Caratteristiche cliniche e biochimiche del paziente settico con IRA su IRC

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AGENDA

- SA-AKI: sepsis associated-acute kidney injury
- FATTORI PROGNOSTICI SA-AKI
- SEPSI E CKD
- CONCLUSIONI

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Consensus statement

Check for updates

Sepsis-associated acute kidney injury: consensus report of the 28th Acute Disease Quality Initiative workgroup

A list of authors and their affiliations appears at the end of the paper

Abstract

Sepsis-associated acute kidney injury (SA-AKI) is common in critically ill patients and is strongly associated with adverse outcomes, including an increased risk of chronic kidney disease, cardiovascular events and death. The pathophysiology of SA-AKI remains elusive, although microcirculatory dysfunction, cellular metabolic reprogramming and dysregulated inflammatory responses have been implicated in preclinical studies. SA-AKI is best defined as the occurrence of AKI within 7 days of sepsis onset (diagnosed according to Kidney Disease Improving Global Outcome criteria and Sepsis 3 criteria, respectively). Improving outcomes in SA-AKI is challenging, as patients can present with either clinical or subclinical AKI. Early identification of patients at risk of AKI, or at risk of progressing to severe and/or persistent AKI, is crucial to the timely initiation of adequate supportive measures, including limiting further insults to the kidney. Accordingly, the discovery of biomarkers associated with AKI that can aid in early diagnosis is an area of intensive investigation. Additionally, high-quality evidence on best-practice care of patients with AKI, sepsis and SA-AKI has continued to accrue. Although specific therapeutic options are limited, several clinical trials have evaluated the use of care bundles and extracorporeal techniques as potential therapeutic approaches. Here we provide graded recommendations for managing SA-AKI and highlight priorities for future research.

Sections

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Box 1

Definition and epidemiology of SA-AKI

Consensus statement 1a
We propose that sepsis-associated acute kidney injury (SA-AKI) be characterized by the presence of both consensus sepsis criteria (as defined by Sepsis-3 recommendations) and AKI criteria (as defined by Kidney Disease: Improving Global Outcomes recommendations) when AKI occurs within 7 days from diagnosis of sepsis (not graded).

Consensus statement 1b
We suggest that sepsis-induced AKI should be considered a subphenotype of SA-AKI in which sepsis is the predominant driver of tissue damage (not graded).

Consensus statement 1c
We suggest that AKI diagnosed within 48 h of the diagnosis of sepsis be defined as early SA-AKI, whereas AKI occurring between 48 h and 7 days of sepsis diagnosis be classified as late SA-AKI (not graded).

Consensus statement 1d
The epidemiology of SA-AKI varies and depends on the patient population and the criteria used to define AKI and sepsis (not graded).

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

Box 1 | Sepsis-3 definitions and quick SOFA (qSOFA) criteria[1]

Sepsis-3 definitions

Sepsis—Life threatening organ dysfunction caused by a dysregulated host response to infection

Septic shock—Sepsis with a requirement for vasoactive therapy to maintain mean arterial pressure ≥65 mm Hg and lactate elevation to >2 mmol/L despite adequate volume resuscitation

qSOFA criteria

- Respiratory rate ≥22 breaths per minute
- Altered mentation
- Systolic blood pressure ≤100 mm Hg

JAMA, 2016

Role of kidney injury in sepsis

Kent Doi

Table 1 Definition and staging of AKI

Definition	AKI is defined as any of the following	
	1) Increase in SCr by >0.3 mg/dL within 48 h	
	2) Increase in SCr to >1.5 times baseline, which is known or presumed to have occurred within the prior 7 days	
	3) Urine volume <0.5 mL/kg/h for 6 h	
Severity	Serum creatinine	Urine output
Stage 1	1.5–1.9 times baseline, or	<0.5 mL/kg/h for 6–12 h
	>0.3 mg/dL increase	
Stage 2	2.0–2.9 times baseline	<0.5 mL/kg/h for >12 h
Stage 3	3.0 times baseline, or	<0.3 mL/kg/h for >24 h, or
	Increase in SCr to >4.0 mg/dL, or	Anuria for >12 h
	Initiation of renal replacement therapy	

SCr serum creatinine

J OF INTENSIVE CARE 2016

Sepsis-induced AKI: From pathogenesis to therapeutic approaches

Fang-Fang He†, Yu-Mei Wang†, Yi-Yuan Chen, Wei Huang, Zi-Qi Li and Chun Zhang *

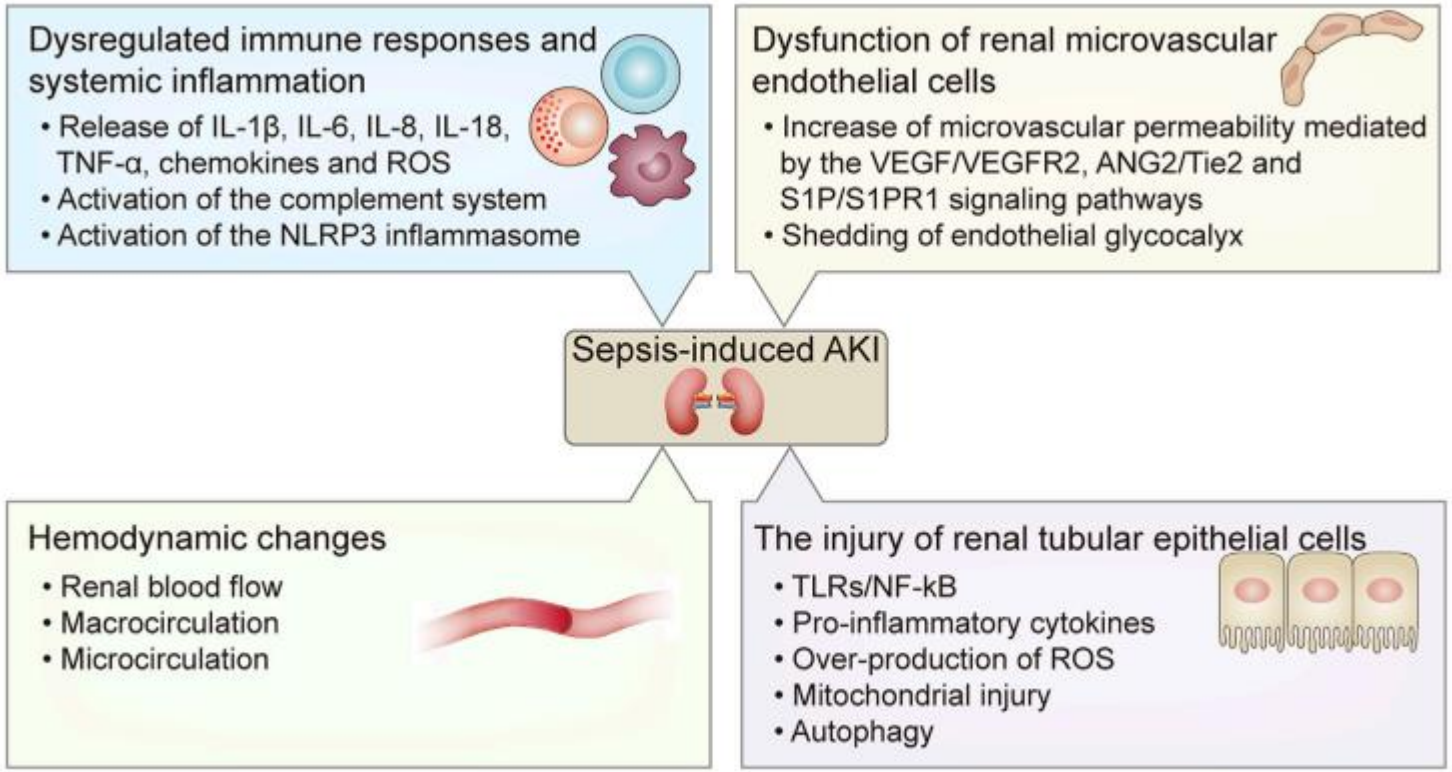

FIGURE 1

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Sepsis associated acute kidney injury

Risk and prognostic factors for acute kidney injury

Sex	Developing AKI	Data inconsistent
Race	Developing AKI	Data inconsistent
Chronic kidney disease[39]	Developing AKI	OR 2.9 (2.7 to 3.1) for eGFR 45-59; 6.2 (5.7 to 6.8) for eGFR 30-44; 18.3 (16.5 to 20.3) for eGFR <30 mL/min/1.73 m^2
	Death with AKI	AKI predictive of mortality, but less predictive for patients with more severe CKD
Diabetes mellitus[40]	Developing AKI	OR 10.3 (7.7 to 13.6) for developing stage III AKI
	Death with AKI	OR 1.2 (1.2 to 1.7)
Hypoalbuminemia[24] 41	Developing AKI	OR 2.34 (1.74 to 3.14) with drop 1 g/dL
	Death with AKI	OR 2.47 (1.51 to 4.05) with drop 1 g/dL
Chronic liver disease[18]	Developing AKI	OR 2.18 (1.16 to 4.10)
Heart failure[18] 38 40	Developing AKI	OR 2.18 (1.12 to 4.44) to 24.0 (18.5 to 31.2)
Caused by acute illness		
Cardiovascular failure[18] 40	Developing AKI	OR 1.84 (1.32 to 2.56)
	Death with AKI	OR 1.8 (1.2 to 2.9)
Mechanical ventilation[42]	Death with AKI	OR 5.1 (2.0 to 12.8)
Liver failure[37]	Death with AKI	OR 1.90 (1.34 to 2.71)
Sepsis[37]	Death with AKI	OR 1.87 (1.33 to 2.62) to 2.1 (1.1 to 1.4)

BMJ 2019, REVIEW

A novel risk-predicted nomogram for sepsis associated-acute kidney injury among critically ill patients

Table 3 Results of the forward stepwise logistic regression analysis of SA-AKI in Primary Cohort

Variable	OR	95 % CI	*P*-Value
BMI	1.40	1.13–1.75	0.003
LOS in ICU	1.65	1.50–1.82	< 0.001
SIRS	1.11	0.98–1.26	0.114
Basline SCr	1.19	1.08–1.30	< 0.001
Anemia	2.24	1.42–3.55	< 0.001
Glucose	1.21	1.11–1.33	< 0.001
Albumin	1.33	1.08–1.63	0.007
Chronic medical conditions			
CKD	1.74	1.31–2.30	< 0.001
Chronic liver disease	1.75	1.13–2.71	0.012
Diabetes	1.04	0.83–1.31	0.752
Coronary disease	1.44	1.09–1.91	0.012
Comorbidity			
Acute pancreatitis	0.88	0.56–1.39	0.590
Lactic acidosis	1.06	0.84–1.35	0.613
Heart failure	1.29	1.03–1.62	0.025
Medication			
Vasoactive drugs	2.15	1.74–2.66	< 0.001
Aminoglycosides	1.15	0.90–1.48	0.267
Human albumin	2.55	1.83–3.56	< 0.001

BMJ Nephrology 2021

Box 4

Biomarkers for diagnosis and guiding treatment in SA-AKI

Consensus statement 4a
We suggest the complementary use of validated measures — including functional, stress and tissue damage-related biomarkers — be considered in combination with the consensus Kidney Disease Improving Global Outcomes (KDIGO) definition to diagnose sepsis-associated acute kidney injury (SA-AKI) (grade 2C).

Consensus statement 4b
We recommend that measures validated to predict an episode of AKI in patients with sepsis be used in combination with available clinical information (grade 1B).

Consensus statement 4c
We suggest that selected functional and stress- or injury-related biomarkers should be used for clinical assessment to identify and discriminate patients with sepsis at risk of transient or persistent SA-AKI. These biomarkers can also enhance the risk assessment of the severity, duration, trajectory of recovery and occurrence of non-renal outcomes in patients with established SA-AKI (grade 1B).

Consensus statement 4d
We suggest that sepsis biomarkers be used to complement functional and tubular injury-related biomarkers for the prognosis of early or late SA-AKI (grade 2C).

Sepsis-associated acute kidney injury: consensus report of the 28th Acute Disease Quality Initiative workgroup

Nature Review Nephrology 2023

MARKERS BIOUMORALI PRECOCI DI SA-AKI

TABLE 2 | Summary of biomarkers used to detect SA-AKI.

Types of biomarker	Biomarker	Source	Potential use in SA-AKI
Inflammation biomarkers	IL-6	Mononuclear macrophages, Th2 cells, vascular endothelial cells and fibroblasts	Baseline IL-6 at admission predicted AKI in patients with severe sepsis, and IL-6 also predicts the development of AKI and need for RRT in patients with severe sepsis (100).
	IL-18	Monocytes, dendritic cells, macrophages and epithelial cells	In a prospective, multicenter cohort, UIL-18 independently predicted the progression of septic AKI (AUC 0.619; 95% CI, 0.525 to 0.731) (101).
	sTREM-1	Activated receptors selectively expressed on the surfaces of neutrophils, macrophages, and mature monocytes	In patients with sepsis, The AUC values of plasma STREM-1 in the diagnosis and prediction of AKI (24h before diagnosis) were 0.794 and 0.746, respectively. The AUC values of urine STREM-1 were 0.707 and 0.778. ACU 0.922 was predicted 48 hours before diagnosis, and urine STREM-1 was a fairly good predictor (102).
Endothelial injury biomarkers	Ang	Ang1 is mainly synthesized by paravascular sertoli cells, vascular smooth muscle cells and tumor cells; Ang2 is mainly synthesized by vascular smooth muscle cells	Ang1 has a protective effect against endotoxemia, increasing vasoconstriction and reducing pulmonary microvascular leakage associated with inflammation (103). Circulating Ang1 levels were suppressed in critically ill patients with septic shock (104). Circulating Ang-2 is a strong independent predictor of mortality in ICU dialysis-dependent AKI patients (105).
	VE-cadherin	Vascular endothelial cell	Plasma sVE-cadherin was independently associated with AKI-RRT, suggesting that disruption of endothelial adhesion and connectivity may contribute to the pathogenesis of organ dysfunction in sepsis (106).
	sTM	Vascular endothelial cell	Compared with sepsis non-AKI group, sTM in SA-AKI group was significantly different ($P<0.0001$); Multivariate logistic regression analysis showed that sTM was an independent predictor of AKI, and AUROC was 0.758($P<0.0001$) (107).
Tubular injury biomarkers	NGAL	Leukocytes, loops of medullary and collecting ducts	SA-AKI patients have higher detectable plasma and urine NGAL compared with non-septic AKI patients. These differences in NGAL values in SA-AKI may have diagnostic and clinical relevance as well as pathogenetic implications (108).
	KIM-1	RTECs	UKIM-1 and sKIM-1 levels were significantly higher in SA-AKI than in patients without AKI. ROC of uKIM-1 and sKIM-1 for AKI prediction was 0.607 and 0.754, respectively (109).
	L-FABP	Liver cells; RTECs	Urinary L-FABP level may be a predictive marker of sepsis severity and mortality, and can serve as a useful biomarker for patients with sepsis complicated with AKI (109).
	Cys C	All nucleated cells	Urine and plasma are of value in the diagnosis and prediction of AKI occurrence (24 hours before diagnosis) in patients with SA-AKI (21). Aydogdu et al. confirmed that plasma and urine Cys-C were good markers for early diagnosis of septic associated AKI (AUCs 0.82 and 0.86, respectively) (110). However, some studies in adults and newborns have shown that sepsis has no effect on plasma or urine levels of Cys-C (111, 112).
AKI risk biomarkers	[TIMP-2] • [IGFBP7]	TIMP-2 is synthesized by RTECs; IGFBP7 is expressed in almost all epithelial cells	[TIMP-2] • [IGFBP7] predicted the development of stage 2 and 3 AKI in high-risk and critically ill patients with sepsis with an AUC of 0.84. The biomarker performed similarly regardless of disease severity (SOFA score), with a sensitivity of 77.5% and specificity of 75% for severe AKI at a cut-off value of 1.0 (113).
	Electronic alerts, electronic risk algorithms	\	Several alarms have shown the ability to predict sepsis and AKI separately, and the combination of biochemical biomarkers may help enrich the detection and risk stratification of SA-AKI (20).

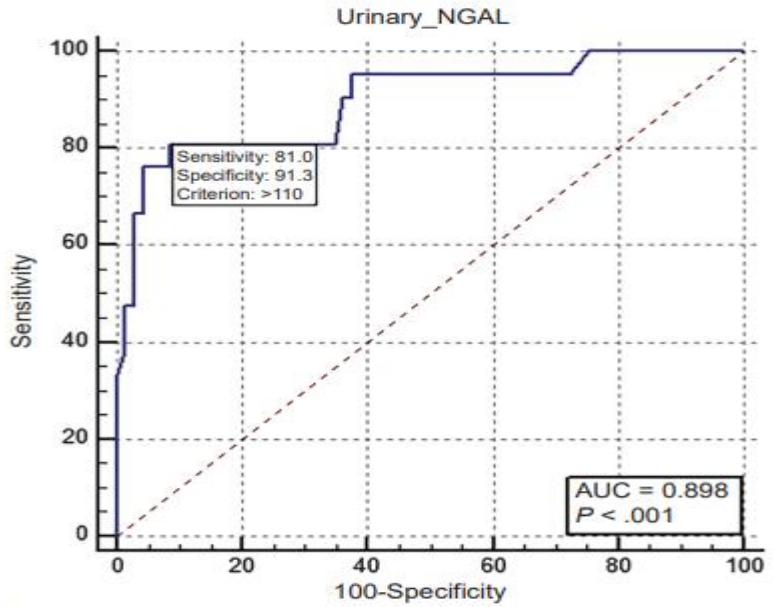
Frontiers in Immunology, 2002

The Application of Urinary NGAL Measurement for Early Detection of AKI in Hospitalized Patients with Poisoning

Table 3. Comparison of Laboratory Test Results in AKI and Non-AKI Patients

Variable	Mean ± SD		T Statistic	*P* (2-tailed)*	Mean Difference	Std. Error of Difference
	AKI	Non-AKI				
Urine NGAL	325.86 ± 276.18	52.33 ± 60.15	1.75	.00	273.53	60.70
Urinary Cr	97.17 ± 68.13	81.46 ± 63.04	1.90	.33	15.71	16.01
Serum Cr1†	1.04 ± 0.21	1.02 ± 0.26	.51	.74	.02	.06
Serum Cr2‡	1.42 ± 0.34	1.05 ± 0.22	.80	.00	.37	.06
Serum Cr3§	1.70 ± 0.39	1.06 ± 0.23	.57	.00	.64	.07

*Independent t-test, df = 88



It shows the Receiver Operating Characteristic (ROC) curve analysis.

CONCLUSION

The urinary NGAL test can be used for early detection of AKI in poisoning. The high specificity and the low false positive rate demonstrate that the test can be very helpful in distinguishing non-AKI patients. The clinical applications (strengths and weaknesses) of urinary NGAL test for early detection of AKI needs to be investigated in broader studies. (i.e., with larger sample sizes and multiple consecutive measurements)

IJKD,2020

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Che cosa succede se aggiungiamo la sepsi ad una condizione pre esistente di CKD ?

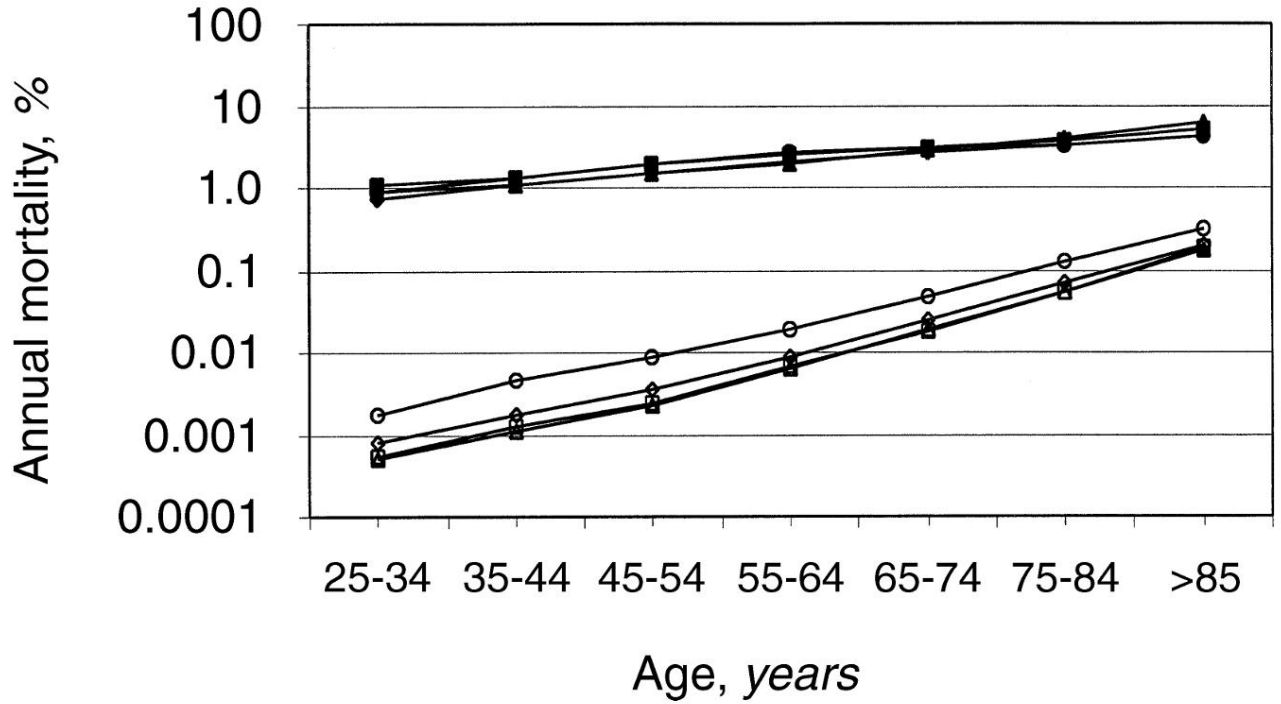

Fig. 1. Mortality caused by sepsis of patients with end-stage renal disease (ESRD) treated by dialysis compared with the general population (GP). Data are stratified by age, gender (◆, dialysis male; ■, dialysis female; ◇, GP male; □, GP female), and race (▲, dialysis black; ●, dialysis white; △, GP black; ○, GP white), and are shown as annual percentage mortality on a logarithmic scale.

Kidney International, Vol. 58 (2000), pp. 1758–1764

DIALYSIS – TRANSPLANTATION

Mortality caused by sepsis in patients with end-stage renal disease compared with the general population

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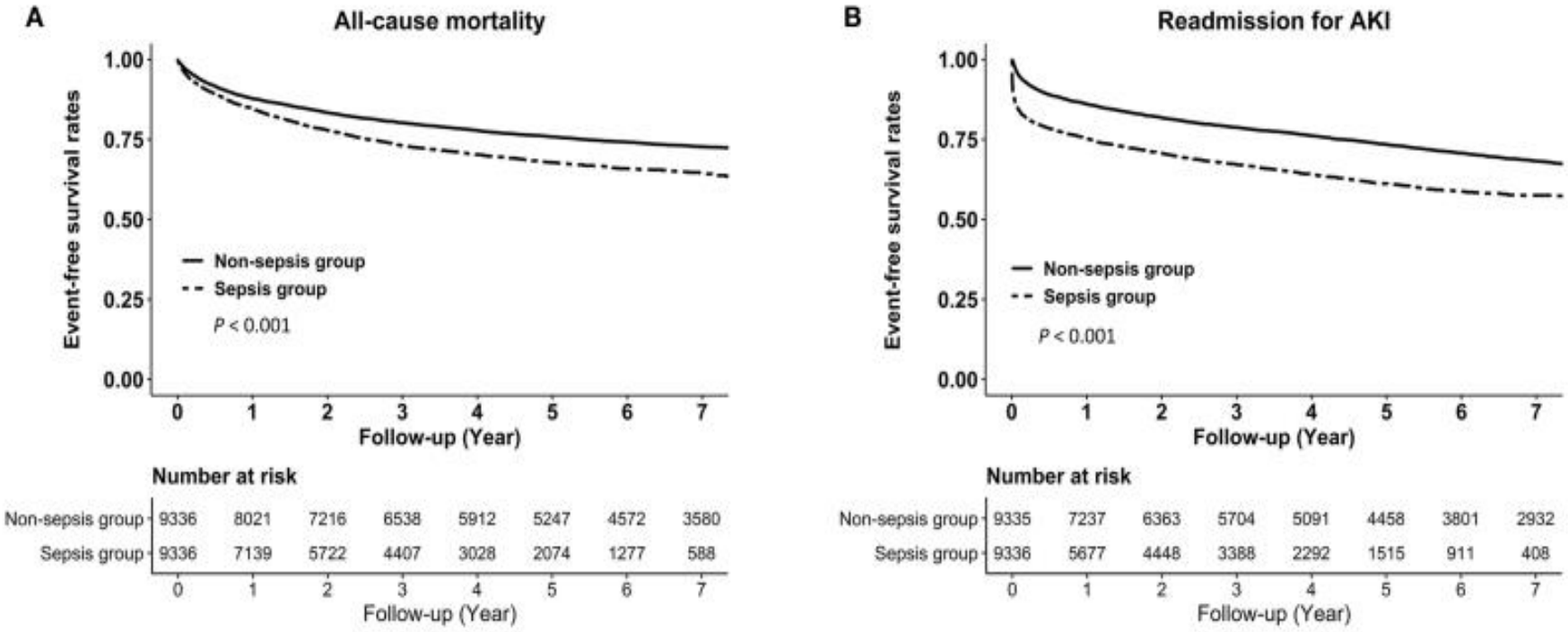
Sepsis and the Risks of Long-Term Renal Adverse Outcomes in Patients With Chronic Kidney Disease



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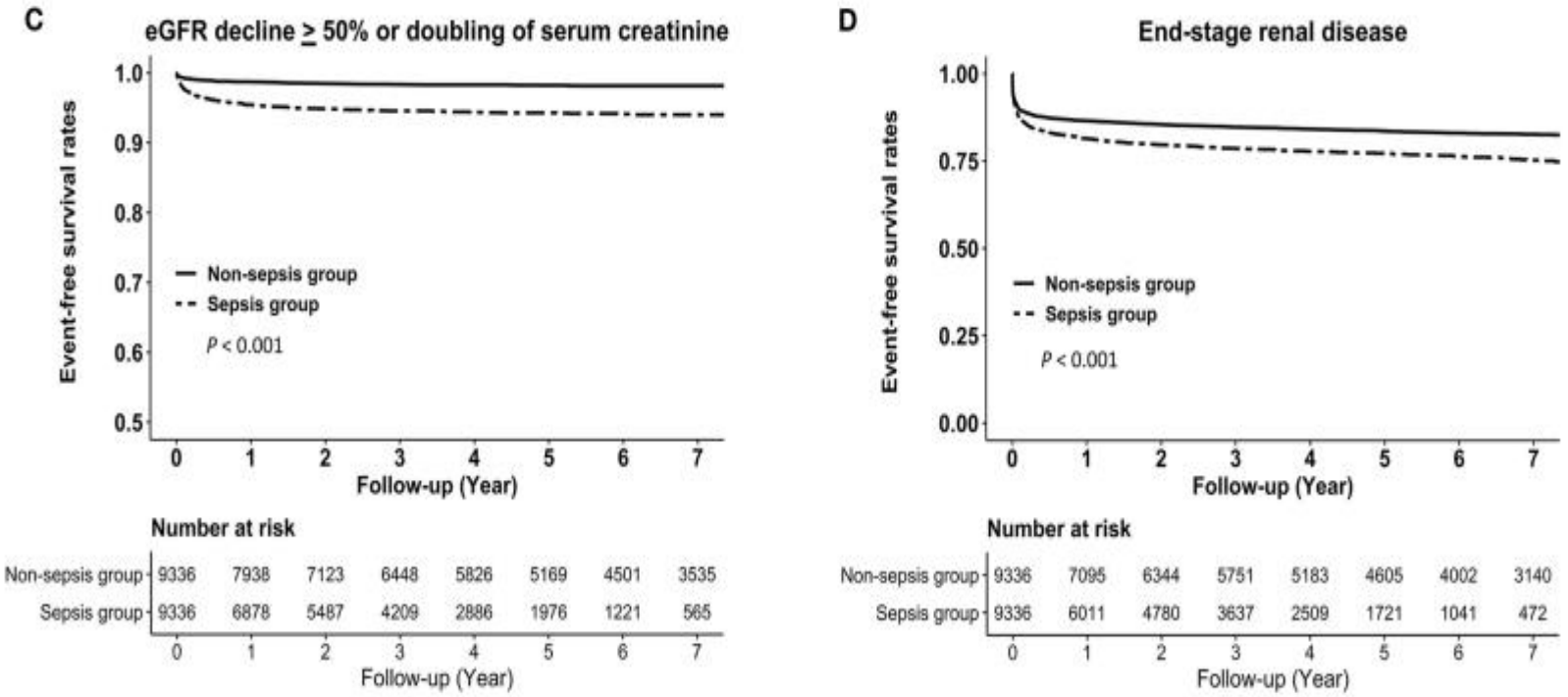
Sepsis and the Risks of Long-Term Renal Adverse Outcomes in Patients With Chronic Kidney Disease



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TAKE HOME MESSAGES

- SA-AKI: entità ancora in via di definizione ma gravata da outcome negativi
- Pre-esistente CKD, diabete mellito, ipoalbuminemia, sono alcuni dei fattori di rischio più importante per SA-AKI
- Diagnosi precoce
- I pazienti con CKD che sviluppano SA-AKI hanno una mortalità più elevata e un maggior rischio di sviluppare ESRD, rispetto ai pazienti che non sviluppano tale sindrome.