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Plasma calprotectin as an indicator of need of transfer to Intensive care in patients with suspected Sepsis at the emergency department

Ayham Maatouk
Corresponding author email: ayhammaatouk@yahoo.com

***Abstract*---**Sepsis frequently necessitates hospitalization & admission to high-dependency units & intensive care units. Sepsis is responsible for twenty percent of all fatalities worldwide, according to the most current Global Burden of Disease Study. Sepsis is reported to have a mortality rate of between twelve percent and twenty percent in western nations. "Neonate" & "adult" categories, nevertheless, both demonstrated high diagnostic effectiveness, indicating that demographic context had not been the primary reason for variability. Heterogeneity can be the result of the sepsis definition detection & treatment of sepsis have improved over the past few decades as a result of extensive study, & criteria have evolved as a result. To improve it, sepsis-3 had been created in 2016 with a stronger emphasis on identifying organ dysfunction in the context of infection understanding of the syndrome is constantly expanding. More investigation into this interesting diagnostic sign utilizing a revised definition is needed, hence.

***Keywords*---**Plasma calprotectin, Intensive care, suspected Sepsis.

Introduction

Sepsis frequently necessitates hospitalization & admission to high-dependency units & intensive care units. Sepsis is responsible for twenty percent of all fatalities worldwide, according to the most current Global Burden of Disease Study. Sepsis is reported to have a mortality rate of between twelve percent and twenty percent in western nations. Thus, World Health Organization has emphasized early detection of sepsis as a major global problem to ensure better care & higher survival rates (1).

Sepsis continues to provide difficulty for most hospitals despite evidence that early diagnosis & treatment can enhance studied case results. Better biomarkers are required to support clinical judgment at all stages of sepsis management. Predictive features of procalcitonin & C-reactive protein, which are

well-established tools primarily used to identify infectious from non-infectious diseases, are still unclear in sepsis management. PCT is suggested by Surviving Sepsis Campaign as an explanation for stopping the antibiotic medication. Neutrophils are frequently activated & lymphocytes are frequently repressed in the early stages of sepsis. Considering these developments, the neutrophil-lymphocyte ratio is suggested as a helpful diagnostic marker of sepsis & is demonstrated to have predictive features (2).

In addition to being expressed on the plasma membrane of monocytes, the protein calprotectin is found in the cytoplasm of neutrophils. Calprotectin enters the bloodstream when neutrophil granulocytes are activated. In reaction to bacteria or endotoxins, calprotectin levels are seen to rise in the bloodstream within hours. Consequently, calprotectin is suggested as a possible biomarker of sepsis in blood samples (plasma or serum). Calprotectin performed better than PCT, CRP, & NLR in identifying bacterial sepsis in the population of patients who were hospitalized. Another study between ICU studied cases discovered that calprotectin outperformed PCT for signs of sepsis & for separating sepsis from non-septic diseases. Calprotectin demonstrated eighty percent sensitivity & forty-six percent specificity for thirty-day mortality with a cut-off of 1.1mg/L. Additionally, calprotectin is demonstrated to be a viable biomarker for differentiating between severe & mild COVID-19 as well as between infectious & non-infectious respiratory diseases (3).

Between studied cases that triggered sepsis warning system & had been evaluated by a multidisciplinary team, novel biomarker p-calprotectin had been higher in studied cases with established infection & outperformed CRP, PCT, & NLR in identifying studied cases who had been transferred immediately to ICU/HDU care (4).

It is demonstrated that P-calprotectin may serve as a biomarker to distinguish sepsis studied cases from other studied cases who are infected. Previous research has concentrated on the function of calprotectin in multi-organ failure since sepsis studied cases might vary greatly in their severities. P-calprotectin in a well-characterized cohort of studied cases who had already entered the emergency department & had clinical suspicion of sepsis to determine whether it can be useful in detecting sepsis early on. We discovered that studied cases with infections who had been transferred to the ICU/HDU by a multidisciplinary team in ED had considerably greater levels of p-calprotectin than those who had been transferred to regular wards. Greater comorbidity (as determined by the Charlson comorbidity score) or disease severity (as shown by an increase in SOFA score) at presentation did not account for this among those transferred to ICU/HDU & those transferred to wards, there had been no appreciable variation in delta-SOFA scores. This demonstrates challenges associated with assessing severity solely based on SOFA score. In the current study, the multidisciplinary team evaluated sepsis alert studied cases and selected where to move studied cases (5).

CRP, PCT, & NLR had been unable to distinguish between patients who had been sent directly to ICU/HDU & those who weren't. Although it had been discovered to be superior to CRP, PCT, & NLR in this issue, ROC curve

research revealed that p-calprotectin has better potential to be beneficial in determining requirements for transfer to ICU/HDU. The AUC for p-calprotectin for immediate transfer to ICU/HDU care was 0.65. Larsson et al.'s recent study of calprotectin in ICU studied cases revealed that it has an AUC of 0.67 for separating sepsis from non-sepsis in ICU & 0.64 for predicting ICU death. Yet, after considering sensitivities, specificities, & predictive values, we discovered that the p-calprotectin value of 4.0 mg/L, which has a sensitivity of 42.5 percent & specificity of eighty-three percent is the optimum cut-off for predicting the necessity for ICU/HDU treatment. optimal calprotectin cut-off was determined by Larsson et al. to be 1.3mg/L for separating sepsis from non-sepsis, with sensitivity of eighty-one percent & specificity of fifty-six percent & 1.1mg/L for predicting ICU death, with sensitivity of eighty percent & forty-six percent This variation may be due to subject chosen or calprotectin assay employed. Contrary to earlier research, the current investigation primarily included studied cases with community-acquired infections with a high risk of sepsis, which may have caused different cut-offs in our outcomes (6).

There had been no discernible variation in p-calprotectin levels among bacterial & viral infections, & p-calprotectin & other biomarkers performed similarly regardless of sex, age, co-morbidity, or source of infection. Nevertheless, since there had been so few viral infections, it was challenging to interpret the data. This had been true for CRP, PCT, & NLR, which could have been caused by the study's sparse enrollment of individuals with viral infections. However, blood cultures are only positive in thirty to forty percent of sepsis studied cases, even if these studied cases are diagnosed with a bacterial infection. It should be highlighted that the distribution of calprotectin had been unrelated to blood culture positivity/negativity. Immunosuppression is reported to influence faecal calprotectin; however, we did not detect any differences in p-calprotectin levels between immunosuppressed and unsuppressed studied cases (7).

Studied cases with initial high p-calprotectin levels who had been later transferred from ward to ICU/HDU within twelve to seventy-two hours of presentation had been first transferred to ward units. According to this research, there can be a higher chance that a stable studied case with a high p-calprotectin level who is not yet in need of ICU or HDU transfer from the ED would eventually need it. Further research ought to be done on p-calprotectin's prognostic capabilities (8).

P-calprotectin & NLR levels decreased in the ED sample & day two-three sample, however, CRP & PCT levels rose. This might be due to biomarkers' various inherent kinetics. But just CRP shared the same pattern as calprotectin in Simm et al. investigation. This can be due to varied sample timing & more diverse set of studied cases than in Simm et al.'s research. Calprotectin rises early in the course of infection, hence it might be a useful biomarker in pre-hospital care settings. To determine its precise function, more research will be required (2).

Sepsis, which is characterized as a life-threatening organ malfunction brought on by dysregulated host response to infection, is a major reason for mortality & critical disease on a global scale. Sequential Organ Failure Assessment score, a crucial component of present sepsis classification, aids in the identification of

individuals with sepsis. In complex medical conditions, it is still challenging to demonstrate infection, & the diagnosis of sepsis quickly & precisely is frequently delayed. Sepsis mortality & financial burden rise with delay in diagnosis & treatment. Additionally, a frequent problem in all sepsis investigations is the absence of a broadly acknowledged biomarker gold standard for sepsis. It is difficult to include a consistent group of studied cases, which limits the applicability & inclusiveness of findings (4).

Thus, biomarkers might be extremely important in the early detection & treatment of sepsis. Diagnostic validity of biomarkers procalcitonin & C-reactive protein is questioned. Even in studied cases who are not infected, surgery & trauma have been observed to affect outcomes. They struggle to discriminate between sterile inflammation and infection. Consequently, it is essential to have biomarkers with high diagnostic sensitivity & specificity (9).

Major leukocyte protein L1 (also known as calprotectin) is a calcium-binding protein that had been first discovered in neutrophils. Myeloid-related protein8 (MRP8) & heavy (MRP14) chains (8 & 14kDa), known as S100A8 & S100A9, which are members of S100protein family, combine to form 24-kDa heterodimer. Sepsis and calprotectin are closely connected. Spontaneous bacterial peritonitis is linked to elevated ascitic calprotectin, & sepsis is the most prevalent cause of death in this condition. Calprotectin levels in amniotic fluid are also reliable indicators of newborn sepsis. Additionally, sepsis-associated encephalopathy & sepsis-induced acute renal injury was reported to have diagnostic significance. Additionally shown to be significantly higher in sepsis, serum calprotectin expression level had a strong diagnostic value outcomes may not be as generalizable as they may be due to the small number of studied cases in each research & fact that the majority of them included participants from a single center. Additionally, outcomes of earlier research were inconsistent (sepsis vs. non-sepsis controls: 42.5 percent-89 percent sensitivity, 56 percent-96 percent specificity). (10).

Dysregulated host response to infection is the cause of the potentially fatal disease sepsis. Immune homeostasis is hampered by sepsis, which modifies innate & adaptive immune responses. SOFA score has helped us detect sepsis, but there are still a few ways to identify infections. Therefore, there is a critical need for accurate & early sepsis diagnostic biomarkers (11).

Biomarker for early detection of sepsis is PCT. nevertheless is thought that various infections because variable degrees of PCT, & in critically ill septic patients, viral infection or systemic inflammatory response syndrome brought on by noninfectious disorders may raise PCT levels. There are numerous published meta-analyses assessing its sepsis diagnostic efficacy. They reported AUC values between 0.80 & 0.87, pooled sensitivities between 0.71 & 0.81, & pooled specificities between 0.76 & 0.79. Our research indicates that calprotectin is a valuable biomarker due to its improved specificity & comparable sensitivity (1).

Calprotectin is a protein that neutrophils & monocytes exude extracellularly or that is liberated into pus after cell death or disruption. a soluble form of calprotectin had been discovered in faeces, intestinal fluid, plasma, urine,

& bodily secretions. It has recently attracted lots of interest for its involvement in a variety of inflammatory & infectious disorders, such as sepsis, rheumatoid arthritis, inflammatory bowel disease, & myocardial infarction. Calprotectin controls inflammation & takes involvement in antimicrobial & immune system functions. As a result, calprotectin is crucial in immune system changes brought on by sepsis (12).

A useful marker of sepsis upon ICU admission may be serum calprotectin. The findings of this initial meta-analysis on the diagnostic utility of calprotectin for sepsis upon ICU admission are encouraging. While there was heterogeneity, we tried to minimize it by performing sensitivity analysis & subgroup analysis (5). Calprotectin demonstrated strong diagnostic significance in both "medical" & "surgical" subgroups in subgroup analysis, suggesting that serum calprotectin may be a possible biomarker to distinguish sepsis from noninfectious inflammatory illness. The main reason for heterogeneity had not been the admission category because heterogeneity still occurred. Since it had been noted that serum calprotectin levels had dramatically increased after delivery and then gradually declined over 1st month of life, we next investigated if population context would have an impact on outcomes (13).

"Neonate" & "adult" categories, nevertheless, both demonstrated high diagnostic effectiveness, indicating that demographic context had not been the primary reason for variability. Heterogeneity can be the result of the sepsis definition detection & treatment of sepsis have improved over the past few decades as a result of extensive study, & criteria have evolved as a result. To improve it, sepsis-3 had been created in 2016 with a stronger emphasis on identifying organ dysfunction in the context of infection understanding of the syndrome is constantly expanding. More investigation into this interesting diagnostic sign utilizing a revised definition is needed, hence (14).

References

1. Parke, A. E, Unge, C, Yu, D, Sunden-Cullberg, J, Stralin, K. (2021). Plasma-Calprotectin as an Indicator for Immediate Need of Intensive Care Treatment in Suspected Sepsis.
2. Larsson, A, Tydén, J, Johansson, J, Lipcsey, M, Bergquist, M, Kultima, K, et al. (2020). Calprotectin is superior to procalcitonin as a sepsis marker and predictor of 30-day mortality in intensive care patients. *Scandinavian Journal of Clinical and Laboratory Investigation*, *80*(2), 156-161.
3. Barichello, T, Generoso, J. S, Singer, M, Dal-Pizzol, F. (2022). Biomarkers for sepsis: more than just fever and leukocytosis—a narrative review. *Critical Care*, *26*(1), 14.
4. Gauchel, N, Rieder, M, Krauel, K, Goller, I, Jeserich, M, Salzer, U, et al. (2022). Complement system component dysregulation is a distinctive feature of COVID-19 disease: A prospective and comparative analysis of patients admitted to the emergency department for suspected COVID-19 disease. *Journal of Thrombosis and Thrombolysis*, 1-10.
5. García de Guadiana-Romualdo, L, Rodríguez Rojas, C, Morell-García, D, Andaluz-Ojeda, D, Rodríguez Mulero, M. D, Rodríguez-Borja, E, et al. (2022). Circulating levels of calprotectin, a signature of neutrophil activation in

prediction of severe respiratory failure in COVID-19 patients: a multicenter, prospective study (CalCov study). *Inflammation Research*, 1-11.
6. Chapuis, N, Ibrahimi, N, Belmondo, T, Goulvestre, C, Berger, A. E, Mariaggi, A. A, et al. (2022). Dynamics of circulating calprotectin accurately predict the outcome of moderate COVID-19 patients. *EBioMedicine*, *80*, 104077.
7. Wollmer, M, Wändell, P, Rosenqvist, M, Larsson, A, Melander, O, Wessman, T, et al. (2021). Plasma calprotectin in the emergency department: a potential clinical biomarker for patients with infectious diseases. *Scandinavian Journal of Clinical and Laboratory Investigation*, *81*(7), 593-597.
8. Christensen, E. E, Binde, C, Leegaard, M, Tonby, K, Dyrhol-Riise, A. M, Kvale, D, et al. (2022). Diagnostic accuracy and added value of infection biomarkers in patients with possible sepsis in the Emergency Department. *Shock: Injury, Inflammation, and Sepsis: Laboratory and Clinical Approaches*, *58*(4), 251-259.
9. Lipcsey, M, Hanslin, K, Stålberg, J, Smekal, D, Larsson, A. (2019). The time course of calprotectin liberation from human neutrophil granulocytes after Escherichia coli and endotoxin challenge. *Innate immunity*, *25*(6), 369-373.
10. Havelka, A, Sejersen, K, Venge, P, Pauksens, K, Larsson, A. (2020). Calprotectin, a new biomarker for diagnosis of acute respiratory infections. *Scientific reports*, *10*(1), 4208.
11. Cherubini, F, Cristiano, A, Valentini, A, Bernardini, S, Nuccetelli, M. (2021). Circulating calprotectin as a supporting inflammatory marker in discriminating SARS-CoV-2 infection: an observational study. *Inflammation Research*, *70*(6), 687-694.
12. Nevejan, L, Strypens, T, Van Nieuwenhove, M, Boel, A, Cattoir, L, Meeus, P, et al. (2022). Prognostic value of circulating calprotectin levels on the clinical course of COVID-19 differs between serum, heparin, EDTA and citrate sample types. *Clinica Chimica Acta*, *525*, 54-61.
13. Van der Slikke, E. C, Boekhoud, L, Bourgonje, A. R, Olgers, T. J, Ter Maaten, J. C, Henning, R. H, et al. (2022). Plasma free thiol levels during early sepsis predict future renal function decline. *Antioxidants*, *11*(5), 800.
14. Reyes, M, Filbin, M. R, Bhattacharyya, R. P, Sonny, A, Mehta, A, Billman, K, et al. (2021). Plasma from patients with bacterial sepsis or severe COVID-19 induces suppressive myeloid cell production from hematopoietic progenitors in vitro. *Science translational medicine*, *13*(598), eabe9599.