the discharged (2331 pg/ml and 2323 pg/ml), while the average PCT value among the discharged is 6.69 mcg/L and among the deceased 11.84 mcg/L, thus obtaining more predictive values. The individual values at entry of the biomarkers can lead to further considerations, not so much because of the average values, which do not differ between the discharged and the deceased (discharged: presepsin 2280, PCT 9.26; deceased: presepsin 2040,9.48), but because of the importance of the individual initial dosage. Specifically, among those discharged, only 4 out of 15 patients presented presepsin values on admission > 1000 pg/ml and PCT values > 10 mcg/L, thus with 73% of patients having values below those mentioned. Even among deaths, the presepsin value on admission seems to have a greater predictive value, with 20% of patients presenting values < 600, 7% between 600 and 1000 and 73% > 1000; for PCT, in fact, only 27% of patients with a poor prognosis presented values > 2 mcg/L, confirming the poor predictive value of this biomarker. However, the processing of presepsin values is altered by the finding of a particular case with extreme values (> 20000 pg/ml) in a patient discharged after 3 days (and therefore not deceased), with a diagnosis of coma in a patient operated on for rupture of the ascending aorta, which changes the average values and therefore also in part the reliability of the prognosis. Focusing on the individual markers, examining only the presepsin values, it was noted that the patients who had, during hospitalisation to the ICU, among the four moments of evaluation contemplated by the study, at least one finding of values > 600 pg/ml (a total of 18 cases out of 26, about 70%), had outcomes with 10 deaths (55% of mortality) and 8 discharges; patients who had values > 1000 pg/ml were a further subgroup of 15 patients out of the 18 mentioned above and in this case hospitalisation led to discharge in only 5 cases (33%) and death in the remaining 10 (66%). Of the 8 patients (approx. 30%) who did not show any definite organ dysfunction, i.e. presepsin < 600pg/ml, only one (12.5%) died after 17 days, with the disease on admission being mainly cardiological (ROSC).

In spite of the small number of patients examined, the following data confirms and reaffirms the greater predictive value of presepsin, which also allows evaluation of the possible evolution of the clinical picture, with an important prediction of a good prognosis at lower presepsin values and a decent incidence of mortality but for significantly high presepsin values. In short, if presepsin is below 600, the prognosis is likely to be favourable; if it is above 1000, a negative prognosis is likely. On the other hand, examining the PCT values and taking the cut-off value of 2 mcg/L in at least one dose, it emerged that there were 13 patients with values above 2 (50% of the cases in the study), resulting in 6 deaths (46%) and 8 discharges. Patients who had values > 10 mcg/L were a further subgroup of 7 patients of the 13 mentioned above, and in this case hospitalisation led to discharge in 4 cases (33%) and death in the remaining 3 (66%). For the other half, who did not have values above 2 mcg/L PCT during hospitalisation, 8 patients (61%) were discharged and 5 died (41%). Patients who had values > 10 mcg/L were a further subgroup of 7 patients of the 13 mentioned above, and in this case the hospitalisation led to discharge in 4 cases (33%) and death in the remaining 3 (66%). For the other half, who did not have values above 2 mcg/L PCT during hospitalisation, 8 patients (61%) were discharged and 5 died (41%).

This fluctuation underlines the lower predictive ability of PCT compared to presepsin on the outcome of the monitored patients. However, the difference between the initial and subsequent values of the PCT itself has a significant influence, confirming the importance of the trend and its regular monitoring. In other words, despite the presence of altered and elevated values on admission, the gradual decrease in PCT values, possibly in response to targeted and adequate therapy, is the most relevant prognostic index compared to single measurements; in cases where values have significantly decreased over days, the outcome of patients is significantly improved. The percentage differences between the first and last values of the biomarker dosages were also evaluated to highlight any correspondence between the two and possible interaction with the patient's developmental picture. The presepsin and PCT curves were found to be independent as they did not always change in the same direction, up or down, but often an increase in one parameter was linked to a decrease in the other. In addition, there was no link between the percent-

age change in biomarkers and patient outcome, i.e. it was not always the case that an increase in values was followed by an improvement in prognosis and vice versa, especially for presepsin. The only significant finding in this respect was that when there was an increase in PCT, the evolution of the picture caused the death of the patient (5 out of 7 patients with a positive percentage change), with the exception of a small positive change with a particularly low starting value (< 0.06, therefore insignificant) and the case of the patient referred to above who had been operated on for a ruptured ascending aorta. This latter aspect highlights the possible interaction of the two biomarkers with other concomitant factors that may alter their value, as in a particularly complex picture such as the one described.

Finally, focusing on the duration of hospitalisation, it can be seen that there is no significant difference between presepsin and PCT in predicting the number of days of hospitalisation; there does not seem to be a correlation between high values and prolonged hospitalisation, since this aspect is influenced by numerous variables that are more or less dependent on the values of the biomarkers. The average values of days of hospitalisation, in fact, for presepsin < 600, > 600 and > 1000 are respectively 10, 14 and 13; for PCT < 2, > 2 and > 10 are respectively 13, 12 and 15 days. To further confirm this aspect, it should be noted that in some of the patients examined, hospitalisation was of short duration due to the seriousness of the clinical picture, which rapidly led to death.

All these evaluations require careful consideration of both the critical aspects of the study and the observations that can be drawn from it, as possible topics for future investigations and analyses. We have already mentioned the aspect of the characteristics of the sample examined, which probably does not guarantee a broad evaluation of the topics dealt with and which would deserve greater representativeness on cases of sepsis only. Obviously, it should be emphasised that the pandemic period in which the following study was carried out created unfavourable conditions for a more in-depth study of the aspects examined. The possibility of extending this data collection to the paediatric population is also considered important for future evaluations, in view of the lack of information and evidence in this regard. The various publications have often focused on adult patients but it is clear that there is a need to develop, for example, updated definitions for paediatric populations and the use of clinical criteria that take into account their age-dependent variability in normal physiological ranges and pathophysiological responses.

The aim of this study was to determine and compare the diagnostic, prognostic and risk stratification performance of PCT and P-SEP in the setting of sepsis in patients admitted to the ICU. Identifying the potential role of these biomarkers and comparing their relevance in existing diagnostic pathways is essential to provide more evidence and support in the creation of guidelines for the diagnosis and management of sepsis.

Sepsis, as has been shown, is not a specific disease, but rather a syndrome involving a pathophysiology that is not yet fully understood. At present, it can be identified by a set of clinical signs and symptoms in a patient with suspected infection, but as there is no gold standard diagnostic test, there is a need to continue the search for clear definitions and supporting clinical criteria. Sepsis is a syndrome with no validated standard diagnostic test at the moment[8]. There is an important need for characteristics that can be identified and measured in individual patients to provide uniformity. Ideally, these clinical criteria should identify all elements of sepsis (infection, host response, and organ dysfunction), be easy to obtain, and be readily available at a reasonable cost.

Furthermore, it should be possible to test the validity of these criteria with large available clinical data sets and ultimately prospectively. In addition, clinical criteria should be available to provide professionals in all settings (out-of-hospital, in-hospital, emergency and non-emergency) with the ability to better identify patients with suspected infection that may progress to a life-threatening state. Such early recognition is particularly important because the prompt management of septic patients can improve their outcome. This is where our study was placed, focusing on the role of the two most promising biomarkers at the time: procalcitonin and presepsin, together with additional supporting tools such as scores, have been shown to effectively differentiate between sepsis or infection and SIRS of non-infectious origin. It has been pointed out that clinical parameters and conventional laboratory markers, such as elevated white blood cell count and C-reactive protein[9], cannot differentiate infectious from non-infectious inflammation. In addition, although isolation and culture of pathogenic microorganisms from the bloodstream is considered the gold standard for diagnosis of aetiology, this can be time-consuming. A careful review of the

literature and analysis of the collected data described above has therefore revealed and reaffirmed the importance of presepsin and procalcitonin in the early identification of septic status and risk stratification in patients on critical care wards. PCT has acquired a significant diagnostic role in this field, but it should be remembered that this biomarker tends to increase in a transient manner under non-septic conditions and SIRS. The diagnostic power of presepsin in detecting sepsis in patients with a documented or suspected infection was highlighted in the parameters examined. However, as the only diagnostic approach, presepsin is not sufficient and its value should always be supplemented with the additional supporting tools available. The validity of biomarkers in the prognosis of critically ill patients has also become apparent, with presepsin being of greater importance. It has been shown that initial values, which allow rapid diagnosis, combined with dosing and serial monitoring, are as predictive as the scores currently in use (such as SOFA), but it is necessary to take advantage of all these aspects, including clinical assessment, to improve management in its complexity.

In order to refine what is already known, further studies could be useful to determine, for example, any new predictors of mortality with high sensitivity and specificity in clinical practice. Presepsin and procalcitonin have aroused considerable interest in recent years and are still the subject of numerous studies aimed at confirming the information available, in the search for further certainty and clarification of the many unknown aspects. The focus on certain aspects in the knowledge of sepsis, the diagnosis of infection and the management of critically ill patients in general may direct and stimulate further study and research, with the common aim of providing the clinician with as simple and straightforward an approach as possible to such a broad and complex subject.

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