Biomarkers of sepsis: Time for a reappraisal

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Additional file 1

Figure S1. Simple schematic of the main pathophysiological pathways influenced by the sepsis biomarkers that have been proposed

Table S1 Cytokine/chemokine biomarkers identified in the literature search (with some selected references)

Name [refs]	Main pathophysiologic role	Main findings
IL-1 receptor antagonists [1-7]	Bind to IL-1 receptors. Anti-inflammatory action [6]	Earlier diagnosis of sepsis in critically ill patients compared to conventional criteria. Predictor of poor outcome. Levels decreased with effective resuscitation
High mobility group box 1 (HMGB1) [8-21]	Pro-inflammatory cytokine secreted by macrophages several hours after their stimulation [20]	Increased 24 h after the initiation of treatment compared to baseline values in non-survivors. Peak observed 48 h after diagnosis
Tumor necrosis factor alpha (TNF-α) [22-27]	Pro-inflammatory cytokine- increases in endothelial permeability [28]	Correlation with APACHE II score
TNF-related weak inducer of apoptosis [29]*	Inflammation amplification, cell death inducer [30]	Higher in non-survivors. Lower levels in critically ill patients with sepsis compared to non-sepsis
A proliferation-inducing ligand [31, 32]*	B-cell activation [33]	Distinguished between survivors and non-survivors; lower in critically ill patients with sepsis compared to non-septic on admission.
Interleukin (IL)-1 beta [24, 34-41]	Pro-inflammatory cytokine released early in sepsis [42]	Conflicting results for identification of bacteremia in infants
IL-2 [43]	Promoting T-cell growth factor [44]	Lower in septic than non-septic patients
IL-4 [45-47]	Proliferation of Th2 cell production. IL-4 might also act as a barrier- sustaining agent to decrease the migration of bacteria	Low values on admission day associated with greater incidence of nosocomial pneumonia

	across the intestinal epithelium [48]	
IL-5 [49, 50]*	Cytokine for eosinophil growth and maturation and neutrophilic recruitment [51]	Increased in neutropenic children with septicemia
IL-6 [5, 11, 52-82]	Initiation of acute phase response [83]	Higher in patients with SIRS and infection compared to other critically ill patients. Persistent increase related to failure of sepsis treatment
IL-8 [78, 79, 84-88]	Regulator of neutrophil migration [89]	High serum levels predicted septic complication in pediatric patients
IL-10 [86, 90-97]	Repress expression of pro-inflammatory cytokines, mainly interferon -γ (IFN-γ) [98]	Diagnosis of septicemia - increased in non-survivors
IL-12 [99-103]	Early inflammatory action-production of IFN-γ [104]	Low IL-12 production after stimulation of whole blood with LPS predicted death from postoperative sepsis
IL-13 [105, 106]	Inhibits IL-6 secretion and TF expression [21, 107]	Higher in non-surviving septic patients
IL-15 [108]*	Blockage of TNFR-1 mediated apoptosis [109]	Persistently elevated levels in non-survivors
IL-17 [110]*	Pro-inflammatory cytokines that activate tissue-infiltrating neutrophils [111]	Higher admission values in trauma patients that later developed sepsis.
IL-18 [112-115]	Induction of IF-1 production by Th1 cells [116]	Distinguished between survivors and non-survivors. Higher in septic surgical patients compared to non-septic

IL-27 [117-120]*	Production from APC for early stimulation Th1 cells [121]	Helpful in the diagnosis of septicemia in combination with PCT in pediatric patients
IL-37 [122]*	Suppresses innate inflammatory reaction by binding to IL-18 receptor [123]	Increased in patients with sepsis compared to healthy controls
Pre B cell-colony enhancing factor (PBEF) [124-128]	Pro-inflammatory, shown to increase inflammatory cytokines, such as TNF-α, IL-1β, IL-16, and TGF-β1, and the chemokine receptor CCR3 [129]	Elevated levels in non-survivors
Monocyte chemotactic protein 1 [50, 87, 130-136]	Monocyte-macrophage recruitment and activation [137]	Increased in parallel with disease severity, prediction of 6-month mortality
Osteopontin [138-141]	Monocyte-macrophage recruitment and stimulation [142]	Persistent elevation in non-surviving septic patients. Diagnosis of sepsis in the emergency department
Leukocyte cell-derived chemotaxin 2 (LECT2) [143]*	Inhibits production of IL-1β, TNF-α, IL-6 [144]	Increased progressively in survivors. Lower in septic patients compared to healthy volunteers
GRO-alpha [145, 146]	Neutrophil recruitment [147]	Distinguished between survivors and non-survivors
Macrophage migration inhibitory factor (MIF) [134, 148-153]	Inhibition of macrophage migration and stimulation of secretion pro-inflammatory cytokines. Activation T-cells [154]	Prediction of death within 48 h. Limited diagnostic value
Regulated upon Activation Normal T cell Expressed and Secreted (RANTES) [155-158]	Chemotactic cytokine-angiogenetic factor [159]	Early diagnosis of sepsis in neonates: contradictory results
IP-10 [160, 161]	Chemokine secreted from cells stimulated with IFN-γ	Higher in neonates with necrotizing enterocolitis and sepsis compared

	and LPS. Plays an important role in recruiting activated T-cells [162]	to those with necrotizing enterocolitis without sepsis. Correlation with severity of acute respiratory infection.
Transforming growth factor (TGF-β) [163-165]	Suppresses the proliferation and differentiation of T- and B-lymphocytes and antigen presenting cells, and promotes fibrosis [166]	Distinguished between survivors and non-survivors with ARDS. No prognostic value in patients with Gram + infection. Differentiated influenza A (H1N1) infection from other causes of community-acquired infection
CXCL12 [167-169]*	Neutrophilic chemoattractive chemokine [170]	Higher in septic neonates and adults compared to non-septic. Predictive of death.
Macrophage inflammatory protein (MIP)-1 and -2 [88, 164, 171, 172]	Chemokine secreted from hematopoietic cells and fibroblasts. Secretion induced by endotoxin, interleukin (IL)-1, and tumor necrosis factor (TNF)-α. Plays a role in the regulation of leukocyte activation [171]	Distinguished between survivors and non-survivors at 28 days.

*new biomarker since earlier review

Table S2 Receptor biomarkers identified in the literature search (with some selected references)

Name	Main pathophysiologic role	Main findings
CRTh2 [173]	PGD$_2$ receptor on Th2 cell receptor-role in Th2 chemotaxis [174]	Lower in septic patients compared to healthy volunteers. Persistent low expression in non-survivors
Serum CXCR-4 [167, 169, 175]*	Neutrophil receptor of CXCL-12. Important for neutrophil mobilization [170]	Higher in septic neonates and adults compared to non-septic. Decreased 48h-72h after treatment initiation
CX3CR1 [176, 177]	Fractalkine receptor on monocytes. Important for monocyte recruitment to epithelial wall [178]	Persistently lower expression in non-survivors
Decoy receptor 3 [179-182]*	Soluble receptor of FasL secreted by APC after TLR-4 activation. Protection of lymphocytes from apoptosis [183]	Higher compared to patients with systemic inflammation without sepsis. Improved diagnostic value when combined with PCT and suPAR. Correlation with APACHE II score. Persistent increase in non-survivors
Soluble Fas [184-189]	Prevention of lymphocyte apoptosis [190]	Correlation to SOFA score
Soluble FLT-1 (VEGFR1) [191-194]	VEGF neutralization [195]	Correlation to SOFA score
Soluble and bound CD163 [54, 196-202]	Macrophage activation marker-T-lymphocyte proliferation inhibition [202]	Higher values in septic patients compared to non-septic critically ill patients. However, no diagnostic value in trauma patients. Distinguished between survivors and non-survivors
Soluble mannose receptor [198, 203, 204]*	Macrophage activation marker [205]	Distinguished between survivors and non-survivors. Higher in septic patients compared to non-septic critically ill patients.

Soluble protein C receptors [206-209]*	Inhibition of activated protein C anticoagulant activity [210]	Elevated levels on admission to ICU predicted sepsis development. Distinguished between survivors and non-survivors
Soluble Receptor for Advanced Glycation Endproducts (RAGE), (sRAGE) [211-217]	Competition with cellular RAGE neutralizing AGE actions [218]	Correlation with SOFA score
Soluble TNF receptors (1&2) [219-221]	Neutralization of TNF alpha- can be cleaved from the cell surface by the matrix metalloproteinase family in response to inflammatory signal [222]	Correlation with SOFA score. Higher in septic patients compared to non-septic healthy or critically ill patients. Validity has been assessed in neonates too.
Soluble triggering receptor expressed on myeloid cells (TREM)-1 [54, 201, 223-233]	Soluble form of TREM-1 secreted by phagocytes [234]	Diagnosis of septicemia- Distinguish between survivors and non-survivors
Soluble urokinase plasminogen activator receptor (suPAR) [235-253]	Facilitate recruitment of neutrophils and monocytes [254]	Distinguished between survivors and non-survivors. Improvement of APACHE II score predictive value. Early identification of bacteremia and VAP. Improve diagnostic value of PCT. Limited diagnostic value as sole biomarker in non-selected critically ill population.
CCR3 [173, 255]	Eotaxin receptor on Th2 cell - role in Th2 chemotaxis [173]	Lower serum levels in septic patients compared to healthy volunteers-Persistent low expression in non-survivors
Soluble IL-2 receptor [54, 256]	Indicative of T-cell activation [257]	Prediction of multiple organ failure development in patients with septic shock
Soluble tumorigenicity 2 (ST2) [258-262]	Attenuate Th2 response by binding to IL-33 [263]	Higher when compared to non-septic trauma or surgical patients. May improve prognostic value of

		PCT
Neutrophilic Toll-like receptor (TLR) 2 [264-266]	Recognition of bacterial peptidoglycan [267]	Higher in patients with sepsis compared to healthy subjects
Complement 5a receptors (C5aR) (cellular and soluble) [268-271]	Receptor of C5a-Complex C5a-C5aR significant for neutrophil migration, apoptosis diminution, coagulopathy reversion [272]	Cellular form: Negative correlation to sepsis severity Soluble form: Increased levels in non-survivors
NKG2D [273]*	Receptor on NK cells-pathogen recognition [274]	Higher than in non-septic critically ill patients
CD28, cellular and soluble [275]	Costimulatory receptor of T-cells [276]	Distinguished between survivors and non-survivors
CD64 [277-299]	High affinity receptor for the Fcγ part of the IgG heavy chain; process related to bacterial phagocytosis; expressed on activated neutrophils [300]	Higher in septic patients compared to non-septic critically ill patients. Sustained elevated levels were related to inappropriate antibiotic therapy.
sCD127 [301]*	Diminish excessive IL-7 signaling [302]	Distinguished between survivors and non-survivors
Presepsin [261, 303-326]*	N-terminal fragment of soluble CD14 (a LPS receptor on macrophage) [327]	Higher in patients with bacterial infection compared to those without bacterial infection. Earlier increase than PCT and CRP in neonates. Comparable diagnostic value with PCT in adults without acute kidney injury. Day-1 values distinguished survivors from non-survivors. Improved prognostic value of PCT. Changes in the levels used to monitor effectiveness of treatment and decision making to continue antibiotic treatment.
CD35 [328-330]	Complement (C4) receptors on dendritic cells. Relation to B-	Distinguished between febrile

	cell activation [331]	bacterial and viral infections
IL-1 receptor 2 [258-260, 332]*	Decoy receptor of IL-1 that inactivates IL-1 [333]	Differentiated critically ill patients with sepsis from patients with SIRS; more efficient for Gram (-) infections
Programmed death-1 (PD-1) receptor [334]*	Cell surface receptor. Negative regulator of immune response [335]	Higher in patients with sepsis compared to healthy controls. Higher in non-survivors septic patients.
CD40, cellular and soluble [275, 336]	Member of tumor necrosis factor (TNF) receptor superfamily. Found on activated macrophages and platelets [337, 338]	Increased in parallel with disease severity.
GP130 [339, 340]	A key receptor regulating activation of the acute-phase response through interleukin (IL)-6 [339]	Increased in sepsis compared with healthy controls
TRPV1 receptor [341]	Receptor situated on leukocytes, macrophages, and endothelial cells. It is related to bacterial phagocytosis and vessel vasodilation [342]	Increased in sepsis compared with healthy controls

*new biomarker since earlier review

Table S3 Cell marker biomarkers identified in the literature search (with some selected references)

Name	Main pathophysiologic role	Main findings
CD10 [343-345]	Lowers expression on immature neutrophil surface [343]	Prediction of patient degradation within 48h after sepsis onset
CD11b [284, 294, 346-351]	Regulation of neutrophil adhesion and migration [352]	Higher in neonates and adults with sepsis compared to healthy volunteers-High negative predictive value in combination with CRP
CD11c [353, 354]	Regulation of neutrophil adhesion and migration [355]	Higher in patients with sepsis compared to patients with non-infectious systematic inflammatory syndrome or healthy controls
CD16 [343, 356]	Negative effect on human monocyte capacity to phagocyte Gram-bacteria [357]	Prediction of patient degradation within 48h after sepsis onset
CD18 [358, 359]	Leukocyte, surface bound antigen. Soluble form is result of seeding from surface antigen induced by TNF-α [359]	Distinguish surviving and non-surviving septic patients
Soluble CD22 [360]*	Fragment of CD22 that is B-cell membrane protein. CD22 acts as an inhibitory coreceptor for B cells. [360]	Higher in patients with intraabdominal infection compared to controls. Correlated with APACHE II score
Soluble CD25 [91, 361-365]	Marker of T regulatory cells; indicative of their expansion [365]	Higher in septic patients compared to non-septic critically ill patients. Prediction of AKI development
CD31 [366]*	Marker of T-cells with angiogenic capacity	Inversely related to SOFA score-Higher in septic patients compared

	related to endothelial repair [367]	to healthy volunteers
CD39 [368]*	Catalyzes the phosphohydrolysis of pro-inflammatory extracellular ATP [369]	Distinguished between survivors and non-survivors
CD41 [370]*	Platelet specific antigen [371]	Distinguished between patients with sepsis secondary to fungal infection and of other etiology
CD48 [372]	Upregulated in activated immune cells. Participates in cell adhesion [373]	Higher expression on monocytes and neutrophils in septic patients compared to those of healthy volunteers. Lower expression on lymphocytes of septic patients compared to those with viral infection
CD80 [275]	Expressed on APC- Co-stimulator factor of T-cells [374]	Higher compared to healthy volunteers. Higher in patients with septic shock compared to septic patients without septic shock
Human leukocyte antigen-G5 (HLA-G5) [375, 376]	Antigen with anti-inflammatory activities (inhibits cytolytic functions of NK and T-cells) [377]	Distinguished between survivors and non-survivors
Human leukocyte antigen-DR (mHLA-DR) [292, 378-381]	Expressed on APC. Related to activation of T-cells [382]	Persistently low levels related to fatal outcome. Limited diagnostic value. Diagnosis of sepsis in combination with PCT in surgical patients
CD69 [383]	Expressed on T-cells early after their activation. Co-stimulatory factor for T-cell activation and proliferation [384]	Higher compared to healthy volunteers

L-selectin [385-388]	Found on neutrophil membrane and contributes to their adhesion to endothelial cells and transmigration across them [389]	Distinguished between survivors and non-survivors. Lower than in healthy volunteers
G protein-coupled receptor (GCPR) [390]*	Chemokine receptor expressed on neutrophils, related to neutrophil migration capacity [391]	Distinguished between survivors and non-survivors

*new biomarker since earlier review

Table S4 Coagulation-related biomarkers identified in the literature search (with some selected references)

Name	Main pathophysiologic role	Main findings
Antithrombin III, and antithrombin activity [392-395]	Coagulation inhibition and anti-inflammatory activity [396]	Distinguished between survivors and non-survivors
Activated partial thromboplastin time (aPTT) (transmittance waveform) [397, 398]	Value depending on CRP-VLDL complex formation. Indicative of CRP activity [399]	Distinguished between septic patients and non-septic critically ill patients
D-dimer [400-402]	Breakdown of fibrinogen and fibrin. Indicative of excessive coagulation activation [400]	Distinguished between survivors and non-survivors
Thrombin-antithrombin complex [403, 404]	Marker of thrombin generation [405]	Distinguished between survivors and non-survivors. Diagnosis of DIC in patients with sepsis
Prothrombin time (PT) [400]	Indicative of consumption and depletion of endogenous hemostasis factors [394]	Distinguished between survivors and non-survivors
Fibrin degradation products [406, 407]	Indicative of excessive coagulation activation [408]	Distinguished between survivors and non-survivors. Higher in septic patients compared to other critically ill patients
Plasminogen activator inhibitor (PAI) 1 [409-412]	Fibrinolysis inhibition [412]	Distinguished between survivors and non-survivors in sepsis-induced DIC
Protein C (PC) [403, 413-420]	Antithrombotic action via inactivation factors V and VIIIa [421]	Distinguished between patients with sepsis and patients with pneumonia without sepsis. Predictive of complications
Alpha-2 plasmin inhibitor (a2PI) [422]	Fibrinolysis inhibitor [423]	Early diagnosis of DIC in septic patients

Fibrinogen [395, 424]	Low activation of secondary fibrinolysis [425]	In combination with CRP, useful in diagnosis of severe sepsis in neutropenic patients
Thromboelastometry lysis index [426]	Indicative of hypercoagulable state [427]	Higher in septic surgical patients compared to non-septic surgical patients; better diagnostic capacity than PCP and CRP
Fibronectin [428-431]*	Clot stabilization, platelet activation and cell adhesion and invasion [432]	Lower in septic patients compared to non-septic patients
ADAMTS-13 [433-440]	von Willebrand factor cleaving protease [441]	Predicted organ dysfunction and mortality in septic patients
von Willebrand factor [440, 442-444]	Platelet adhesion and accumulation promotion [445]	Distinguished between survivors and non-survivors
Microparticles [446-448]	Fragments originating from plasma membrane, secreted by activated cells with procoagulation activity [449]	Development of DIC in patients with septic shock
Beta-thromboglobulin [450]	Platelet specific protein secreted by activated platelets. Proteolytic product of platelet factor 4 [451]	Higher in septic patients compared to healthy controls
Plasmin alpha2-antiplasmin complex [452]	A stable inactive complex; marker of plasmin production and fibrinolytic activation [453]	Prediction of MOF development
TIMP-1 [454-457]	Natural inhibitor of matrix metalloproteinases with anti-fibrinolytic function [458]	Distinguished between survivors and non-survivors

Tissue factor [459]	Transmembrane glycoprotein, is expressed by various cell types that activates coagulation cascade by binding to the factor VIIa [460]	Higher in patients with sepsis-induced ARDS compared to other patients with ARDS. Distinguished between survivors and non-survivors
Platelet factor 4 [461]	Platelet secreted protein, indicative of platelet activation [451]	Higher compared to healthy volunteers
Reduced coagulation factor XI (rFXI) [462]	Coagulation factor related to intrinsic coagulation system [463]	Increased in septic patients compared to healthy controls. Correlation with disease severity

*new biomarker since earlier review

Table S5. Microcirculation related biomarkers identified in the literature search (with some selected references)

Name	Main pathophysiologic role	Main findings
Angiopoietin-1, 2 [136, 464-472]	Secreted by peri-endothelial cells. Activation of Tie2 related to vascular integrity [473]. Angiopoietin-2 is an Angiopoietin 1 antagonist; binds to Tie-2 without inducing signal transduction [474]	Distinguished between survivors and non-survivors
Endothelial leukocyte adhesion molecule (ELAM)-1 [475, 476]	Endothelial specific molecule which mediates leukocyte adhesion to endothelium [476]	Higher in septic patients compared to non-septic trauma patients. Distinguished between survivors and non-survivors
Circulating endothelium progenitor cells, (cEPC) [477, 478]	Related to endothelium repair [479]	Higher in septic patients compared to healthy volunteers
Intercellular adhesion molecule (ICAM) [385, 480-486]	Contribute to neutrophil adhesion and transendothelial migration [487]	Diagnosis of sepsis in neonates. Correlation with the severity of sepsis.
Vascular cell adhesion molecule (V-CAM) 1 [385, 488-490]	Adhesion protein expressed by endothelial cells which binds to lymphocytes [491]	Prediction of sepsis encephalopthy development
Vascular adhesion protein (VAP)-1 [492]	Transmembrane glycoprotein in the vascular wall with two functions: enzymatic activity as monoamine oxidase and an adhesion molecule for lymphocytes [493]	Higher in septic patients compared to healthy controls
Serum laminin [494]	Component of extracellular matrix lamin derived by its	Distinguished between fungal and bacterial infection

	hydrolization [494]	
Syndecan-1 [492, 495-498]*	Glycocalyx component-Indicative of glycocalyx damage [499]	Distinguished between survivors and non-survivors. Early identification of sepsis complications in trauma patients. Prediction of respiratory failure in patients with sepsis due to pneumonia
Hepatocyte growth factor (HGF), cellular and soluble [500-502]	Pleiotropic factor synthetized by vascular cells and stimulates endothelial cells growth [503]	Response to antibiotic treatment
Neopterin [199, 504, 505]	Pyrazino-pyrimidine compound derived from GTP secreted by macrophage and endothelial cells after stimulation by TNF-α and INF-γ [506]	Higher in septic patients compared to non-septic critically ill patients
Platelet-derived growth factor, PDGF–BB [507]	Stimulates the proliferation of endothelial cells [508]	Distinguished between survivors and non-survivors
Vascular endothelial growth factor, VEGF, VEGF-A [191, 509-513]	Stimulates the proliferation of endothelial cells and inhibits endothelial apoptosis [514]	Distinguished between survivors and non-survivors; higher levels compared to healthy volunteers
E-selectin [515-518]	Arrest and facilitation of the migration of activated neutrophils at sites of vascular inflammation [519]	Prediction of acute kidney injury in critically ill patients with severe sepsis
Cysteinyl-leukotriene [520]	Eicosanoid derived from arachidonic acid via the 5-lipoxygenase pathway causing vascular leakage and neutrophil extravasation [521]	Distinguished between survivors and non-survivors
Heparin binding protein [522-	Protein founded in azurophilic granulae of	Prediction of MOF development. Monitoring response to treatment

530]*	neutrophils and secreted in the presence of bacteria; induces vascular leakage [531]	Higher in patients with sepsis compared to patients with infection or healthy controls
Raftlin [532]*	Major protein in lipid rafts produced by the endothelial protein C receptor-dependent cleavage of protease activated receptor 1 [533]	Higher compared to healthy controls; correlation with sepsis severity
Xanthine oxidase [534]	Oxygen dependent enzyme; adherence of activated polymorphonuclear neutrophils with endothelial cells lead to conversion of xanthine dehydrogenase to xanthine oxidase within the endothelium leading to the killing of endothelial cells [535]	Distinguished between survivors and non-survivors
Thrombomodulin [495, 517, 536, 537]	Membrane glycoprotein expressed on endothelial cells, which plays a major role in the protein C anticoagulation pathway [538]	Early prediction of MOF. Distinguished between survivors and non-survivors
Endocan [440, 539, 540, 540-544]	Soluble peptidoglycan that is expressed in human endothelial cells in response to pro-inflammatory cytokines. Enhances production of pro-inflammatory cytokines, increases microvascular permeability [545]	Persistent increased levels predicted death in patients admitted to ICU with sepsis. Diagnosis of pulmonary infection after cardiac surgery 48h before conventional diagnosis in patients with chronic kidney disease
14 kDA endocan fragments	Indicative of endocan	Higher in septic patients compared

[546, 547]	proteolysis [546]	to healthy volunteers

*new biomarker since earlier review

Table S6. Vasodilation-related biomarkers identified in the literature search (with some selected references)

Name	Main pathophysiologic role	Main findings
Adrenomedullin [547-555]	Peptide secreted by vascular smooth muscle cells and vascular endothelial cells that induces vasodilation mainly via generation 3,5cAMP [556]	Distinguished between survivors and non-survivors. Increased vasopressor needs
Pro-adrenomedullin [308, 551, 557-567]	Fragment of precursor of Adrenomedullin [558]	Distinguished between survivors and non-survivors. Prediction of organ failure. Improved the diagnostic value of PCT
Pro-vasopressin [558]*	Fragment of precursor of vasopressin [558]	Distinguished between survivors and non-survivors, in patients with septic shock
C-type natriuretic peptide [565, 568-572]	Secreted by endothelium and hyperpolarizes the underlying smooth muscle causing vasodilation [573]	Early diagnosis of sepsis in trauma patients. Treatment response monitoring. Higher in septic patients with brain lesions on MRI compared to septic patients without brain lesions
Substance P [574-576]	Secreted by macrophage lymphocytes and eosinophils; Acts via NK-1R receptor and has pro-inflammatory and vasodilatory activities; Increases also the vessels permeability [577]	Distinguished between survivors and non-survivors
Tetrahydrobiopterin [578, 579]	Endothelial nitric oxide synthase co-factor [580]	Higher in septic patients compared to non-septic critically ill patients

Vasoactive intestinal peptide (VIP) [581-583]	Neuropeptide that has vasodilatory activity by increasing adenylyl cyclase activity and cAMP concentration [584]	Higher in patients with septic shock compared to septic patients without shock
Elastin peptides [585]	Prostanoid synthesis and increased NO [586]	Lower in septic patients compared to healthy volunteers
Nitrite/nitrate [587-589]	NO bioreactor products [590]	Higher in patients with septic shock than patients with cardiogenic shock
CGRP [574, 591, 592]	Vasodilatory activity by increasing adenylyl cyclase and NO [593]	Correlation to APACHE II score
47kD HK [594]	Cleaved product of high molecular weight kininogen (bradykinin precursor molecular); indicator of bradykinin release [594]	Distinguished between survivors and non-survivors
Asymmetric dimethylarginine (ADMA) [595-597]*	Nonspecific NO synthase inhibitor [598]	Distinguished between survivors and non-survivors
FAAH mRNA [599]*	Enzyme which converts anadamide (a potential vasodilator) to arachidonic acid [600]	Lower in septic patients compared to healthy controls. Prediction of septic shock development
Hemoglobin subunit beta (Hbβ) [601]*	Component of Hemoglobin related to NO transfer and release [602]	Higher in septic shock patients compared to healthy controls
Cyclic nucleotides [603]	Single phosphate nucleotide. Producing vascular smooth muscle relaxation and vasodilatation [604]	Distinguished between survivors and non-survivors at 28 days
Neuropeptide Y [591, 605]	Vasoconstrictor peptide secreted by perivascular	Higher in patients with sepsis compared to healthy volunteers

	nerves [606]	

*new biomarker since earlier review

Table S7. Biomarkers of organ dysfunction in sepsis identified in the literature search (with some selected references)

Name	Main pathophysiologic role	Main findings
Pro-atrial natriuretic peptide (ANP) [607-612]	Secreted by atrial distention [613]	Distinguished between survivors and non-survivors. Could not predict the need of hospital admission for patients admitted to the ED with pyelonephritis
Brain natriuretic peptide (BNP) [568, 614-629]	Secreted by ventricular distention [613]	Distinguished between survivors and non-survivors. Fast decline of BNP may indicate response to treatment. Comparable predictive value with PC. Early sepsis diagnosis in trauma patients
Angiotensin converting enzyme (ACE) [630-636]	Localized to the luminal surface of pulmonary endothelial cells; it converts angiotensin I and activates bradykinin- Indicative of pulmonary endothelial cell dysfunction [633]	Lower in patients with septicemia and pneumonia compared to non-septic critically ill patients. It has no prognostic value
Endothelin-1, preproendothelin-1 [561, 637-641]	Peptide with vasoconstrictor and inotropic activities secreted by failing cardiac cells or liver endothelial cells [642]	Diagnosis of heart/liver dysfunction. In combination with pro-ADM can be used as predictor of death. Low diagnostic value in infants
Club cell secretory protein (CC)-16 [643]*	Protein secreted by bronchiolar club cells [644]	Identification of ARDS development
Chromogranin A [645, 646]*	A glycoprotein co-released with catecholamines from the adrenal medulla and peripheral nerve endings with vasodilatory activity. Indicative of adrenergic	Prediction of septic shock development

	activation and cardio-vascular dysfunction [647]	
Glial fibrillary acidic protein (GFAP) [648]	Secreted from activate astrocyte and is related to reactive gliosis [649]	Diagnosis of septic encephalopathy in children
Neuron specific enolase (NSE) [650-652]	Gamma isomer of enolase, a cytoplasmic enzyme of glycolysis located predominantly in neurons [653]	Diagnosis of septic encephalopathy. Distinguished between survivors and non-survivors
Neurofilament chains (plasma) [654]*	Proteins that are important for the neural cytoskeleton. Biomarkers of neuro-axonal injury [655]	Prediction of poor cerebral function outcome in sepsis survivors
Surfactant protein [643, 656, 657]*	Complex of lipids and proteins, functions to keep alveoli from collapsing at expiration. Serum concentration increase indicator of lung parenchymal destruction [658]	Early diagnosis of ARDS in septic patients
Parkinson disease 7 (PRK7) [659] [664]*	Multifunctional peptide involved in antioxidant defense of cells [660]	Early prediction of ARDS development in patients with sepsis or septic shock
Troponin-I [661-672]	3-unit complex located on actin filament, essential for cardiac muscle contraction [673]	Distinguished between survivors and non-survivors
Neutrophil gelatinase associated lipocalin (NGAL) [618, 674-686]*	Belongs to the lipocalin superfamily. Lipocalin secreted by activated neutrophils and epithelial cells [687]	Higher in septic patients with acute kidney injury compared to other septic patients. Prediction of myocardial dysfunction and fatal outcome. Prediction of renal function recovery. Urine NGAL had

		prognostic value in infants
Heart-type fatty acid-binding protein [688-690]*	Constitutes 5–15 % of the cardiac cells' cytosolic protein pool [691]	Diagnosis of heart dysfunction in sepsis- Distinguished between survivors and non-survivors
(alpha) glutathione S-transferase, urinary [692, 693]	detoxification enzymes electively present in the distal tubule [694]	Higher in septic patients compared to non-septic critically ill patients
Secretoneurin [695, 696]*	33-aminoacid peptide secreted by neuroendocrine cells and myocardium in states of heart failure as compensatory mechanisms. It enters cardiac cells by endocytosis and binds directly to calmodulin improving calcium homeostasis [697]	Levels on day 1 of ICU admission distinguished between survivors and non-survivors in patients with septic shock
MEGX test [698, 699]	Monoethylglycinexylidide measurement; lidocaine metabolite through cytochrome P-450 [700]	Correlation to SAPS II score. Diagnosis of liver dysfunction
Micro-RNA-122 [701-703]*	Micro-RNA specifically secreted from liver cells. It is secreted to plasma after hepatic cell damage [704]	Differentiated sepsis from infection within 24h after ICU admission. Improved the prognostic value of the SOFA score
Noncoding RNA [705, 706]*	Non protein-coding RNA with pro-inflammatory action [707]	Higher in septic patients compared to healthy controls. High levels can distinguish survivors and non-survivors in sepsis
S-100B (beta) [651, 652, 708-710, 710]	Calcium-binding protein released predominantly by astroglial cells after brain injury. Marker of the disruption of the blood	Higher in patients with sepsis encephalopathy compared to other septic patients. Distinguished between survivors and non-survivors

	brain barrier [711]	
C-terminal agrin fragment [712]*	Fragment produced by cleavage of agrin by neurotrypsin cleared via glomerular filtration [713]	Correlation with creatinine. Predicted need for renal replacement therapy
Proenkephalin [714, 715]*	Encephalin precursor expressed in epithelial cells of glomeruli [716]	Diagnosis of acute kidney injury in septic patients. Distinguished between survivors and non-survivors
Urinary human kidney Injury molecule type 1 (KIM-1) [717, 718]*	Cell-surface protein highly up-regulated on the surface of injured kidney epithelial cells [719]	Early diagnosis of acute kidney injury -Persistent elevation in non-survivors
Glutamate/glutamine [720]	Amino acid used by hepatic cells. Indicative of liver dysfunction [721]	Distinguished between survivors and non-survivors
Netrin-1 [718, 722]*	Lamin-like protein highly expressed in tubular epithelial cells after ischemia [723]	Early diagnosis of acute kidney injury

*new biomarker since earlier review

Table S8. Acute phase proteins used as biomarkers in sepsis identified in the literature search (with some selected references)

Name	Main pathophysiologic role	Main findings
Serum amyloid A (SSA) [724-734]	Apolipoprotein secreted by many cells triggered by IL-1, IL-6, and TNFa- ligand to TLR2 [735, 736]	Higher in septic neonates compared to healthy controls. Persistent high levels predict fatal outcome
Group II phospholipase A2 (PLA2-II) [68, 296, 737-742]	Enzyme secreted by different cells (e.g phagocytes and platelets) with bactericidal activity [743]	Higher compared to non-septic critically ill patients. Increased values on admission predicted fatal outcome. Limited diagnostic value in trauma patients
Ceruloplasmin [744, 745]	A copper containing glycoprotein synthesized in the liver increasing as part of acute-phase response; it has pro-inflammatory and anti-inflammatory properties [746]	Higher in septic neonates compared to healthy controls
C-reactive protein (CRP) [55, 63, 234, 285, 363, 552, 747-776]	Protein synthetized in the liver with multiple physiological roles: complement activation, pro and anti-inflammatory effects [777]	Distinguished between survivors and non-survivors
Ferritin [778]	Acute phase protein with a role in modulation host immune activity [779]	Distinguished between survivors and non-survivors, in children with sepsis
Transferrin [780]*	Acute phase protein with long half-life; transferrin sialic acid content indicative of neuraminidase activity [781]	Correlation with sepsis severity

Alpha-1-acid glycoprotein (AGP) [782-786]*	A heavily glycosylated protein; decreases the activity of neutrophils, it has an antiagreggant effect and possibly pro-inflammatory and anti-inflammatory effects [787]	Distinguished between survivors and non-survivors. Higher in patients with sepsis compared to non-septic critically ill patients
Hepcidin [788, 789]	Peptide that inhibits iron absorption in the small intestine [790]	Higher in neonates with sepsis compared to those without
Apolipoprotein C2 [791]	Downregulation in sepsis [792]	Higher in septic neonates compared to non-septic neonates
α-2 macroglobulin [793-796]	Binding protein, proteinase inhibitor [797]	Diagnosis of sepsis in surgical critically ill patients. Limited prognostic and diagnostic value in neonates
Apolipoprotein E [798, 799]	Increased concentration because of decrease in clearance [800]	Higher in children with bacterial infection compared to children without infection or non-bacterial infection
Lipopolysaccharide-binding protein (LBP) [17, 72, 801-810]	Connects to LPS of Gram (-) bacteria; facilitates the connection of LPS to CD14 [810]	Higher in surgical patients with sepsis than surgical patients with infection. Diagnostic accuracy comparable to CRP. Combination with other biomarkers (PCT, CRP) did not improve diagnostic efficiency. Serial measurement in patients with sepsis predicted ARDS development and fatal outcome
Procalcitonin (PCT) [55, 63, 120, 234, 285, 323, 362, 363, 505, 552, 618, 748-776, 806, 811-870]	Prehormone of calcitonin-Its secretion is stimulated mainly by IL-6, IL-1, TNF-a [871]	Higher in patients with septicemia compared to other critically ill patients
Pentraxin 3 (PTX3) [136, 872-885]	Secreted by macrophages and dendritic cells, can facilitate pathogen	Distinguished between survivors and non-survivors. Higher in septic patients compared to healthy

	recognition and removal [886]	controls. Improved the predictive value of PCT. Better prognostic value in patients with VAP
Complement factors C5a,C3a [887-890]	Fragment of C5 factor with chemoattractant components [891]	Higher in septic patients compared to healthy volunteers-Inverse relationship with SOFA score
HSP 70 [892-896]	Heat shock protein released by liver and spleen as acute phase reactant and participate in activation and maturation of DCs and protection of cells (antiapoptic effect) [897]	Higher in patients with septic shock compared to healthy controls
Pancreatic stone protein [362, 850, 898-904]	Acute phase protein secreted from pancreas stimulated by TNF-α, IL-6, IF-γ [905]	Distinguished between survivors and non-survivors in patients with peritonitis. Higher in infected compared to non-infected patients in ED and after cardiac operation
Fetuin-A [906]*	Acute phase protein that is counter-regulated by pro-inflammatory cytokines. [907]	Lower in non-survivors with sepsis. Negative correlation with APACHE II score

*new biomarker since earlier review

Table S9 Diverse sepsis biomarkers identified in the literature search (with some selected references)

Name	Main pathophysiologic role	Main findings
Apolipoprotein CI [908, 909]	HDL apolipoprotein that induces inflammatory response via its connection to LPS [910]	Distinguished between survivors and non-survivors
Selenoproteins [911-913]	Selenium rich protein with high antioxidant capacity [914]	Lower in septic patients compared to healthy volunteers. Septic shock prediction
Copeptin [915-921]	Reflects AVP levels as released in equimolar ratio with AVP [922]	Distinguished between survivors and non-survivors- Higher in patients with respiratory infection compared to non-septic ED patients. Not efficient in pediatric patients
Gc-globulin [923]	Protein of extracellular actin-scavenger system [924]	Prediction of development of respiratory failure and sepsis in trauma patients
Cold inducible RNA binding protein [925]*	Damage-associated protein secreted by damaged tissues that stimulates pro-inflammatory cytokine release. Contribution to endothelial dysfunction [926]	Distinguished between survivors and non-survivors
Coenzyme Q10 [927]*	Lipid founded in mitochondria, its role is an electron shuttle of the respiratory chain cofactor of dehydrogenases and an	Lower in septic patients compared to healthy volunteers

	antioxidant factor [928]	
F2-isoprostanes [929, 930]	Products of non-enzymatic lipid peroxidation [931]	Prediction of multiorgan failure development
Homocysteine [932]*	Secreted by activated mononuclear cells [933]	Distinguished between survivors and non-survivors
Malondialdehyde [934]*	Product of lipid peroxidation [933]	Distinguished between survivors and non-survivors
Uric acid [935-937]	Oxidative product of purine metabolism with antioxidant activity and nephrotoxic effects [938, 939]	Elevated uric acid at admission related to higher mortality
Myoglobin [940]*	Heterodimer composed of a peptide chain and heme found in the cytoplasm of myocardial and skeletal muscle cells. Rapid release into the blood circulation in case of injury [941]	Positive correlation with SOFA score 24h after ICU admission
Urinary 8-hydroxy-2'-deoxyguanosine (8-OhdG) [942]	Nucleoside produced by oxidative DNA damage [943]	Distinguished between survivors and non-survivors
Urinary bilirubin oxidative metabolites (BOMs) [944]	Bilirubin metabolites excreted in urine indicative of antioxidant activity of bilirubin [945]	Increased in parallel with disease severity
Cholesterol (total, LDL-C, HDL-C) [946-952]	Neutralizes bacterial endotoxin, enhances the antigen-presenting function of monocytes and principal precursor for steroid biosynthesis	Distinguished between survivors and non-survivors

		[952]
Phosphatidylethanolamine(18:0/20:4) [953]*	Aminophospholipid localized in the inner leaflet of plasma membrane. It is released to plasma after cellular blebbing [954]	Increased on day 1 in neutropenic patients with sepsis or septic shock
Diiodotyrosine [955]	Phagocytosing leukocytes metabolize T_4 to diiodotyrosine [956]	Increased in parallel with disease severity
Erythropoietin (EPO) [957]	Glycoprotein whose production is stimulated by tissue hypoxia [958]	Distinguished between survivors and non-survivors
Leptin [959-963]	Leptin is secreted by mononuclear cells ; it contributes in mononuclear activation, stimulates the production of pro-inflammatory cytokines and enhances the production of Th1 cells [964]	Higher in septic patients compared to non-septic critically ill patients
Adiponectin [965]*	Hormone secreted by adipocytes; via anti-inflammatory mechanism it limits leukocyte chemotaxis/infiltration and endothelial cell activation [966]	Distinguished between survivors and non-survivors
Renin [957]	Enzyme secreted by renal juxtaglomerular cells in response to sympathetic nervous system activation and decrease glomerular filtration [967]	Increased in parallel with disease severity

G-CSF and GM-CSF [968-972]	Hematopoietic growth factor central role functional activation of immature and mature neutrophils [973]	Distinguished between survivors and non-survivors
Procollagen III [974, 975]*	Component of Type III collagen; reflects collagen synthesis and tissue reparative process [976]	Higher in patients with severe sepsis compared to healthy volunteers. Predicted severe sepsis development
Albumin [977-981]	Indicative of increased vascular permeability [982]	Distinguished between survivors and non-survivors in patients with community-acquired bloodstream infection. Lactate/albumin was superior prognostic index than single lactate measurement for predicting 28-day mortality
Annexin V binding leukocytes [983]	Protein that shows high affinity for the surface presented phosphatidylserine; indicative of apoptosis [984]	Lower in surgical patients with sepsis compared to healthy volunteers
Anti-endotoxin core antibodies (EndoCab) [985, 986]	Indicative of endotoxin level and evaluation of endogenous immunity against endotoxin [987, 988]	Distinguished between survivors and non-survivors
Bactericidal/permeability increasing protein (BPI) [741]*	Cationic protein stored in polymorphonuclear leukocytes with bactericidal activity for Gram (−) bacteria; inhibit the numerous biological effects of LPS [989]	Higher in septic patients compared to non-septic patients admitted to emergency department
Cell-free DNA (cfDNA) [990-1000]	Coming from dead cells of	Distinguished between

	damaged tissue; indicative of tissue damage due to inflammation [1001]	survivors and non-survivors. Early sepsis diagnosis in patients with inflammatory reaction. Worse performance compared to PCT. Normal concentration can exclude sepsis in febrile patients
Ceramide [1002]	Product coming from hydrolysis of sphingomyelin by acid sphingomyelinase; acid sphingomyelinase is activated in response to stimulation with LPS, TNFα [1003]	Prediction of multiorgan failure development in sepsis
Circulating nucleosomes [1004-1007]	Complexes formed by DNA and histone proteins released by apoptotic cell death [1008]	Prediction of MOF development. Higher compared to non-septic critically ill patients. Markedly elevated in septic patients with severe coagulopathy
Dendritic cell [1009, 1010]	Cells that induce primary immune leading to T-cell activation [1011]	Correlation to SAPS and SOFA score
Factor VII activating protein, FSAP [1012, 1013]*	Plasma serine protease is activated by dead cells and removes nucleosomes from apoptotic cells [1014]	Distinguished between survivors and non-survivors
Granzyme A [1015]*	Serine-protease present in the intracytoplasmatic granules increased in agreement with NK activation [1014]	Distinguished between survivors and non-survivors. Lower in septic burned patients compared to non-septic
H-ficolin [1016]*	Protein related to activation of the lectin	Low in neutropenic children with septicemia

	complement pathway-indicative of innate immunity [1017]	
Catalytic antibodies [1018]*	Antibodies with enzyme-like properties [1019]	Distinguished between survivors and non-survivors
Inter-alpha inhibitor proteins [1020, 1021]	Protein that binds bikunin (a pro-inflammatory protein active when it is free)-Regulator of free bikunin levels [1022]	Lower in neonates with septicemia compared to others
Lactotransferrin (LTF) [1023-1025]	Protein secreted by neutrophils that limits microbial growth [1026]	Response to antibiotic treatment
Nociceptin/orphanin FQ (N/OFQ) [1027]	Opioid secreted by polymorphonuclear cells and monocytes with pro-inflammatory activity; increases capillary leakage and leads to immune cell chemotaxis [1028]	Distinguished between survivors and non-survivors
Peptidoglycan [1029]	Cell wall component [1030]	Diagnosis of bacteremia
Plasmalogen [1031]*	Phospholipid that protects cell membranes from oxidative stress [1032]	Lower in septic patients compared to healthy volunteers
Resistin (RETN) [1033-1038]	Cysteine-rich protein released by neutrophils with pro-inflammatory activity. Its pro-inflammatory role is related to the NF-kappa B signaling pathway [1039, 1040]	Distinguished between survivors and non-survivors-Higher in septic patients compared to non-septic

Selenium binding protein-1 [1041]*	Increased inversely with selenium concentration; inverse relation with glutathione peroxidases [1042]	Distinguished between survivors and non-survivors
Trefoil factor 2 [1043]*	Structural peptide secreted by predominantly by gastric mucous neck cells; secretion upregulated in gut injuries [1044]	Predicted MOF development
YKL-40 [1045]*	Glycoprotein consisting matrix protein of specific granules secreted early by activated neutrophils and macrophage [1046]	Distinguished between survivors and non-survivors
Bcl-2 [1047]	Protein that prevents dendritic cell apoptosis [1047, 1048]	Distinguished between survivors and non-survivors
Caspase-1 [1049]	Enzyme that converts proIL-1β to IL-1β and related to macrophage apoptosis [1050]	Higher in septic patients compared to healthy controls
Dipeptidylpeptidase activity [1051]	Cell surface protease that selectively removes N-terminal dipeptide from peptides [1052]	Decreased in septic patients compared to healthy controls
Gelsolin [1053, 1054]	Actin binding protein [1055]	Distinguished between survivors and non-survivors. Lower in septic patients compared to non-septic critically ill patients
Elastase [1056-1058]	Protein released by neutrophils to form neutrophilic extracellular	Response to antibiotic therapy in patients with osteomyelitis

	traps [1059]	
Growth arrest specific protein (Gas 6) [1060, 1061]	A vitamin K dependent protein released mainly by leukocytes and epithelial cells; participates in cell survival (neutrophils and epithelial cells) [1062]	Higher in septic patients compared to patients with infection but without sepsis
Elastase-alpha-1-proteinase inhibitor complex [1056, 1063]	A1-proteinase inhibitor inactivates elastase by forming complexes with it [1064]	Higher in neutropenic children with septicemia compared to others
Hyaluronan [1065, 1066]	Connective tissue polysaccharide; serum levels are regulated by production and influx via lymph and clearance by the liver [1067]	Distinguished between survivors and non-survivors
Intracellular nitric oxide in leukocyte [447, 1068]	Indicative of total NO concentration [447]	Negative correlation with SOFA score
Lysophosphatidylcholine [837, 1069, 1070]*	Endogenous lysophospholipid related to macrophage 1 stimulation [1071]	Serial measurement distinguished survivors and non-survivors
Matrix-metalloproteinases [454, 456, 457, 685, 1072, 1073]	Zn^{2+} dependent endopeptidase secreted by neutrophils and involved in extracellular matrix degradation [1074]	Limited predictive value for death. No diagnostic value
NF-kB activity [1075]	Transcriptional regulatory factor that plays fundamental role in activation of the cytokine cascade and production of other pro-inflammatory	Distinguished between survivors and non-survivors

	mediators [1076]	
Ischemia-modified albumin [1077-1079] *	Produced after modification of the N-terminus albumin by reactive oxygen species [1080]	Higher in septic patients compared to healthy controls
Sphingomyelinase [1081]	Hydrolyzes the ubiquitous sphingophospholipid sphingomyelin to ceramide which is associated to apoptosis [1082]	Distinguished between survivors and non-survivors
Sulfite [1083]	Inorganic substance released by activated IIb neutrophils [1084]	Response to treatment
Citrulline [1085-1088]*	Amino acid that is synthesized solely by the gut. An intermediate amino acid in urea cycle for L-arginine synthesize and NO production [1089]	Decreased levels predict development of ARDS in patients with sepsis. Decreased levels on day 1 in patients with neutropenic fever and bacteremia. Low levels of citrulline in catheter-related bloodstream infections
Histidine-rich glycoprotein [1090, 1091]*	Multidomain protein produced by liver. Maintains neutrophils and vascular endothelial cells in an inactive state. Decreases rapidly in sepsis [1091]	Decreased levels could differentiate diagnosis of sepsis versus patients with SIRS. Low levels on day 1 were associated with higher mortality
Calprotectin [1092-1097]*	Protein of cytosolic fraction of neutrophils released in circulation after their activation [1098]	Prediction of bacterial infection within 24h of admission. Better diagnostic value than PCT. Differential diagnosis bacterial sepsis to viral infection
Uncoupling protein 2 (UCP2) [1099]*	Mitochondrial protein	Higher compared to healthy

	that cause a decrease in ATP synthesis [1100]	controls. Correlation with the severity of sepsis. Decreased after effective antibiotic treatment initiation
Soluble CD154 (CD40L) [1101]*	Expressed on a variety of cells. Ligand to CD40 receptor related to T-cells stimulation [337]	Distinguished between survivors and non-survivors. Higher compared to healthy volunteers
P-selectin [385, 1102-1107]	Glycoprotein that is stored in endothelial cells or in platelets. It is associated with leukocyte recruitment [1108]	Higher in critically ill patients that developed an infection after their admission compared to others that never developed infection. High levels related to fatal outcome
Anadamide [1109]	Endocannabinoid that modulates NO production [1110]	Increased in sepsis compared with healthy controls
2-arachidonoylglycerol [1111]	Endocannabinoid with anti-inflammatory activity [1112]	Increased in sepsis compared with healthy controls
Carbamoyl phosphate synthase [1113, 1114]	Protein primarily localized in mitochondria [1114]	Increased in sepsis compared with healthy controls
Terminal complement complex [1115]	Product of final common reaction sequence of complement activation [1115]	Decreased in plasma in sepsis compared to healthy controls
Ghrelin [959, 1116]	Peptide produced by the stomach with anti-inflammatory activity, reestablishing the proliferation of CD4 T cells [1117]	Increased in sepsis compared with healthy controls
H2S [1118, 1119]	H2S is generated from cysteine metabolism, a reaction catalyzed by	Detection in expired gas of children. Higher in septic than non-septic mechanically

	phosphotyrosine-5'-phosphate-dependent enzymes. Different biological effects including pro-inflammatory, anti-inflammatory and vasodilatory [1120]	ventilated children and neonates
Serum lysozyme (enzyme activity) [1121]	Protein that is released from leukocytes and macrophages, a mediator of myocardial depression and vasodilation. It also deposits in the systemic vasculature causing acute organ failure [1122]	Higher in septic transplant recipients patients compared to those with graft rejection without any infection.
Neurotensin [1123]	Neuropeptide that induces hypotension [1124]	Increased in sepsis and related to death
PIGF [1125]	A member of the vascular endothelial growth factor family with pleiotropic activities. It counteracts the production of VEGF protective hosts from heart dysfunction and vascular leakage [1126]	Increased in sepsis and related to death
Selenium [1127, 1128]	An essential trace metal, which has direct antioxidant activity by incorporating into selenoproteins. Low levels are associated with increased oxidative stress [1129]	Low levels predicted fatal outcome
Myeloperoxidase [1130, 1131]*	Enzyme secreted by activated neutrophils	Increased in sepsis compared to non-septic critically ill

	[1132]	patients
Tenascin-C [1133]*	Glycoprotein which increases pro-inflammatory cytokines secretion by macrophages inhibiting at the same time the synthesis of anti-inflammatory cytokines [1133]	Increased in sepsis compared to non-septic critically ill patients. Association with sepsis severity and fatal outcome
Fibroblast growth factor-21 [1134]*	Amino acid predominantly produced by the liver. It has an anti-inflammatory effect [1135]	Distinguished between survivors and non-survivors
Developmental endothelial locus-1 [1136]*	Endogenous inhibitor of leukocyte adhesion to endothelium [1137]	Higher in septic patients compared to healthy control. Higher in more severely ill septic patients
Apoptosis inhibitor of macrophage (AIM) [1138]*	IgM-binding protein which acts as recognition molecule. It also has apoptosis inhibitor function for macrophages, T-cells and NKT cells [1139]	Higher in septic patients compared to healthy control. Distinguished between survivors and non-survivors at ICU admission
Acylcarnitine [1140]*	Acetylated form of L-carnitine [1140]	Distinguished between survivors and non-survivors
C1q/tumor necrosis factor-like protein 3 (CTRP3) [1141]*	Adipokine with metabolic (inhibition of gluconeogenesis, lowering glucose levels) and anti-inflammatory effects [1142]	Lower in critically ill patients with sepsis compared to critically ill patients without sepsis. Correlation with disease severity
Delta-like canonical Notch ligand 1 (DLL1) [1143]*	Monocyte transmembrane protein, upregulated during	Higher in septic patients than in patients after major surgery or trauma patients without

	infection and plays a role in monocyte accumulation and amplification of pro-inflammatory cytokine response [1144]	infection or healthy controls

*new biomarker since earlier review

Table S10. QUADAS-2 score [1145] for quality assessment for the studies that included >300 patients where ROC curve analysis was used

	Patient selection		Index test		Reference standard		Flow and Timing
	Risk of Bias	Applicability	Risk of Bias	Applicability	Risk of Bias	Applicability	Risk of bias
Diagnosis of Sepsis							
Hanna et al 2015 (interleukin-27) [120]	Low	Low	Unclear	Low	Low	Low	Low
Chaaban et al 2019 (inter-alpha inhibitor proteins) [1021]	Low	High	High	Low	High	Low	Unclear
Dimoula et al 2014 (CD64) [298]	Low	Low	High	Low	Low	Low	Low
Sakr et al 2008 (lipopolysaccharide-binding protein) [810]	Low	Low	High	Low	Low	Low	Low
Nakamura et al 2019 (presepsin) [867]	High	Low	High	Low	Low	Low	Unclear
Henning et al 2019 (IL-6) [82]	Low	Low	High	Low	Low	Low	Low
Survival prognosis							
Giamarellos-Bourboulis et al 2012 (uPAR) [239]	Low	Low	High	Low	Low	Low	Low

Novotny et al 2006 (IL-12) [101]	Unclear	High	High	Low	Low	Low	Low
Chen et al 2009 (BNP) [615]	Unclear	Low	High	Low	Low	Low	Unclear
Chen et al 2013 (adrenomedullin) [550]	Low	Low	High	Low	Low	Low	Low
Saeed et al 2019 (pro-adrenomedullin) [567]	Low	Low	High	Low	Low	Low	Low
Rodelo et al 2012 (D-dimer) [402]	Low	Low	High	Low	Low	Low	Low
Kornblit et al 2013 (YKL-40) [1045]	Low	Low	High	Low	Low	Low	Low
Dimoula et al 2014 (CD64) [298]	Low	Low	High	Low	Low	Low	Low
Ranniko et al 2018 (cell-free DNA) [1146]	Unclear	Low	High	Low	Low	Low	Low

IL: interleukin

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