Soluble FcγRIA expressed on monocytes (sCD64): A new serum biomarker of acute kidney injury in patients with suspected infection at emergency department admission

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Dear Editor,

acute kidney injury (AKI) has been proven to be an independent risk factor for prolonged hospitalization and mortality in patients with sepsis [1]. Although measurement of the serum creatinine concentration is widely used for the detection of AKI, it does not predict its early occurrence, since AKI precedes a significant rise in serum creatinine [1]. Numerous studies have attempt to identify new serum biomarkers to diagnose AKI at an earlier stage [1]: for example, soluble triggering receptor expressed on myeloid cell-1 (sTREM-1) has been associated with sepsis-related renal damage [2]. It has been hypothesized that sTREM-1 may be released in blood circulation by infiltrating inflammatory cells as result of alteration in glomerular filtration barrier membrane pore size and charge [2].However, many mechanisms are consistent during sepsis-associated AKI as global renal blood flow, microcirculatory dysfunction, and metabolic reprogramming: renal damage could be the result of the complex interplay of all those factors [3]. Thus, it is hard to image that a single biomarker of AKI, that reflect just a one mechanism pathway, could predict renal damage in all patients at risk.

In 2009, Yi Li et al. demonstrated that circulating monocytes activated by immune complexes and/or inflammatory cytokines upregulated the surface expression of Fcγ receptor I (CD64) in patients with systemic lupus erythematosus . Notably, the extent of expression was higher in cases with class III, IV, and V lupus nephritis than those without lupus nephritis [4]. Since even bacterial and viral pathogens may lead to acute glomerulonephritis due to deposition of in-situ or circulating immune complex in renal tissue [5], we speculated that median serum concentrations of soluble FcγRIA expressed on monocytes (sCD64) could be a surrogate of CD64 expression on monocytes and directly linked to AKI in patients with sepsis. Therefore, in this secondary analysis of the Need Speed trial [6], we aimed to derive a multivariable model (based on creatinine, sTREM-1 and sCD64) that could predict the occurrence of renal damage within 72 h of emergency department (ED) admission better than basal creatinine among patients with suspected infection.

Out of the 836 patients previously enrolled in the inception cohort

Abbreviations: AKI, acute kidney injury; sTREM-1, soluble triggering receptor expressed on myeloid cell-1; sCD64, soluble FcγRIA expressed on monocytes; ED, emergency department; ROC, receiver-operating characteristic; AUC, area under the ROC curve.

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Table 1a
Clinical characteristics of the patients with suspected infection according to the occurrence of acute kidney injury within 72 h of emergency department admission.

Characteristics	AKI n = 60	Non-AKI n = 748	*p*	OR (95% CI)
Demographics				
Male	29 (48)	363 (49)	0.977	1.008
Median age	83 (75–88)	79 (69–87)	0.005	(0.595–1.706)
				1.027
				(1.005–1.050)
Comorbidities				
Charlson Index	3 (2–4)	2 (1–4)	0.784	0.984
Diabetes	11 (18)	133	0.914	(0.874–1.107)
Cardiovascular	9 (15)	147 (18)	0.380	1.038
diseases	10 (17)	139 (18)	0.713	(0.526–2.050)
-Chronic heart	2 (3)	65 (9)	0.148	0.721
failure	7 (12)	54 (7)	0.210	(0.347–1.499)
-Previous acute	2 (3)	20 (3)	0.763	0.876
myocardial	4 (7)	73 (10)	0.432	(0.434–1.771)
infarction	6 (10)	75 (10)	0.749	0.362
-Other	12 (20)	139 (19)	0.364	(0.087–1.518)
Cancer	21 (35)	181 (24)	0.063	1.697
-Solid	1 (2)	27 (4)	0.429	(0.736–3.914)
-Haematologic	0 (0)	3 (0)	0.623	1.255
Chronic renal				(0.286–5.503)
failure				0.660
Chronic liver				(0.223–1.874)
disease				0.997
				(0.415–2.395)
Chronic				0.739
pulmonary disease				(0.385–1.422)
Dementia				1.687
Chronic				(0.967–2.942)
rheumatologic				0.453
disease				(0.060–3.390)
AIDS				0.000
Antibacterials within	14 (23)	200 (27)	0.565	0.834
30 day				(0.449–1.550)
Prosthetic devices	14 (23)	75 (10)	0.002	2.731
				(1.434–5.200)
Objective				
examination	37 (36–38)	36.3	0.375	0.922
Body temperature	85 (77–95)	(37.2–38)	0.006	(0.725–1.174)
(°C)	100	84 (69–96)	0.428	0.986
MAP (mmHg)	(85–110)	100	0.155	(0.969–1.004)
Heart rate (beats/	25 (21–32)	(92–109)	<0.001	1.001
min)	15 (11–15)	22 (20–26)		(0.986–1.017)
Respiratory rate		15(15–15)		1.081
(breaths/min)				(1.035–1.128)
Glasgow Coma				0.848
Scale				(0.765–0.940)
Laboratory			V	
C-reactive protein	85 (32–169)	51	0.196	1.003
(mg/dl)	13 (8–15)	(15–132)	0.837	(1.000–1.005)
White blood cell	12.3	11 (8–16)	0.040	1.000
count x1000/mm^3	(10.2–14.3)	12.4	0.007	(1.000–1.000)
Hemoglobin (g/dl)	37 (33–43)	(11–13.8)	0.849	0.946
Hematocrit (%)	186	38 (34–42)	0.453	(0.837–1.070)
Platelets count	(110–271)	229	<0.001	0.983
x1000/mm^3	43 (35–56)	(170–307)	0.064	(0.944–1.024)
BUN (mg/dl)	1.1	35 (25–45)	0.698	1.000
Creatinine (mg/dl)	(0.9–1.4)	0.9	0.387	(1.000–1.000)
*	136	(0.7–1.1)	0.668	1.015
Sodium (mEq/L)	(133–140)	136	0.256	(1.003–1.027)
Potassium (mEq/	4 (3.5–4.3)	(133–139)	0.219	8.280
L)	25 (18–34)	3.8	0.722	(4.832–14.200)
AST (U/L)	15 (12–24)	(3.4–4.2)		1.018
ALT (U/L)	1.4	24 (17–39)		(0.972–1.067)
Total bilirubin	(0.7–1.7)	18 (11–31)		1.544
(mg/dl)	1.3	0.9		(0.983–2.426)
INR	(1.1–1.5)	(0.6–1.4)		1.000
Fibrinogen (mg/	451	1.2 (1–1.3)		(0.998–1.002)
dl)	(356–627)	434		1.000
		(345–576)		(0.999–1.002)
				1.120
				(0.995–1.260)
				0.986
				(0.722–1.347)
				1.001
				(0.999–1.002
Biomarkers				
sTREM-1 (pg/ml)	474	328	0.001	2.165
sCD64 (ng/ml)	(331–726)	(224–471)	<0.001	(1.372–3.415)
	1.4	0.2		1.148
	(0.2–2.8)	(0.1–1.0)		(1.066–1.236)
SOFA score	4 (2–6)	2 (1–3)	<0.001	1.593
				(1.409–1.800)
Mortality at 30 days	22 (37)	99 (13)	<0.001	3.795
				(2.155–6.685)

List of abbreviations: AKI = acute kidney injury, OR = odds ratio, CI = confidence interval, AIDS = acquired immune deficiency syndrome, MAP = mean arterial pressure, BUN = blood urea nitrogen, sTREM-1 = soluble triggering receptor expressed on myeloid cell-1, sCD64 = soluble FcγRIA expressed on monocytes, SOFA = sequential organ failure assessment.
*The effect of creatinine was modeled by transforming into a quadratic scale (OR for a 1-unit increase in the quadratic transformation).

Table 1b
Independent predictors of acute kidney injury in patients with suspected infection at emergency department admission.

Clinical variables	Adjusted OR	95% CI	*p*
Creatinine*	5.707	3.134–10.390	<0.001
Log sCD64	1.40	1.148–1.714	0.001
SOFA score	1.459	1.263–1.685	<0.001

List of abbreviations: OR = odds ratio, CI = confidence interval, sCD64 = soluble FcγRIA expressed on monocytes, SOFA = sequential organ failure assessment.
Covariates at baseline: age, dementia, prosthetic devices, mean arterial pressure, Glasgow Coma Scale, hemoglobin, hematocrit, creatinine, sodium, SOFA score, Log sTREM-1, and Log sCD64.
*The effect of creatinine was modeled by transforming into a quadratic scale (OR for a 1-unit increase in the quadratic transformation).

[4], 28 patients fulfilled AKIN [1] criteria at ED admission and were excluded from this secondary analysis. Thus, specifically for this study, baseline concentration of sCD64 were measured in the frozen aliquots of serum of 808 patients with suspected infection (antibodies-online.com; catalogue number: ABIN814813). STREM-1 was analyzed as previously reported [4]. The occurrence of AKI within 72 h of ED admission was prospectively adjudicated according to AKIN criteria. Starting from a full multivariable model containing all candidate predictors with an unadjusted p value ≤ 0.1, a selection procedure was applied based on finding the independent predictors of AKI. A multivariable model predictive of renal damage was built integrating the clinical variables proved to be independently correlated with AKI. The predictive performance of creatinine and multivariable model was measured using C statistics. An internal validation procedure using bootstrap was also applied.

Table 1c
Independent predictors of acute kidney injury in patients with suspected sepsis at emergency department admission.

Clinical variables	Adjusted OR	95% CI	*p*
Creatinine*	6.603	3.333–13.082	<0.001
Log sCD64	1.459	1.165–1.828	0.001
SOFA score	1.556	1.299–1.863	<0.001

List of abbreviations: OR = odds ratio, CI = confidence interval, sCD64 = soluble FcγRIA expressed on monocytes, SOFA = sequential organ failure assessment.
*The effect of creatinine was modeled by transforming into a quadratic scale (OR for a 1-unit increase in the quadratic transformation).

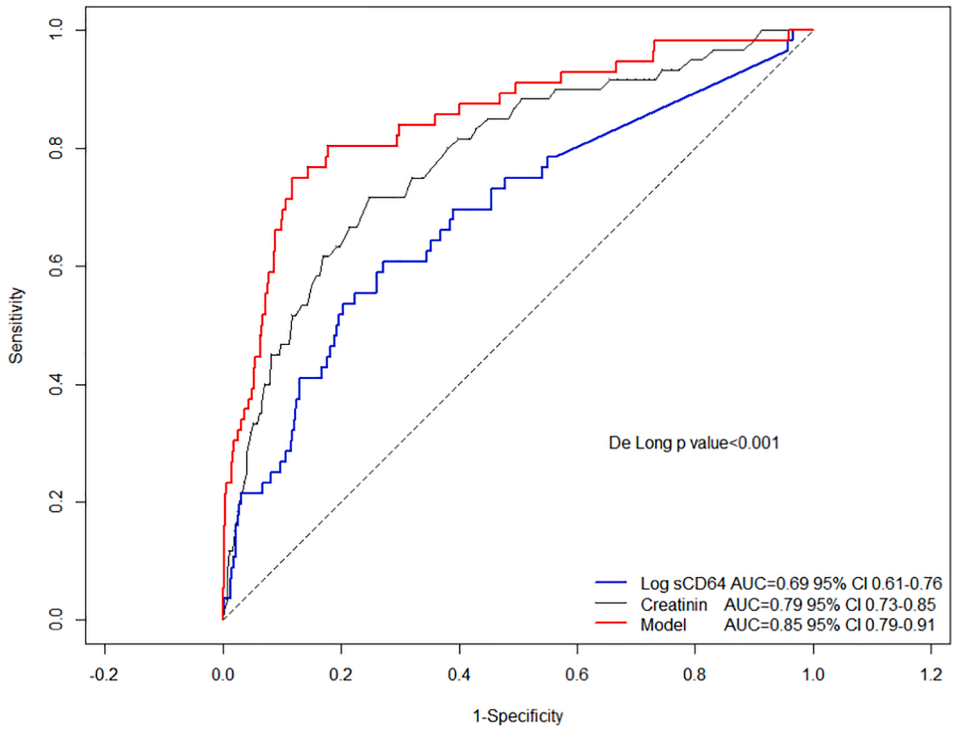

Fig. 1a. Receiver-operating characteristic curve and area under the receiver-operating characteristic curve of creatinine, Log sCD64 and the multivariable model for predicting acute kidney injury within 72 h of emergency department admission in patients with suspected infection. AUC = area under the receiver-operating characteristic curve, CI = confidence interval.

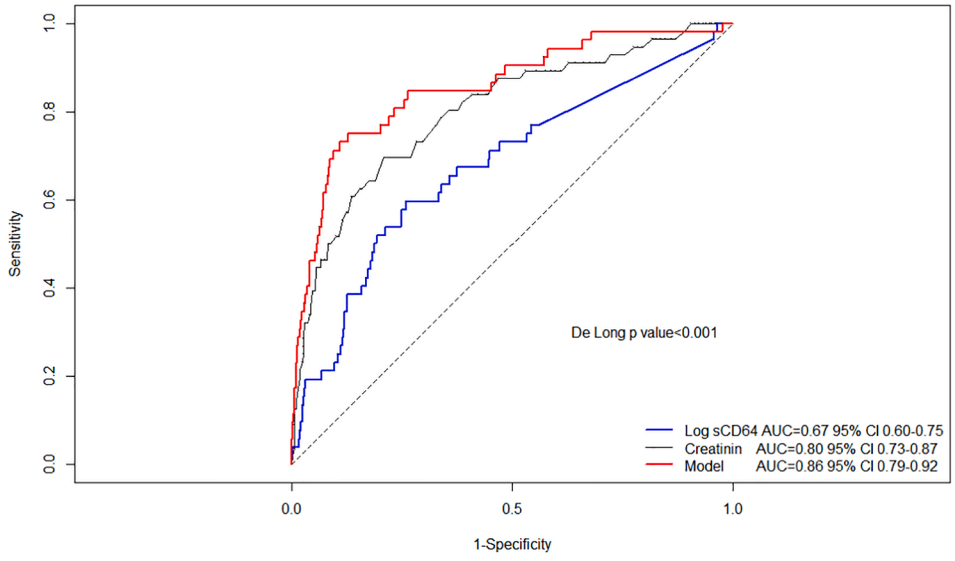

Fig. 1b. Receiver-operating characteristic curve and area under the receiver-operating characteristic curve of creatinine, Log sCD64 and the multivariable model for predicting acute kidney injury within 72 h of emergency department admission in patients with suspected infection: the patients with chronic renal failure are excluded from this analysis.

Patients with AKI (60) were sicker than non-AKI patients (748, Table 1a). Creatinine, sCD64 and SOFA score resulted independently correlated with the development of renal damage (Table 1b). Notably, sTREM-1, a promising biomarker of sepsis-associated AKI [2], did not result independently linked with renal damage when sCD64 was included in multivariable analysis. The latter biomarker was proved to be an independent predictor of AKI also in the subgroup of patients with suspected sepsis according to Sepsis-3 definition (Table 1c). Receiver-operating characteristic (ROC) curves of sCD64, creatinine and multivariable model for predicting renal damage are shown in Fig. 1a. The area under the ROC curve (AUC) of multivariable model for predicting AKI (0.85, 95 %CI 0.79–0-81) significantly exceeded that of creatinine alone (0.79, 95 %CI 0.73–0.85) and of sCD64 alone (0.69, 95 %CI 0.61–0.76). When the patients with chronic renal failure (77) were excluded from the analysis we found similar diagnostic performance (AUC 0.86, 0.80, and 0.67, respectively; Fig. 1b).

For the first time in literature, we demonstrated that the combination of SOFA score with serum concentrations of creatinine and sCD64 is more useful than creatinine alone for early diagnosis of AKI among patients with suspected infection at ED admission.

Ethical approval and consent to partecipate

The study protocol was approved by the medical ethical committee of Trieste. Informed consent before study enrolment or deferred consent was obtained from all patients or their legal representatives or surrogates.

Consent for publication

Not applicable

Availability of supporting data

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Author contributions

Study concept and design: Filippo Mearelli.

Patients enrollment: Filippo Mearelli,

Drafting of the manuscript: Filippo Mearelli.

Critical revision of the manuscript for important intellectual content: Claudio Ronco, Gianni Biolo.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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