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Added value of serial bio-adrenomedullin measurement in addition to lactate for the prognosis of septic patients admitted to ICU

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To the editor:

Sepsis mortality decreased over the last decades, although it remains dramatically high [1]. The implementation of guidelines such as the Surviving Sepsis Campaign (SSC) contributed to these progresses. SSC recommends to guide resuscitation on normalization of lactate levels [2]. Guiding resuscitation on lactate reduction is highly debated [3]. Anyway, normalization of lactate is associated with improved outcome [4]. We have recently shown that plasma levels of bio-adrenomedullin (bio-ADM), a peptide regulating vascular integrity and endothelial function, were associated with patient outcome during sepsis [5]. Interestingly, we observed that patients with elevated bio-ADM levels at admission and with low bio-ADM levels 2 days later had similar outcome to patients with persistently low bio-ADM levels. We therefore aimed to evaluate the added value of bio-ADM to lactate measurement in the AdrenOSS-1 cohort.

The AdrenOSS-1 study is a prospective observational study conducted in 24 centers within 5 European countries and included 583 septic patients from June 2015 to May 2016 [5]. The primary endpoint was 28-day mortality. We evaluated the relationship between the association of initial evolution of lactate plasma levels and bio-ADM level at 24 h and outcome in patients for whom both markers were available at admission and 1 day later ("24 h"). As described previously, bio-ADM levels below or above 70 pg/mL were considered respectively as low and high [5].

In patients with high lactate levels (> 2 mmol/L) at admission ($n = 328$) (Table 1), lactate normalization (< 2 mmol/L) at 24 h was associated with better outcome than in patients with persistently high lactate at 24 h (28-day mortality 15.9% vs 41.9% respectively, HR 3.3 [2.0–5.3], $p < 0.001$) (Fig. 1).

Interestingly, among patients with decreasing lactate, high and low bio-ADM levels at 24 h identified patients with substantially different outcomes (28-day mortality 7% vs 26% for low vs high bio-ADM respectively, HR 4.4 [1.6–11.7], $p < 0.005$) (Fig. 1). High and low bio-ADM levels at 24 h also differentiated outcome of patients with persistently elevated lactate (HR 4.5 [1.6–12.3], $p < 0.005$).

In patients with low initial lactate ($n = 234$ admitted and $n = 171$ alive at 24 h), overall 28-day mortality was 11.2%, neither lactate nor bio-ADM added prognostic value.

For all analyses, similar results were obtained, when missing 24 h data were replaced by the last available values.

Accordingly, our data suggest that measurement of bio-ADM in addition to lactate may help physicians to refine risk stratification and therefore to guide resuscitation during sepsis.

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Table 1 Clinical characteristics of septic patients admitted with a lactate level > 2 mmol/L and alive at 24 h ($n = 269$)

Patient characteristics	All	24 h lactate < 2 mmol/L and bio-ADM < 70 pg/mL	24 h lactate < 2 mmol/L and bio-ADM > 70 pg/mL	24 h lactate > 2 mmol/L and bio-ADM < 70 pg/mL	24 h lactate > 2 mmol/L and bio-ADM > 70 pg/mL	*p* value	Number of patients (if not indicated $n = 269$)
Number of patients (*n*, %)	269 (100)	75 (27.9)	70 (26.0)	28 (10.4)	96 (35.7)		
bio-ADM at admission (pg/ml)	113.7 [59.3–206.4]	46.7 [33.1–63.0]	137.3 [103.2–217.8]	61.5 [36.3–84.3]	192.4 [129.0–355.6]	< 0.0001	
Lactate at admission (mmol/l)	3.6 [2.6–5.5]	2.8 [2.3–3.5]	3.3 [2.5–4.5]	3.5 [2.7–4.6]	5.4 [3.5–8.8]	< 0.0001	
Age (years)	65.7 [54.7–75.6]	64.0 [54.4–71.8]	65.7 [58.5–74.3]	67.6 [56.8–76.9]	67.8 [54.6–77.4]	0.4697	
Male sex (*n*, %)	171 (63.6)	52 (69.3)	45 (64.3)	18 (64.3)	56 (58.3)	0.5253	
Body mass index (kg/m^2)	26.1 [23.1–30.8]	26.1 [23.9–29.4]	25.1 [20.5–30.4]	26.4 [22.9–31.3]	27.3 [23.6–31.8]	0.3834	$n = 232$
Septic shock at admission (*n*, %)	172 (63.9)	34 (45.3)	46 (65.7)	15 (53.6)	77 (80.2)	0.0001	
Type of ICU admission						0.1378	
Medical (*n*, %)	198 (73.6)	62 (82.7)	49 (70.0)	24 (85.7)	63 (65.6)		
Surgical—emergency procedure (*n*, %)	60 (22.3)	10 (13.3)	18 (25.7)	4 (14.3)	28 (29.2)		
Surgical—elective procedure (*n*, %)	11 (4.1)	3 (4.0)	3 (4.3)	0 (0.0)	5 (5.2)		
Origin of sepsis						0.0156	
Lung (*n*, %)	87 (32.3)	28 (37.3)	16 (22.9)	15 (53.6)	28 (29.2)		
Bloodstream (*n*, %)	35 (13)	14 (18.7)	8 (11.4)	4 (14.3)	9 (9.4)		
Urinary tract (*n*, %)	46 (17.1)	4 (5.3)	15 (21.4)	4 (14.3)	23 (24)		
Catheter (*n*, %)	15 (5.6)	4 (5.3)	3 (4.3)	3 (10.7)	5 (5.2)		
Peritonitis (*n*, %)	16 (5.9)	6 (8.0)	3 (4.3)	0 (0.0)	7 (7.3)		
Endocarditis (*n*, %)	14 (5.2)	4 (5.3)	4 (5.7)	1 (3.6)	5 (5.2)		
Bile duct infection (*n*, %)	4 (1.5)	0 (0.0)	2 (2.9)	0 (0.0)	2 (2.1)		
CNS (*n*, %)	1 (0.4)	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)		
Skin and soft tissue (*n*, %)	4 (1.5)	4 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)		
Gynecologic (*n*, %)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)		
Other (*n*, %)	46 (17.1)	10 (13.3)	19 (27.1)	1 (3.6)	16 (16.7)		
Medical history							
Any cardiac comorbidity (*n*, %)	184 (68.4)	43 (57.3)	49 (70)	18 (64.3)	74 (77.1)	0.0481	
Chronic heart failure (*n*, %)	29 (10.9)	6 (8.0)	5 (7.2)	3 (11.1)	15 (15.8)	0.2684	
Hypertension (*n*, %)	143 (53.8)	33 (44.0)	38 (55.1)	14 (50.0)	58 (61.7)	0.1407	
Diabetes mellitus (*n*, %)	76 (28.4)	21 (28.0)	19 (27.5)	3 (10.7)	33 (34.4)	0.1102	
Any noncardiac comorbidity (*n*, %)	198 (73.6)	51 (68.0)	55 (78.6)	21 (75.0)	71 (74.0)	0.5447	
Chronic renal disease (*n*, %)	31 (11.7)	6 (8.1)	10 (14.5)	2 (7.1)	13 (13.7)	0.4978	
Active/recent malignant tumors (*n*, %)	60 (22.5)	10 (13.3)	19 (27.9)	7 (25.0)	24 (25.0)	0.1565	
Smoking (active) (*n*, %)	57 (21.8)	17 (23.0)	15 (22.1)	5 (19.2)	20 (21.5)	0.9827	
COPD (*n*, %)	35 (13.1)	9 (12.0)	12 (17.4)	5 (17.9)	9 (9.5)	0.4156	

Table 1 Clinical characteristics of septic patients admitted with a lactate level > 2 mmol/L and alive at 24 h ($n = 269$) *(Continued)*

Patient characteristics	All	24 h lactate < 2 mmol/L and bio-ADM < 70 pg/mL	24 h lactate < 2 mmol/L and bio-ADM > 70 pg/mL	24 h lactate > 2 mmol/L and bio-ADM < 70 pg/mL	24 h lactate > 2 mmol/L and bio-ADM > 70 pg/mL	*p* value	Number of patients (if not indicated $n = 269$)
Any chronic medication (*n*, %)	176 (65.4)	42 (56.0)	53 (75.7)	16 (57.1)	65 (67.7)	0.0632	
Immunosuppressive therapy (*n*, %)	26 (9.7)	5 (6.7)	5 (7.1)	3 (10.7)	13 (13.5)	0.3963	
Physiological values at admission							
Temperature (°C)	37.2 [36.3–38.3]	37.2 [36.4–38.3]	37.2 [36.4–38.2]	36.9 [35.8–37.7]	37.2 [36.3–38.4]	0.6926	
Mean blood pressure (mmHg)	73 [62–92]	82 [68.5–99]	70.5 [60–84]	77.5 [58–94.2]	69 [58.5–86]	0.0009	$n = 266$
Heart rate (beats/min)	108 [96–122]	110 [93–123.5]	107 [95.2–118.7]	106 [97.7–115]	112.5 [97.7–130.2]	0.2976	
Central venous pressure (mmHg)	8 [5–12]	8 [5–13]	7 [3–11]	8 [7–8]	9 [6–12]	0.3535	$n = 75$
Glasgow Coma Scale score (points)	15 [13–15]	15 [14–15]	15 [14–15]	14 [13–15]	15 [13–15]	0.4721	$n = 253$
Fluid balance (mL)	2500 [1141–4716]	1930 [892–2626]	2156 [1375–3939]	2820 [1292–4323]	3657 [1426–5750]	0.0002	$n = 235$
Urine output for 24 h (mL)	1000 [354–1867]	1350 [941–2667]	675 [301–1619]	1562.5 [951–2220]	600 [177–1480]	< 0.0001	$n = 248$
PaO_2/FiO_2	220 [131–330]	254 [155–362]	231 [145–321]	211 [96–330]	190 [115–314]	0.1637	$n = 244$
Laboratory values at admission							
Arterial pH	7.36 [7.27–7.42]	7.41 [7.34–7.45]	7.37 [7.26–7.42]	7.38 [7.31–7.44]	7.31 [7.22–7.38]	< 0.0001	$n = 261$
Bilirubin (μmol/L)	12 [7–22]	13 [6.75–22.2]	11 [5.5–20.5]	12 [8–20.5]	12 [7–22]	0.7229	$n = 259$
Platelets (10^9/L)	188 [116–265]	180 [128–261]	176 [110–284]	243 [135–336]	181 [110–245]	0.2770	$n = 268$
Creatinine (mg/dL)	1.5 [1.02–2.26]	1.13 [0.85–1.63]	1.79 [1.23–2.65]	1.03 [0.74–1.45]	1.72 [1.2–2.62]	< 0.0001	
Urea (mg/dL)	66 [41–109.91]	50.45 [36.04–78.34]	85.29 [53.6–118.77]	52 [33.48–77.27]	73.57 [46.7–120.84]	0.0001	
Hematocrit (%)	35 [30–39]	36 [30–39]	35 [30–40]	35 [31–37]	34 [29–40]	0.9579	$n = 265$
White blood cell count (per mm^3)	11,690 [6037–18,142]	13,400 [8390–18,700]	11,115 [5497–16,500]	11,770 [7780–15,950]	10,780 [4200–17,722]	0.1827	$n = 268$
Troponin T, maximum at admission (ng/mL)	41.73 [18–219]	24 [14–50.5]	40.86 [19.5–126.75]	14 [13–47]	87.5 [27.82–329.25]	0.0535	$n = 73$
Troponin I, maximum at admission (ng/mL)	100 [29.9–323]	79 [19.25–327.23]	135 [37.02–233.68]	114.95 [22.48–230]	100 [31.9–312.95]	0.9752	$n = 77$
PCT, maximum at admission (ng/mL)	19.17 [6.33–79.32]	10.36 [4.35–37.93]	27.62 [7.75–60]	5.42 [2.24–11.21]	43.64 [9.6–103.41]	0.0054	$n = 144$
PCT, central laboratory (ng/mL)	15.34 [5.37–48.43]	8.21 [2.4–18.21]	22.55 [9.68–53.25]	7.12 [2.04–20.73]	29.22 [8.73–64.8]	< 0.0001	$n = 269$
BNP, maximum at admission (pg/mL)	376.2 [159–1132]	376.2 [169.5–1011]	356.1 [228–540.2]	219 [143.7–324]	757 [141.7–1619.5]	0.4335	$n = 49$
NT-proBNP, maximum at admission (pg/mL)	5119 [1620–17,118]	1847 [621–6709]	3873 [2594–23,052]	792 [249–3074]	7097 [4884–24,340]	0.0135	$n = 54$
Organ support at admission							
Mechanical ventilation						0.0008	
Invasive (*n*, %)	125 (46.5)	24 (32.0)	29 (41.4)	12 (42.9)	60 (62.5)		
Noninvasive (*n*, %)	49 (18.2)	16 (21.3)	9 (12.9)	7 (25.0)	17 (17.7)		
None (*n*, %)	95 (35.3)	35 (46.7)	32 (45.7)	9 (32.1)	19 (19.8)		
Renal replacement therapy (*n*, %)	28 (10.4)	1 (1.3)	7 (10.0)	3 (10.7)	17 (17.7)	0.0070	
Vasopressors/inotropes at admission (*n*, %)	192 (71.4)	41 (54.7)	51 (72.9)	18 (64.3)	82 (85.4)	0.0001	

Table 1 Clinical characteristics of septic patients admitted with a lactate level > 2 mmol/L and alive at 24 h ($n = 269$) *(Continued)*

Patient characteristics	All	24 h lactate < 2 mmol/L and bio-ADM < 70 pg/mL	24 h lactate < 2 mmol/L and bio-ADM > 70 pg/mL	24 h lactate > 2 mmol/L and bio-ADM < 70 pg/mL	24 h lactate > 2 mmol/L and bio-ADM > 70 pg/mL	*p* value	Number of patients (if not indicated $n = 269$)
ICU scoring systems							
SOFA (points)	8 [6–11]	6 [4–9]	8 [7–11]	8 [5–9]	10 [7–11.5]	< 0.0001	$n = 240$
APACHE II (points)	17 [13–22]	15 [10–18]	17 [12.2–21]	18.5 [13.7–23]	19 [15–23.2]	< 0.0001	
ICU length of stay (days)	6 [3–11]	5 [3–7.5]	7 [4–13]	5.5 [2.7–9.5]	7 [3–16.2]	0.0170	
Mortality							
28-day, deaths (*n*, %)	75 (27.9)	5 (6.7)	18 (25.7)	4 (14.3)	48 (50.0)	< 0.0001	
90-day, deaths (*n*, %)	93 (34.6)	10 (13.3)	22 (31.4)	6 (21.4)	55 (57.3)	< 0.0001	

Data are presented as median [IQR] or *n* (%)

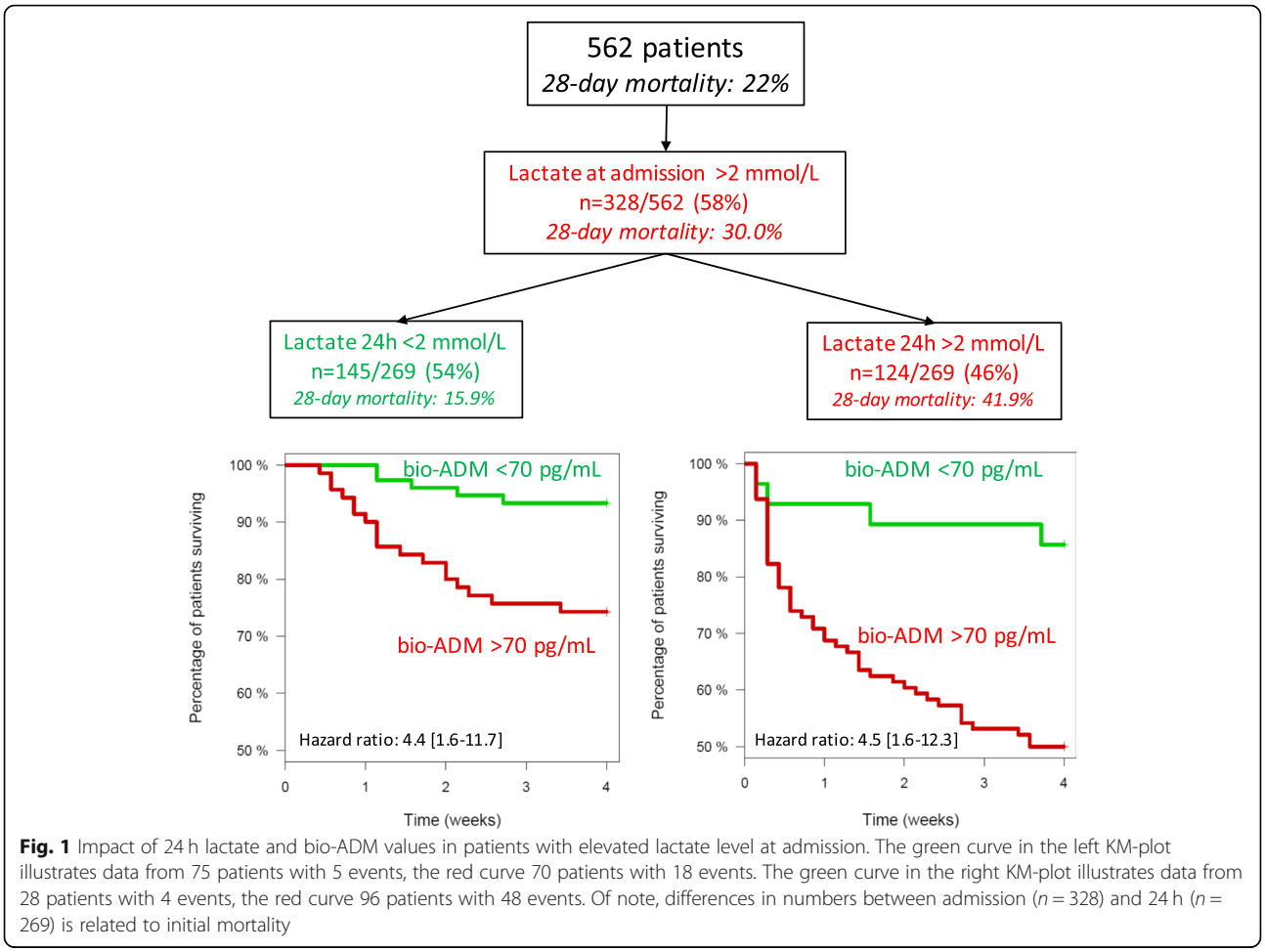

Fig. 1 Impact of 24 h lactate and bio-ADM values in patients with elevated lactate level at admission. The green curve in the left KM-plot illustrates data from 75 patients with 5 events, the red curve 70 patients with 18 events. The green curve in the right KM-plot illustrates data from 28 patients with 4 events, the red curve 96 patients with 48 events. Of note, differences in numbers between admission ($n = 328$) and 24 h ($n = 269$) is related to initial mortality

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Ethics declarations

Charles de Roquetaillade works as a resident in the Saint Louis Lariboisière University Hospitals. Alice Blet is an attending physician in the Department of Anesthesiology and Critical Care of Saint Louis Lariboisière University Hospitals. Oliver Hartmann and Joachim Struck are employees of sphingotec GmbH, the company that developed and holds patent rights in the bio-ADM assay. The other authors are members of the steering committee and/or investigators in the Adrenoss study.

Authors' contributions

All authors contributed to the study concept and design. BC, EG, AM, and JS contributed to the acquisition of data. BC, AB, CR, OH, JS, EG, and AM contributed to the analysis and interpretation of data. BS, JS, and AM drafted the manuscript. All authors critically revised the manuscript for important intellectual content. OH contributed to the statistical analysis. EG and AM obtained funding. EG and AM provided administrative, technical, or material support. EG and AM supervised the study. All authors read and approved the final manuscript.

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Availability of data and materials

AM had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Ethics approval and consent to participate

The present study was conducted in France, Belgium, The Netherlands, Italy, and Germany. The study protocol was approved by the local ethics committees, and the study was conducted in accordance with Directive 2001/20/EC as well as good clinical practice (International Conference on Harmonization Harmonized Tripartite Guideline version 4 of May 1, 1996, and decision of November 24, 2006) and the Declaration of Helsinki. Patients were included from June 2015 to May 2016.

Consent for publication

Not applicable.

Competing interests

AM has received speaker's honoraria from Novartis, Orion, and Servier and fees as a member of the advisory board and/or steering committee from Cardiorentis, Adrenomed, sphingotec, Sanofi, Roche, Abbott, and Bristol-Myers Squibb. EG has received consulting fees from Adrenomed, Roche Diagnostics, and Magnisense and lecture fees from Edwards Lifesciences. OH and JS are employees of sphingotec GmbH, the company that developed and holds patent rights in the bio-ADM assay. BC received fees as a member of an advisory board from Roche Diagnostics. The other authors declare that there are no competing interests.

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