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Endothelial cell-specific molecule–1/endocan: Diagnostic and prognostic value in patients suffering from severe sepsis and septic shock

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ABSTRACT

Purpose: This study aims to assess the diagnostic and prognostic value of endocan in patients with severe sepsis or septic shock on a medical intensive care unit (ICU).
Methods: 150 patients suspected for at least severe sepsis were enrolled on a medical ICU. On days 1, 3, and 8, plasma levels of endocan, procalcitonin (PCT), and interleukin (IL)-6 were measured. Follow-up on all-cause mortality was performed after 30 days and 6 months.
Results: Endocan correlated with Acute Physiology and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA), and Simplified Acute Physiology Score II (SAPS II) ($P < .006$). Endocan was higher in patients with at least severe sepsis compared with systemic inflammatory response syndrome (SIRS) or sepsis patients ($P = .0006$) on days 1, 3, and 8. With a minimum sensitivity of 70%, uniform cutoff levels were set for ≥ sepsis at 1.8 ng/mL, for ≥ severe sepsis at 2.6 ng/mL, for ≥ septic shock at 2.9 ng/mL. On day 1, endocan levels of the fourth quartile were significantly associated with 30-days and 6-months mortality compared to lower levels. After adjustment in Cox regressions, endocan still revealed prognostic value.
Conclusions: Endocan showed diagnostic capacity to diagnose patients with severe sepsis and septic shock and revealed prognostic information for 30-days and 6-months all-cause mortality.

1. Introduction

Sepsis is among the most common causes of death on internal intensive care units (ICUs) with an estimated mortality rate greater than 25% in patients suffering from septic shock [1–3]. Early recognition and treatment might prevent the development of multiorgan failure, septic shock, and sepsis-related death [2]. Currently, only a combined judgment of clinical signs as well as hemodynamic and laboratory parameters appears to improve objective and correct diagnostic decision making of severe sepsis and septic shock [4]. A wide range of biomarkers has been evaluated within the last decades, but only few showed sufficient sensitivity or specificity to reliably diagnose or predict the future course of these patients [2,5–7]. Biomarkers being used in today's clinical practice, such as C-reactive protein (CRP) and procalcitonin (PCT), reveal only moderate accuracy as potential biomarkers for sepsis in recent studies [2]. This lack of sufficient biomarker knowledge raises the need for ongoing research on new and more evidence of reliable biomarkers.

Endothelial cell-specific molecule–1 (ESM-1)—so-called endocan—is a soluble proteoglycan that is expressed by the vascular endothelium [8]. Its expression is regulated by several cytokines and growth factors, such as vascular endothelial growth factor [9–12]. However, limited data attribute a mediating role in the pathogenesis of sepsis to endocan because it was correlated with the severity and outcome in small cohorts of patients with sepsis, severe sepsis, or septic shock [12–15,11]. Therefore, this study aims to evaluate the diagnostic as well as short- and long-term prognostic value of endocan in these patients during the first week of treatment on a medical ICU.

2. Materials and methods

2.1. Study patients, design, and data collection

The Mannheim Sepsis Study (clinicaltrials.gov identifier: NCT01535534) is a single-center, prospective, controlled study performed on a medical ICU at the First Department of Medicine, University Medical Centre Mannheim, in Mannheim, Germany. Patient enrollment started in October 2011. The study was carried out according to the principles of the Declaration of

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Table 1
Baseline characteristics of the Mannheim Sepsis Study

	Controls (n = 60)	SIRS (n = 14)	Sepsis (n = 9)	Severe sepsis (n = 35)	Septic shock (n = 92)
Age, y (mean, range)	62 (42-87)	70 (42-81)	65 (35-83)	66 (26-87)	67 (26-88)
Sex, n (%)					
Male	29 (48)	10 (71)	5 (56)	24 (69)	65 (71)
Female	31 (52)	4 (29)	4(44)	11 (31)	27 (29)
Site of infection, n (%)					
Lung	–	0 (0)	7 (78)	23 (66)	55 (60)
Urinary tract	–	0 (0)	0 (0)	4 (11)	6 (7)
Abdominal	–	0 (0)	0 (0)	5 (14)	13 (14)
Central nervous system	–	0 (0)	1 (11)	0 (0)	0 (0)
Skin	–	0 (0)	0 (0)	1 (3)	4 (4)
Heart	–	0 (0)	1 (11)	1 (3)	2 (2)
Neutropenia	–	0 (0)	0 (0)	1 (3)	4 (4)
Blood	–	0 (0)	0 (0)	0 (0)	0 (0)
Others	–	0 (0)	0 (0)	0 (0)	8 (9)
Laboratory values, mean ± SEM					
WBCs, 10^9/L	–	14.2 ± 2.4	16.8 ± 2.4	17.8 ± 2.6	19.2 ± 1.6
Platelets, 10^9/L	–	193 ± 29	250 ± 27	220 ± 20	182 ± 13
Bilirubin, mg/dL	–	0.9 ± 0.2	0.5 ± 0.1	1.9 ± 0.8	3.1 ± 0.7
Creatinin, mg/dL	–	1.8 ± 0.5	1.2 ± 0.2	2.3 ± 0.3	2.7 ± 0.2
CRP, mg/L	–	82 ± 18	129 ± 23	180 ± 20	202 ± 11
PCT, ng/dL	–	9.4 ± 6.4	4.4 ± 2.3	7.1 ± 1.9	19.9 ± 3.7
IL-6, pg/mL	–	724 ± 289	122 ± 30	1251 ± 726	6728 ± 2806
MCP-1, pg/mL	–	2499 ± 1315	479 ± 75	1430 ± 530	2819 ± 499
pCO_2, mm Hg	–	44 ± 4	47 ± 8	42 ± 3	44 ± 2
Positive blood cultures, n (%)	–	0 (0)	0 (0)	11 (31)	36 (39)
ICU parameters, mean ± SEM					
ICU days	–	8 ± 2	13 ± 6	11 ± 2	13 ± 1
Ventilation days	–	3 ± 1	4 ± 1	6 ± 2	9 ± 1
Catecholamine days	–	2 ± 0.7	3 ± 1	2 ± 0.9	7 ± 0.8
Renal replacement therapy days	–	0 ± 0	0 ± 0	2 ± 0.7	3 ± 0.6
APACHE II, mean ± SEM	–	24 ± 2	19 ± 2	19 ± 2	27 ± 1
SOFA score, mean ± SEM	–	10 ± 1.4	7 ± 1.3	8 ± 0.7	12 ± 0.4
SAPS II, mean ± SEM	–	44 ± 3	35 ± 5	39 ± 3	46 ± 1.5
All-cause mortality, n (%)					
30 days					
Death	0 (0)	8 (57)	3 (33)	12 (34)	53 (58)
Survivor	60	6 (43)	6 (67)	23 (66)	39 (42)
6 months					
Death	0 (0)	9 (64)	4 (44)	16 (46)	67 (73)
Survivor	60 (100)	5 (36)	5 (56)	19 (54)	25 (27)

Helsinki and was approved by the medical ethics commission II of the Faculty of Medicine Mannheim, University of Heidelberg, Germany. Written informed consent was obtained from all participating patients or their legal representatives.

The study was designed to reflect a representative cohort of patients with a minimum age of 18 years who had proven criteria of severe sepsis or septic shock found typically on a medical ICU [7]. The medical ICU at University Medical Centre Mannheim, Mannheim, Germany, consists of 28 ICU beds and is under the supervision of the First Department of Medicine. Critically ill patients from all departments of internal medicine (ie, cardiology, pneumology, angiology, nephrology, rheumatology, gastroenterology, oncology, hematology, and geriatrics), the neurologic department and the emergency department, as well as from emergency medical services are treated. Surgical or trauma patients are usually treated on a separated operative ICU. The medical ICU comprises all types of invasive and noninvasive mechanical ventilation, renal replacement therapies (ie, hemodialysis, hemodiafiltration, plasmapheresis, kidney transplant), as well as invasive cardiopulmonary support (eg, cardiac assist devices such as the Impella [AbioMed, Danvers, MA] or the CardioHelp system [Maquet GmbH, Rastatt, Germany]). A cardiac catheterization laboratory is available 24 hours, and a hybrid operating room is present. Main exclusion criteria were any traumatic or postoperative cause of sepsis development. Diagnosis of systemic inflammatory response syndrome (SIRS) and of sepsis severity was based on established criteria [7,16,17]: when patients revealed a microbiologically or clinically proven infection, they were assigned to the sepsis group. Patients were categorized to the severe sepsis group if they developed at least one of the following newly developed,

Table 2
Univariate correlations of presepsin with laboratory and clinical parameters in all patients (n = 150) at day 1

	r	*P* value
Laboratory values		
Albumin	−0.16	.05
WBCs	0.24	.004
Platelets	−0.19	.02
PCT	0.17	.04
Base excess	−0.24	.004
Lactate	−0.23	.006
pH value	−0.20	.02
ICU parameters		
Renal replacement days	0.20	.02
Days of survival	−0.22	.008
Systolic blood pressure	−0.18	.02
Mean arterial pressure	−0.21	.008
Scores		
GCS	−0.23	.005
SOFA score	0.30	.0005
SAPS II score	0.25	.006
APACHE II score	0.27	.001

GCS indicates Glasgow Coma Scale.

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