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EXPERTS' OPINION

Presepsin as a biomarker in perioperative medicine

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ABSTRACT

Presepsin is the soluble fragment of CD14, a multifunctional glycoprotein expressed on the surface of innate immune cells. In healthy individuals, presepsin is present in very low concentrations with reference values ranging from 60 to 382 pg/mL. Several studies have shown that presepsin is a valuable biomarker for sepsis diagnosis in adults. Only lately, presepsin has been evaluated for prediction and early detection of neonatal sepsis and septic shock. Elevated plasma presepsin concentration has also been reported in patients undergoing cardiac and non-cardiac surgery and it has further been evaluated as a potential independent predictor of perioperative cardiovascular complications and mortality. Combined cardiac and inflammatory biomarker evaluation may offer additive predictive information, but further investigations in large populations are required to determine presepsin diagnostic and prognostic value, in order to personalize therapy and reduce surgical patients' morbidity and mortality.

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Presepsin is a novel, emerging biomarker, known as an early indicator of inflammation. Presepsin is the soluble 13 kDa N-terminal truncated fragment of the cluster-of-differentiation marker protein 14 (CD14). CD14 is a multifunctional glycoprotein having a key role in the recognition of pathogen- and damage-associated molecular patterns (PAMPs and DAMPs). It is commonly expressed on the surface of innate immune cells, mainly by monocytes and macrophages. Membrane-bound CD14 acts as a coreceptor of toll-like receptors (TLRs). In the presence of infectious agents or non-infectious stimuli, CD14 activates TLR-4. This, in turn, results in the activation of pro-inflammatory intracellular signaling cascades and NF-kB, eventually leading to the expression of pro-inflammatory cytokines such as IL-1b, IFN-y, TNF-a, IL-6 and IL-8.[1] This process is accompanied by shedding and releasing membrane-bound CD14 into the circulation. Soluble CD14 (sCD14) is subsequently processed by plasma proteases resulting in the generation of soluble CD14-subtype (sCD14-ST),[2] also called presepsin.[3]

In a reference population of healthy individuals, presepsin is present in very low concentrations with reference values ranging from 60 to 382 pg/mL. There are negligible differences between males and females but increasing presepsin levels were reported in older patients (>70 years; median [IQR] 470 [380; 601]).[4] Presepsin serum levels rapidly increase in response to the recognition of bacterial lipopolysaccharide (LPS) or other surface bacterial ligands includ-

ing gram-positive peptidoglycans, or to sterile, non-infectious monocyte or neutrophil activation.[5] Accordingly, presepsin has been identified as a marker of sepsis, with good sensitivity and specificity compared to other markers of inflammation, rendering it a valuable tool for early sepsis diagnosis and for the assessment of disease severity and prognosis. Elevated plasma presepsin concentration has also been reported in patients undergoing cardiac and non-cardiac surgery. Therefore, presepsin has further been evaluated as a potential independent predictor of perioperative cardiovascular complications and mortality.

The aim of this review was to summarize the current knowledge of the use of presepsin in critical patients including neonates and infants, adults, and patients undergoing major surgery.

Presepsin use in sepsis diagnosis and stratification

Presepsin is considered a valuable biomarker for sepsis diagnosis and evaluation of prognosis in septic patients. Sepsis is a complex syndrome caused by infection and characterized by dysregulated host-immune response resulting in various degrees of organ dysfunction. Septic shock, the most severe complication of sepsis, is associated with high a mortality rate up to 40%.[6] Sepsis care involves infection control, hemodynamic stabilization, organ support, and modulation of the sepsis response.[7] Yet, the availability of therapies which restore patients' endogenous immune capacity is still at the stage of development.[8] Moreover, the search for robust and reliable surrogate biomarkers for diagnosis, prognosis and monitoring of therapy is experienced as a pressing need by the intensive care community. Even though presepsin is not specific for sepsis, its characteristics — rapid activation kinetic (two hours following a bacterial or mycotic infection) and early peak of concentration (within three hours) — render it an appealing novel tool for early sepsis diagnosis and monitoring. Compared to procalcitonin (PCT) and C-reactive protein (CRP), presepsin kinetics is quicker. Blood levels of PCT rise within 3-4 hours after the onset of systemic infection and reaches its peak level within 8-24 hours, while serum CRP reaches its maximum peak within 48-72 hours.[9]

The cut-off value of presepsin for sepsis diagnosis is usually very high, 600 pg/mL or above, in order to obtain a sufficient specificity.[10] Presepsin increase has also been observed depending on disease severity.[11, 12] Patients with severe sepsis (median [IQR] 787 [464; 1249] pg/mL) present with higher presepsin levels compared to patients with systemic inflammatory response syndrome (SIRS) (212 [143; 300] pg/mL; $P<0.0001$) and moderate septic patients (325 [210; 480] pg/mL; $P<0.0001$); maximum values were measured in patients with septic shock (1084 [695; 2365], $P<0.0001$).[12] Moreover, multiple studies have shown that presepsin is a valuable marker to differentiate between non-bacterial SIRS and sepsis.[10, 12, 13] In neonates, plasma presepsin levels exceeding 600 pg/mL are considered normal and were reported in complete absence of clinical signs or symptoms of local or systemic infection.[14] Although a number of studies report increased diagnostic performance of presepsin compared to established sepsis markers,[11-13, 15, 16] a recently published meta-analysis concluded that there is no difference in the diagnostic performance of PCT and presepsin for sepsis diagnosis in critically ill patients.[17]

When presepsin is used for mortality prediction, higher cut-off values must be chosen.[18] When compared to other inflammatory biomarkers including CRP and PCT, several studies report that presepsin had better prognostic capacity for predicting short and long-term mortality in sepsis patients.[19, 20] A meta-analysis of six studies evaluating presepsin for mortality predicition revealed a considerable heterogeneity of presepsin cut-offs (ranging 556 to 2455 pg/mL) and corresponding sensitivities and specificities.[21] In a limited case series, Hassan found that presepsin levels in survivors declined significantly on day three compared to their admission levels and concluded that using presepsin levels to monitor the efficacy of antimicrobial therapy is feasible.[20]

Presepsin levels further depend on renal function, since it is a small protein filtered by the kidney. Therefore, these cut-off data are even more

difficult to rely on in the sepsis setting, where renal function is often compromised or altered by continuous renal replacement therapy (CRRT).[22]

Presepsin use in neonatal and pediatric sepsis

Neonatal sepsis constitutes a major cause of newborn morbidity and mortality.[23] Annually, invasive infections account for more than 1.4 million neonatal deaths worldwide.[24] Non-specific symptoms and laborious culture-based microbiological diagnostics hamper early sepsis diagnosis in neonates and infants, often leading to a significant delay of appropriate therapeutic treatment initiation.[25]

Several studies demonstrate increased presepsin levels among neonates diagnosed with bacterial sepsis compared to controls.[26-30] Similarly, presepsin is found elevated among early-onset *vs*. late-onset sepsis patients[30] as well as in non-survivors compared to survivors.[12, 26, 27, 30] In contrast, different than in adults, presepsin is unable to discriminate between neonatal bacterial sepsis and non-bacterial SIRS.[12, 27] Compared to common sepsis biomarkers including CRP, hs-CRP, PCT, IL-6, and WBC, several studies report superior discriminatory performance of presepsin for diagnosis of sepsis.[12, 27, 29, 31] Contradictory, Rashwan *et al.* report poorer discriminatory ability of presepsin compared to hs-CRP (P=0.005) and PCT (P=0.004).[30] Chen *et al.* monitored inflammatory biomarker dynamics in response to anti-infection therapy in 96 early-onset newborns.[12] As expected, presepsin, PCT, CRP and WBCs decrease three and five days upon treatment initiation. Moreover, presepsin positively correlates with APACHE-II score before and after therapy[12] suggesting to be a suitable marker for therapeutic treatment response monitoring. Gad *et al.* further assessed presepsin's relation to sepsis severity and mortality in 31 neonates and found a significant positive correlation between presepsin levels measured on day one of life and Tollner's sepsis severity score.[26]

El Gendy *et al.* extent these findings to pediatric patients. They prospectively studied 80 children with mean age of 14 months admitted to pediatric intensive care units (PICU), most frequently due to infections. Children with sepsis show higher presepsin levels compared to healthy controls (P<0.0001), but no difference was found between septic and non-septic PICU patients (P=0.39); neither between survivors and non-survivors (P=0.84). However, presepsin is associated with higher rates of mechanical ventilation (P=0.048) as well as longer PICU and hospital stay (P=0.012), suggesting being an appropriate indicator of disease severity.[32]

Pediatric oncology patients frequently develop chemotherapy-related febrile neutropenia, a major risk factor for bacterial infection. Urbonas *et al.* evaluated presepsin utility to predict bacteremia and sepsis in 37 pediatric haemato-oncological patients (median age six years). Presepsin was measured after confirmation of febrile neutropenia and patients were grouped into bacteramia/sepsis and fever of unknown origin group. Presepsin failed to discriminate between both groups.[33] Similar results were obtained by Plesko *et al.* (N.=33; mean age seven years). Presepsin showed no discriminatory ability for bacterial sepsis (AUC=0.49) and was unable to distinguish between gram-positive and gram-negative bacteremia.[9]

Multiple studies have demonstrated improved accuracy of presepsin in non-oncologic infants. Early and reliable detection of neonatal and pediatric sepsis is critical to reduce misdiagnosis and avoid excessive antibiotic therapy. As in adults, presepsin rises more rapidly compared to PCT and CRP.[29] The earlier the diagnosis of sepsis is raised, the more favorable may be the outcome predicted, provided that therapies are started as soon as possible. In this context, presepsin's greatest advantage may be its potential to speed up the diagnosis of sepsis. Therefore, presepsin constitutes a promising, rapid-responding biomarker for early sepsis diagnosis in neonates and infants.

Perioperative use of presepsin in cardiac and non-cardiac surgery patients

Annually, more than 310 million surgeries are performed worldwide.[34] Approximately 17% of patients undergoing elective in-patient surgery develop at least one postoperative complication

during hospitalization. Postoperative complications associated with major surgery substantially increase the risk of in-hospital mortality (OR 3.01 95% CI [1.65; 5.47]).[35] Major surgery evokes an inflammatory host-immune response. Excessive or misguided immune activation in response to surgical trauma, mechanical ventilation or other perioperative stress factors might lead to the development of adverse perioperative complications.[36] Accurate risk assessment is pivotal to identify patients, who might benefit from preoperative optimization or intensified postoperative monitoring to improve patient outcome. In recent years, there has been a growing interest in evaluating the utility of presepsin for the prediction of adverse complications and mortality following surgical procedures.

In multiple studies, researchers have shown a time-dependent increase of plasma presepsin concentration during major surgery indicating an inflammatory response to the intervention.[37-40] This effect is independent of the type of surgical procedure and is present in both, cardiac[38-40] as well as non-cardiac surgery patients.[37] Postoperative elevation of systemic inflammation markers is a common finding. However, Popov *et al.* noted that the risk of infectious complications after cardiac surgery (N.=51) depends on the type of perioperative presepsin dynamic. Patients with persistent presepsin increase throughout the postoperative period of six days are at highest risk to develop postoperative infectious complications.[41] Similarly, the authors of another study (N.=107) reported increased postoperative presepsin concentrations in heart-transplanted patients suffering from post-transplant infections.[42]

Aside from infectious complications, adverse cardiovascular events constitute another major cause of perioperative morbidity and mortality.[35] A significant proportion of perioperative myocardial infarctions results from atherosclerotic plaque rupture and subsequent coronary thrombosis[42] possibly triggered by non-specific inflammation associated with surgical stress. Atherosclerotic plaque progression and destabilization is mainly driven by monocyte-derived macrophages.[43] During monocyte activation and differentiation from the classical to the non-classical subtype, sCD14 is shed from the cell membrane and further processed to presepsin. Therefore, presepsin may be used to quantify monocyte activation.[44] Handke *et al.* investigated the association between perioperative leukocyte subset counts and presepsin concentration with the incidence of cardiovascular complications after non-cardiac surgery (N.=38). They demonstrated that enhanced monocyte mobilization accompanied by elevation of presepsin in response to the surgical intervention is restricted to patients who develop perioperative cardiovascular complications.[37]

Individual risk assessment before surgery is vital to identify patients at high risk for postoperative complications and to improve their prognosis. Current preoperative risk prediction relies on clinical risk indices and biomarkers. High-sensitivity cardiac biomarker assays allow detection of vascular and myocardial remodeling processes and have become indispensable prognostic tools in clinical routine. However, they do not allow evaluation of a patient's inflammatory state constituting the underlying mechanism in the development of cardiovascular events. This emphasizes the need to complement cardiac biomarker-based risk assessment by inflammatory biomarkers, which are directly involved in atherogenesis. A clinical study evaluating the additive value of preoperative presepsin for the prediction of perioperative cardiovascular complications after non-cardiac surgery found increased preoperative presepsin concentrations to be associated with the incidence of cardiovascular events (N.=38). Moreover, preoperative presepsin improved preoperative risk evaluation based on high-sensitivity cardiac troponin T (hs-cTnT; NRI=0.18 [0.04; 0.31]; P=0.014) and N-terminal pro-brain natriuretic peptide (NT-proBNP; NRI=0.33 [0.15; 0.49]; P=0.001) mainly by increasing correct reclassifications in the non-event group. Combined measurement of NT-proBNP and presepsin resulted in a 16% higher classification accuracy improvement compared to the combination of hs-cTnT and presepsin.[37] Presepsin was also tested in other surgical populations. Bomberg *et al.* demonstrated an independent association between preoperative presepsin and postoperative mortality in elective cardiac surgery patients (N.=856). After adjustment for con-

TABLE I.—*Overview of the perioperative use of presepsin (sCD14-ST) in cardiac and non-cardiac surgery patients.*

Reference	Year of publication	Study design	N. of subjects	Endpoint	Time of measurement
Cardiac surgery					
Popov *et al.*[41]	2015	Prospective	51	Infectious complications	POD 1
				In-hospital mortality	POD 3
Bomberg *et al.*[45]	2017	Prospective	856	30-day mortality	Pre-OP
				6-month mortality	Pre-OP
				2-year mortality	Pre-OP
Franekova *et al.*[40]	2017	*Post-hoc*	107	Infectious complications	POD 1
					POD 3
					POD 10
Stroeder *et al.*[46]	2018	*Post-hoc*	839	Mild non-occlusive mesenteric ischemic	Pre-OP
					POD 1
				Severe non-occlusive mesenteric ischemic	Pre-OP
					POD 1
Clementi *et al.*[47]	2019	Prospective	122	Renal complications	POD 2
				Respiratory complications	POD 2
				Cardiovascular complications	POD 2
				In-hospital mortality	POD 2
				30-day mortality	POD 2
				6-month mortality	POD 2
Non-cardiac surgery					
Handke *et al.*[37]	2019	*Post-hoc*	38	Cardiovascular complications	Pre-OP

AUC: area under the curve; CI: confidence interval; PPV/NPV: positive/negative predictive value; OR: odds ratio; POD: postoperative day; pre-OP: preoperative
*Values not reported in this publication were calculated based on the distribution of subjects in the event and non-event group, sensitivity and specificity. In detail, the number of patients who reached the endpoint and presented with presepsin above the respective cut-off (true positive rate) was computed by multiplying the total number of patients in the event group with the sensitivity; the number of patients with favorable

founders (*e.g.* age and eGFR), presepsin remains an independent predictor of 30-day (OR=14 [4.8; 40]; P<0.001), six-month (OR=12 [5.6; 25]; P<0.001) as well as 2-year mortality (OR=5.6 [3.2; 9.9]; P<0.001) and was superior (AUC=0.88 [0.81; 0.96]; P<0.001) when compared to established biomarkers for preoperative risk stratification including procalcitonin (AUC=0.59 [0.48; 0.69]; P=0.013), natriuretic peptides (AUC=0.77 [0.68; 0.84]; <0.001) and cystatin C (0.76 [0.64; 0.87]; P<0.001).[45] The same study cohort served to evaluate the association between presepsin and the occurrence of non-occlusive mesenteric ischemia (N.=839). Patients who suffer from non-occlusive mesenteric ischemia after cardiac surgery present with increased pre- and postoperative presepsin levels. However, only postoperative presepsin measured on the first day after surgery is an independent risk factor of non-occlusive mesenteric ischemia and correlates with disease severity.[46] Clementi *et al.* prospectively evaluated the predictive utility of postoperative presepsin for adverse complications following elective cardiac surgery (N.=122). Patients who die during hospitalization as well as patients with renal, respiratory and cardiovascular complications present with significantly higher presepsin concentrations on postoperative day two compared to patients without adverse outcome. Compared to procalcitonin (PCT), presepsin shows higher predictive value for in-hospital ($AUC_{PSEP=}$0.83 *vs*. AUC_{PCT}=0.66, P=0.025), 30-day ($AUC_{PSEP=}$0.72 *vs*. AUC_{PCT}=0.56, P=0.035) and six-month mortality ($AUC_{PSEP=}$0.78 *vs*. AUC_{PCT}=0.60, P=0.003) (Table I).[37, 40, 41, 45-47]

Renal function plays an essential role in the evaluation of plasma biomarkers as their concentration vastly depends on renal excretion. Likewise, plasma presepsin concentration rises with increasing renal impairment.[22] Saito *et al.* studied presepsin dynamics in end-stage kidney disease patients undergoing living kidney transplantation. Baseline presepsin levels are markedly higher compared to normal patients. After kidney transplantation, presepsin concentration consistently decreases indicating an association of presepsin with kidney function.[48] However, this does not seem to compromise presepsin util-

AUC [95% CI]	p_{AUC}	Cut-off [pg/mL]	Sensitivity [%]	Specificity [%]	PPV [%]	NPV [%]	OR [95% CI]	p_{OR}
0.75 [0.6; 0.89]		702	72	66	56*	80*	4.9 [1.4; 18]	
0.79 [0.63; 0.95]		683	80	68	28*	96*	8.4 [0.8; 84]	
0.88 [0.81; 0.95]	<0.001	293	84	83	13	99	21 [7.7; 56]	<0.001
0.87 [0.82; 0.92]	<0.001	289	77	84	23	98	16 [8.3; 32]	<0.001
0.81 [0.76; 0.86]	<0.001	215	77	74	25	96	9.3 [5.5; 16]	<0.001
		1100	75	52	22	92		
		1100	75	66	28	94		
		1100	56	82	35	91		
0.63 [0.54; 0.71]	0.009	154	76	49	7	98		
0.80 [0.74; 0.87]	<0.001	371	92	59	10	99	16 [4.9; 53]	<0.001
0.83 [0.73; 0.92]	<0.001	295	82	84	17	99		
0.91 [0.85; 0.96]	<0.001	639	89	85	20	99	44 [13; 147]	<0.001
0.76 [0.67; 0.83]		337.5	86	62	60*	87*		
0.67 [0.58; 0.75]		496.5	69	63	34*	88*		
0.84		1149.5	75	82	12*	99*		
0.83		675	86	73	16*	99*		
0.72		675	71	72	9*	99*		
0.77		675	80	74	3*	100*		
0.96 [0.85; 1]	0.001	184	100	82	45	100	47 [2.3; 952]	<0.001

outcome and presepsin below the respective cut-off (true negative rate) was calculated by multiplying the total number of patients in the non-event group with the specificity. Given these data, PPV and NPV were calculated by dividing the number of true positives by the total number of patients with presepsin above the respective cut-off (positive test result) or by dividing the number of true negatives by the total number of patients with presepsin below the respective cut-off (negative test result), respectively.

ity for prediction of major postoperative complications. Even after adjustment for renal dysfunction using multivariable modelling, presepsin was found to independently predict mortality[45] and non-occlusive mesenteric ischemia[46] after major cardiac surgery.

Currently, an international observational multicenter study is underway to prospectively validate preoperative presepsin as a marker for the identification of patients prone to develop major cardiovascular complications after non-cardiac surgery (Presepsin (sCD14-ST) for Prediction of Perioperative Risk - MET-REPAIR Nested Cohort Study; NCT03489486).

Independent of surgery and among non-infectious monocyte and neutrophil activation causes, presepsin increase has further been described in myocyte necrosis, reperfusion injury after acute myocardial infarction and heart failure (HF) occurrence. Caglar *et al.* measured presepsin in 48 ST elevation myocardial infarction (STEMI) patients, undergoing primary percutaneous coronary intervention, and within six hours of symptom onset. Presepsin was found significantly higher in STEMI patients compared to controls without coronary artery disease (1989 ± 3102 *vs*. 914 ± 911 pg/mL; P=0.001). Discriminatory performance of presepsin (AUC=0.69 95%CI [0.59; 0.78]; P=0.001) was lower compared to cTn-T (AUC=0.97 95%CI [0.94; 1], P=0.001). The authors defined a cut-off value of presepsin to detect STEMI (447 pg/mL), yielding a high sensitivity (88%), but low specificity (44%). Low specificity may be caused by the very large range (111 to 4000 pg/mL) of presepsin concentration found in the plasma of healthy subjects.[49]

Biyik *et al.* described an increase of presepsin level in the serum of 50 patients admitted to coronary care unit, because of acute decompensated HF, defined as having New York Heart Association Classification 2 to 4 and left ventricular ejection fraction lower than 40%. HF patients presented with elevated presepsin concentration compared to age-matched controls (1108 ± 1001 *vs*. 540 ± 527 pg/mL; P=0.001). Cut-off value for detecting HF was 472 pg/mL with 76% sensitivity and 63% specificity. C statistics (AUC= 0.73 95% CI [0.64; 0.84], P=0.001) indicate that

presepsin has moderate diagnostic efficiency. Univariate correlation analysis showed no correlation between presepsin and NT-proBNP, hsCRP or WBC (P>0.05). However, NT-proBNP showed better discriminatory performance for the detection of decompensated HF (AUC=0.99 95%CI [0.64; 0.84], P=0.001) than presepsin.[50]

Qi *et al.* measured plasma presepsin and PCT levels after resuscitation (day 0) and on days one and three after return of spontaneous circulation (ROSC), in 165 out-of-hospital cardiac arrest (OHCA) patients with ROSC longer than 12 hours. The immunologic profile of OHCA patients resembles septic patients and in fact, significantly increased presepsin levels were found in the circulation within four hours after ROSC (P<0.001). Moreover, within the first three days of ROSC, presepsin levels are persistently lower in 28-day survivors and patients with favorable neurologic outcome compared to non-survivors and patients with poor neurologic outcome, respectively. ROC analyses showed that presepsin has moderate discrimination for predicting 28-day mortality (AUC: 0.75 on day 0; 0.79 on day one, and 0.74 on day 3) and a similar discrimination for predicting 28-day favorable neurologic outcome (cerebral performance category (CPC) 1–2): AUC: 0.8 on day 0; 0.84 on day one, and 0.75 on day three.[51]

Multiple groups demonstrated that presepsin is a promising independent predictor of cardiovascular complications following major surgery. Several studies have proven a superior predictive performance of presepsin compared to established cardiac and inflammatory biomarkers. Yet, a limited number of studies have demonstrated increased plasma presepsin concentration after acute coronary syndromes and independent of surgery. Prognostic capacity of presepsin was only moderate and poorer than those of established cardiac biomarkers.

However, dysregulated activation of inflammatory cells is critical for development and progression of cardiovascular disease. Cardiac biomarkers, such as troponins and natriuretic peptides, convey strong predictive value for cardiovascular complications and mortality, but only rise as a consequence of myocardial injury or HF. Markers of inflammation, such as presepsin, directly reflect a patient's immunological state. Combined cardiac and inflammatory biomarker evaluation may offer additive predictive information by additionally identifying patients with yet clinically silent underlying cardiovascular disease, thereby substantially improving acute coronary event diagnosis and risk stratification.

Conclusions

Inflammatory biomarkers constitute a valuable tool to facilitate and accelerate diagnosis, identify high-risk patients, and for monitoring disease progression and therapy response. Measuring presepsin serum levels is convenient and fast by using commercial instrumentations (*e.g.* TOSOH Bioscience which apply fluorescent immunoassay, PATHFAST™ which apply chemiluminescent enzyme immunoassay). Its 24/7 bedside availability qualifies presepsin for a routinely tested biomarker and determining reference ranges of presepsin in stratified patient populations (*e.g.* age, comorbidities, timing of measurement, etc.) will be possible in near future. Moreover, variables known to affect other biomarker levels, such as CRP and PCT, should be considered. To improve diagnostic and prognostic accuracy, a multimarker strategy with simultaneous measurement of presepsin and established inflammatory or cardiac biomarkers should be anticipated. Future investigations in large groups of diverse patients are required to determine presepsin diagnostic and prognostic value in order to personalise therapy and improve patient outcome.

Key messages

- Presepsin is a biomarker for sepsis diagnosis in adults which has been recently evaluated for early detection of neonatal sepsis and septic shock.
- Presepsin increase has been described in myocyte necrosis, reperfusion injury after acute myocardial infarction and heart failure occurrence, independently of infectious monocyte activation causes.
- Presepsin is a promising independent predictor of cardio-vascular complications following major surgery.

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