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Comparison of total calprotectin levels with S100A8 and S100A9 subunit levels in critically ill patients

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ABSTRACT

Calprotectin is a 24 kD heterodimer of calcium-binding proteins S100A8 and S100A9. At present, there is a lack of knowledge about the specificity of various methods for calprotectin detection, whether they measure only dimers between S100A8 and S100A9, S100A8-S100A8 dimers, S100A9/S100A9 dimers, or free subunits. This study aimed to compare total calprotectin levels with those of its subunits, S100A8 and S100A9, in ICU patients. This prospective observational study includes 271 sepsis and non-sepsis patients. Inclusion criteria were admission to intensive care and the presence or need for an arterial catheter. Plasma total calprotectin was measured at ICU admission and the following two days by particle-enhanced turbidimetric (PETIA) calprotectin reagents from Gentian AS and a Mindray BS380 chemistry analyzer. S100A8 and S100A9 were analyzed by commercial sandwich ELISA DY4570-05, and DY5578, R&D Systems, respectively. Sepsis was defined according to Sepsis-3 as suspected infection and a Sequential organ failure assessment (SOFA) >2 on admission. Receiver operating characteristic (ROC) analysis showed that total calprotectin had a larger area under the curve (AUC) for distinguishing sepsis from non-sepsis patients (0.67) compared to S100A8 (0.59) and S100A9 (0.52). For predicting 30-day mortality, S100A9 had a higher AUC value (0.64) than S100A8 (0.59). However, weak correlations between total calprotectin and its subunits suggest no significant predictive relationship for 30-day mortality, while also highlighting potential assay harmonization challenges across manufacturers.

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Introduction

Calprotectin was first discovered as an antimicrobial protein present in the cytosol of neutrophil granulocytes [1]. Later, it was recognized as a promising marker of inflammation, [2,3] It has also been shown that calprotectin is involved in the recruitment of inflammatory cells by interacting with endothelial cells [4] and that calprotectin may influence physiological homeostasis through a zinc-capturing function [5].

Initially, calprotectin was denoted as major leukocyte protein L1 or 27E10. Later calprotectin was identified as a combination of S100A8 and S100A9, that also have several different synonyms: myeloid-related proteins-8 and-14 (MRP-8 and MRP-14), and calgranulin A and B [6,7]. Calprotectin is a soluble protein belonging to the S100 protein family that is mainly expressed by myelomonocytic cells [7]: monocytes and neutrophils, but also in early differentiation stages of macrophages [8] and represents 40–60% and 5% of the cytosolic protein content of neutrophils and monocytes/macrophages, respectively. It is rapidly released upon neutrophil activation [7,9,10].

The multiple functions of calprotectin are mainly associated with active inflammatory processes, including antibacterial defence mechanisms, or with Th1-mediated responses, including

allograft rejection or autoimmune reactions. Serum calprotectin may be an alternative to acute phase proteins as a biomarker in infection and autoimmune disease. Recent data has shown that calprotectin responds rapidly, within 2h, to induction of inflammation [11]. Further, data show that the performance of calprotectin in differentiation between bacterial, mycoplasma and viral infections was better than the performance of heparin-binding protein (HBP, also known as azurocidin or cationic antimicrobial protein of 37kDa/CAP37) and procalcitonin (PCT) [12].

Recent data show that intracellular S100A9 promotes myeloid-derived suppressor cells during late sepsis [13]. Accordingly, several studies have shown that calprotectin is a promising biomarker for sepsis [14–17]. In a Swedish study in intensive care unit (ICU) patients, calprotectin was superior to PCT for distinguishing between ICU patients with sepsis and non-sepsis patients. Calprotectin also had a higher predictive ability for 30-day mortality [17].

However, we presently lack knowledge of which of several calprotectin conformations is crucial for its activity and correlates best to the presence of sepsis and its outcome. Calprotectin consists of a 24 kD heterodimer (or 48 kD tetramer) of 2 calcium-binding proteins S100A8 and S100A9 [18–21]. Different

forms of dimers are also problematic when it comes to calibrations and comparisons between different suppliers. At present, there is a lack of knowledge about the specificity of various methods for calprotectin detection, whether they measure only dimers between S100A8 and S100A9, S100A8-S100A8 dimers, S100A9/S100A9 dimers, or free subunits. There is also a lack of knowledge about the role of calprotectin sub-components in inflammatory processes. The aim of this study was to compare the levels of total calprotectin with S100 A8 (subunit) and with S100A9 (subunit) in a cohort of ICU patients.

Materials and methods

Study population

The ICU cohort included a total of 271 patients and was a prospective observational study. Inclusion criteria were admission to the ICU and the presence of or need for an arterial catheter. Exclusion criteria were patients transferred from other ICUs and aged less than 18 years. The final diagnosis was determined retrospectively by chart review. Sequential organ failure assessment (SOFA) scores were recorded daily. Simplified acute physiology score 3 (SAPS3) was recorded on admission [22]. SOFA scores were also recorded on admission and the following two days [23]. Sepsis was defined according to Sepsis-3 as a suspected infection and a SOFA >2 on admission [24].

Blood sampling and biomarker analyses

Blood samples were collected from the arterial catheter on admission to the ICU and the following two days in ethylenediaminetetraacetic acid (EDTA) tubes. Plasma was centrifuged and stored at -80°C until analysis. Total calprotectin was measured by particle-enhanced turbidimetric assay (PETIA) using calprotectin reagents from Gentian AS (Moss, Norway) and a Mindray BS380 chemistry analyzer (Mindray, Shenzhen, China) as previously described [17]. S100A8 (subunit) was analyzed by a commercial sandwich ELISA (DY4570-05, R&D Systems, Minneapolis, MN) and S100A9 (subunit) was analyzed by a commercial sandwich ELISA (DY5578, R&D Systems, Minneapolis, MN). R&D Systems ELISA kits were used for both the S100A8 and S100A9 assays. In these assays, a mouse monoclonal antibody was used as the capture antibody, while detection was achieved with a biotinylated affinity-purified polyclonal antibody followed by streptavidin-HRP for signal development. The Gentian Calprotectin PETIA (Particle-Enhanced Turbidimetric Immunoassay) uses avian polyclonal antibodies (IgY) raised in chickens against native human calprotectin (heterodimer S100A8/A9, also known as MRP8/MRP14).

Statistical analysis

Data are presented as median (range) or number of observations (percentage of total number of observations). The area under the curve (AUC) of the receiver operating characteristic (ROC) was calculated. Scatterplots were used to illustrate

the relationship between total calprotectin, S100A8, and S100A9. STATISTICA software version 14.1 (StatSoft, Tulsa, OK) and GraphPad Prism version 7.0 for Windows (GraphPad Software Inc., La Jolla, CA) were used for calculations and figures. $p < 0.05$ was considered significant.

Ethical considerations

The study was approved by the regional ethical review board in Linköping (Dnr 2018-16-32) and has been performed following the ethical standards of the 1964 Declaration of Helsinki and its later amendments. Verbal consent was provided by the patient or next of kin if the patient was not able to provide the consent. Consent was documented on the patient's inclusion sheet. Verbal as opposed to written consent was chosen as many of the ICU patients were not able to write due to the severity of illness. This procedure was approved by the ethics review board.

Results

Baseline characteristics

A total of 271 patients (179 (66%) men and 92 (34%) women) were included in the present study. The patient's median age was 68 years (19–96 years). The cohort was divided into four main groups: sepsis group (77 patients); trauma group (32 patients), presumed to have inflammation without infection on admission; other medical conditions group, refers to patients without sepsis or evident systemic inflammation, such as those with hyponatremia, diabetic ketoacidosis, intoxications, intracerebral hemorrhage, hypothermia, or status epilepticus (82 patients); and finally miscellaneous conditions group includes patients without sepsis or trauma but with possible systemic inflammation, such as those with gastrointestinal bleeding, intestinal ischemia, pancreatitis, burn injury, cardiac arrest, ruptured aortic aneurysm, or postoperative care (80 patients). Total baseline characteristics for the full group and the subgroups are shown in Table 1 [17].

Total calprotectin, S100A8 and S100A9

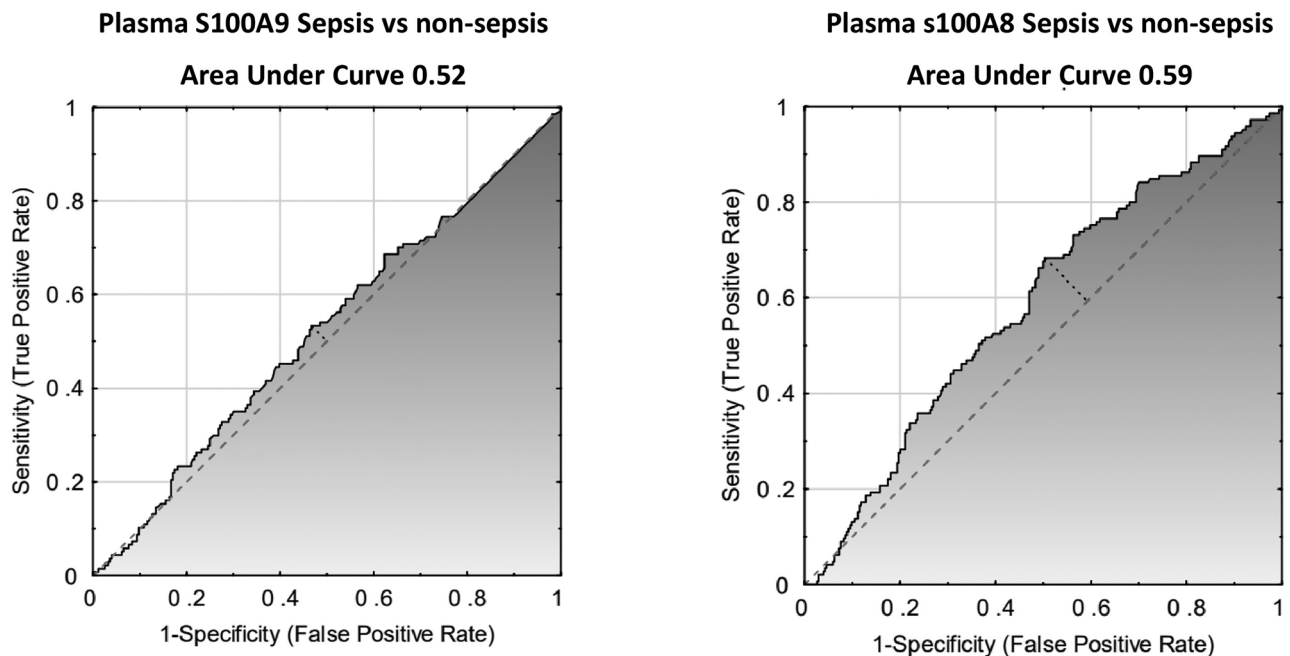
The median for the S100A8 subunit was 8341 (5624–13161) ng/L and the median for S100A9 was 849 (285–2427) ng/L in all patients group. The median for S100A8 was higher than S100A9 in all patient groups (Table 2). AUC values for discriminating sepsis vs. non-sepsis patients (Figure 1), were higher for total calprotectin (0.67) and S100A8 (0.59) than S100A9 (0.52) (Table 3). Receiver operating characteristic (ROC) analysis showed a larger area under the curve (AUC) value for S100A9 (0.64) than for S100A8 (0.59) for 30-day mortality (Figure 2). AUC values for discriminating survivor vs. non-survivor at 30 days were essentially the same for total calprotectin (0.64) and S100A9 (0.64) (Table 2). However, the correlation between total calprotectin and S100A9 ($r = 0.34$), total calprotectin and S100A8 ($r = 0.57$),

Table 1. Clinical and demographic characteristics of patients. Values are presented as median (range) or n (%).

Characteristics/medications	Patient group				
	All patients n=271	Sepsis n=77	Trauma n=32	Miscellaneous n=80	Other medical n=82
Age, years	68 (19–96)	72 (28–90)	50 (21–96)	70 (23–95)	63 (19–93)
Sex					
Male	179 (66)	56 (73)	27 (84)	54 (67)	42 (51)
Female	92 (34)	21 (27)	5 (16)	26 (33)	40 (49)
Max SOFA	6 (0–20)	7 (3–20)	4 (0–18)	7 (1–17)	5 (0–17)
SAPS3 score	58 (29–108)	63 (41–105)	47 (29–74)	60 (32–108)	52 (30–85)
Mortality at 30 days	62 (23)	16 (21)	3 (9)	25 (31)	18 (22)

Table 2. Total calprotectin, S100A8 and S100A9 levels in plasma.

Patient group	All patients	Sepsis patients	Non-sepsis patients	Survivor at 30 d	Non-survivor at 30 d	Missing status patients
Variable (units)						
n	207	62	145	167	40	n/a
Median (IQR)	1.6 (0.6–3.6)	2.3 (1.4–5.1)	1.1 (0.5–2.6)	1.3 (0.5–3.1)	2.3 (1.2–5.8)	n/a
Mean	3.8	4.8	3.4	3.1	6.7	n/a
Min	0.0	0.1	0.0	0.0	0.1	n/a
Max	97.5	42.0	97.5	33.6	97.5	n/a
Variable (units)						
n	234	62	144	167	39	28
Median (IQR)	8341 (5624–13161)	8407 (6443–13726)	8579 (5114–12983)	8566 (5590–13016)	8872 (6005–14168)	7297 (5436–13094)
Mean	12440	12758	12670	11952	15882	10552
Min	782	1364	782	782	2186	1704
Max	144887	58412	144887	66925	144887	39446
Variable (units)						
n	216	58	132	152	38	26
Median (IQR)	849 (285–2427)	1087 (426–2565)	831 (191–2355)	831 (250–2373)	1163 (564–2827)	808 (371–2523)
Mean	2399	3378	2123	2533	2400	1617
Min	104	104	107	107	104	150
Max	80000	80000	29315	80000	29315	7533

**Figure 1.** Receiver operating characteristic curves for plasma levels of S100A9 and S100A8. Discrimination between sepsis vs non-sepsis is displayed.

and between S100A9 and S100A8 ($r=0.53$) was weak ($p<0.05$). (Figure 3).

Discussion

Receiver operating characteristic (ROC) analyses showed a larger area under the curve (AUC) value for total calprotectin

(0.67) [17] than for subunit S100A8 (0.59) or S100A9 (0.52) when used as a sepsis marker. The reason for this discrepancy is unknown, but we speculate that there is a shift of calprotectin subtypes during different stages of sepsis, with S100A8 and S100A9 being released from the neutrophils in the early phase of sepsis/infection dimerizing to calprotectin, contributing to the immediate inflammatory response.

Importantly, these dynamic changes in calprotectin subunits may not only reflect acute neutrophil-driven inflammation but may also signal a transition in the underlying immune cell landscape as sepsis progresses. Specifically, as the disease advances to later stages, there is an expansion of myeloid-derived suppressor cells (MDSCs), particularly the Gr1+CD11b+subset, which are known for their potent immunosuppressive properties during prolonged inflammation, such as in sepsis. A key feature of these cells in late-stage sepsis is the nuclear translocation of S100A9, a process crucial for driving their immunosuppressive phenotype. Normally residing in the cytoplasm, intracellular S100A9 translocates to the nucleus in late sepsis, facilitated by IL-10 signaling. This translocation transcriptionally activates immune repressor mediators, including miR-21 and miR-181b, which play central roles in immune evasion and systemic immunosuppression associated with sepsis [13].

The AUC in our study was basically the same for total calprotectin and S100A9, but lower for S100A8, when correlating to 30-day mortality.

The commercial sandwich ELISA used to analyze S100A8 (subunit) in our study measures free A8 or A8 complexed with other subunits, including calprotectin. The S100A9 ELISA measures free A9 and also shows cross-reactivity with calprotectin. This dual reactivity in both assays

(measuring monomers and complexes) may contribute to differences in correlation between methods. Despite relatively similar AUC, there was no significant correlation between the markers. The results indicate that it may be difficult to co-calibrate calprotectin methods from different manufacturers to a common standard.

Calprotectin is detected and quantified by assays that depend on antibodies as affinity reagents, such as ELISA, lateral flow assays (LFA), chemiluminescence immunoassays (CLIA), and turbidimetric assays. While the mono- or polyclonal antibodies used in such assays allow for sensitive and quantitative detection of calprotectin, side-by-side comparisons of immunoassays differ up to fivefold in reported calprotectin concentrations [25,26]. The observed variations may stem from heterogeneous standardization across assays from different providers but are likely also caused by general limitations of antibodies, such as protein heterogeneity, inter-batch variations, temperature-induced denaturation, and challenges in site-selective antibody immobilization [27–29]. Furthermore, calprotectin can occur as a dimer or tetramer, depending on the sample type and treatment, and some antibodies recognize the different species to different extents. Binding studies with the various forms of calprotectin or epitope mapping by phage display have shed light on the binding sites of some calprotectin antibodies [30], but none have characterized the structure of the antibody-antigen complex. Thus, many of the commercially applied assays cannot specify whether calprotectin is detected as a dimer, tetramer, or both, which may be one of the main sources of variability between assay manufacturers. There is a need to create an international calibration standard for calprotectin. We know that there are clear differences between the different fecal calprotectin methods, and it could very well depend on which subunits and multimer forms the different kits react against. A calprotectin kit could react against S100A8, S100A9, only dimers of S100A8 and S100A9 or have a selectivity for only multimer forms. It

Table 3. Comparison as AUC for total calprotectin, S100A8 and S100A9 sepsis and non-sepsis, as well as death at 30 days. AUC values for total calprotectin correspond to the same samples and data as previously published (17).

Sepsis:	AUC
Total calprotectin	0.67 (ref.17)
A8	0.59
A9	0.52
Mortality at day 30:	
Total calprotectin	0.64 (ref.17)
A8	0.59
A9	0.64

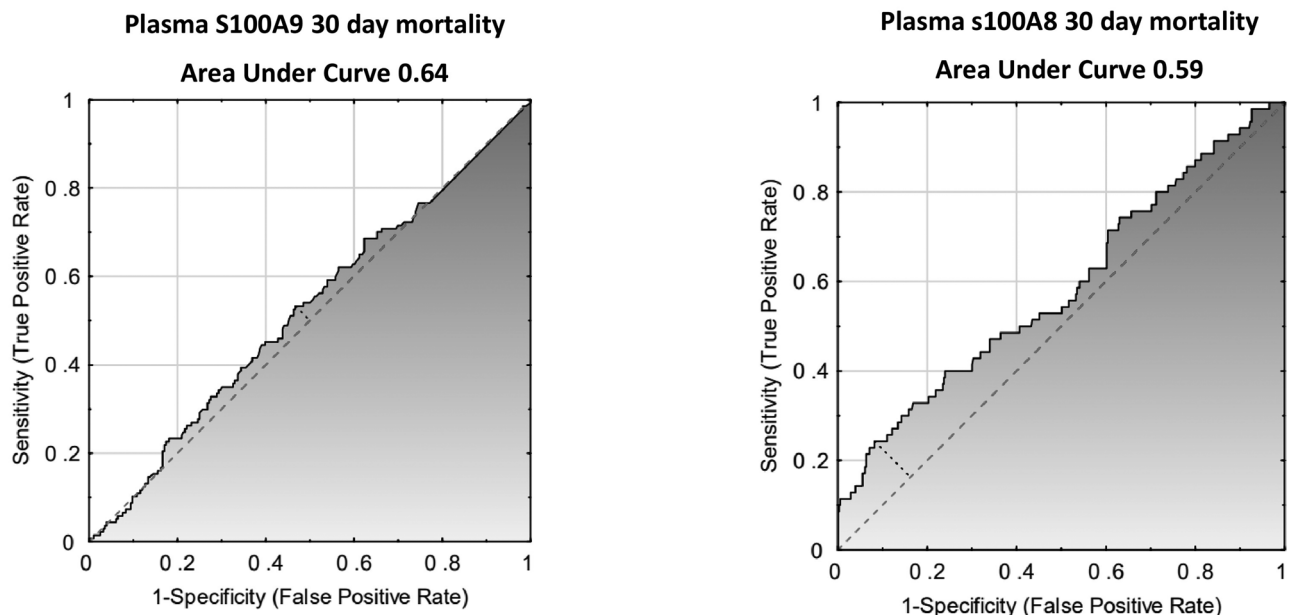


Figure 2. Receiver operating characteristic curves for plasma levels of S100A9 and S100A8. Discrimination between death vs survival at day 30.

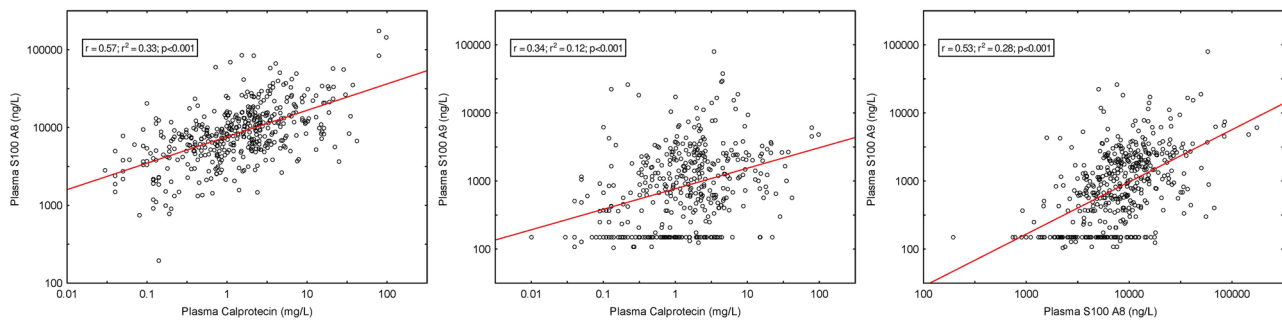


Figure 3. Scatterplot of log S100A8 (ng/L) against log plasma calprotectin (mg/L), scatterplot of log S100A9 (ng/L) against log plasma calprotectin (mg/L), and scatterplot of log S100A9 (ng/L) against log S100A8 (ng/L).

is difficult to interpret from the product insert which epitopes the kit reacts against. It will be problematic to harmonize calprotectin methods from different manufacturers to a common standard. The larger AUC for total calprotectin and the poor correlation between total calprotectin and S100A9, total calprotectin and S100A8, and between S100A9 and S100A8 serve as an argument to measure both forms, not just one subunit. To mitigate potential cross-reactivity issues in S100A8/A9 analysis, alternative approaches such as targeted mass spectrometry (e.g. multiple reaction monitoring) or hydrogen-deuterium exchange mass spectrometry could be used. These methods provide increased specificity by directly measuring peptides unique to each subunit or evaluating conformational states without relying on antibody-based detection.

Strengths and limitations

This is the first time that total calprotectin levels have been consistently compared to the levels of calprotectin subunits. The current study has several limitations, such as its cross-sectional design, which focuses solely on North European patients and includes a limited number of participants across different diagnostic groups. Additionally, there is an unequal gender distribution, insufficient representation of younger age groups, and reliance on just one commercial method for measuring total calprotectin. Nonetheless, all diagnoses are clearly defined.

Conclusions

Despite relatively similar AUC for identifying sepsis patients, there was no significant correlation between the different calprotectin markers (total, S100A8, versus S100A9). The results indicate that it is problematic to co-calibrate calprotectin methods from different manufacturers to a common standard. The AUC for sepsis was basically the same for calprotectin and S100A9, but lower for A8 in 30-day mortality. We speculate that the latter is because of reactivity against S100A9 (free or in calprotectin complex) in commercial calprotectin kits.



Disclosure statement

Aleksandra M. Havelka is employed by Gentian Diagnostics AB, Stockholm, Sweden. Other authors declare no competing interests.

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