Serum DcR3 as a New Predictor of Renal Outcomes in Patients With Sepsis-Associated Acute Kidney Injury

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Abstract

Decoy receptor 3 (DcR3) impacts the severity of conditions like sepsis, ARDS, and hemorrhagic fever with renal syndrome, with its role in sepsis-associated acute kidney injury (SA-AKI) being less understood. This study, a single-center prospective cohort from 2022 to 2023, focused on SA-AKI patients needing renal replacement therapy (RRT). It found no significant correlation between serum DcR3 levels and mortality in 114 SA-AKI patients. However, higher DcR3 levels were associated with a greater likelihood of long-term dialysis dependency among survivors. Particularly, patients with DcR3 levels ≥ 28 ng/ml had poorer renal recovery. In vitro experiments with THP-1 cells showed that lipopolysaccharide (LPS) stimulation increased mRNA expression of TNFRSF6B and inflammatory cytokines, which was mitigated by DcR3 blockade using siRNA, suggesting DcR3's role as an upstream regulator in cytokine storms. The study indicates that elevated DcR3 levels may increase long-term dialysis risk in SA-AKI patients, highlighting its potential as a target for immunomodulatory strategies in managing SA-AKI.

Introduction

Decoy receptor 3 (DcR3), also known as tumor necrosis factor receptor superfamily member 6B (TNFRSF6B), is implicated in the severity of several conditions, including sepsis, ARDS, and hemorrhagic fever with renal syndrome. While serum DcR3 levels in septic patients positively correlate with CRP, IL-6, and procalcitonin, its elevated levels have been linked to unfavorable outcomes in ARDS patients. However, its role in sepsis-associated acute kidney injury (SA-AKI) remains largely unexplored. This study sought to elucidate the role of DcR3 on the outcomes of SA-AKI patients.

Methods and Materials

We conducted a single-center prospective cohort study, enrolling patients with SA-AKI necessitating dialysis in intensive care units between 2022 and 2023. During hospitalization, demographic and laboratory details were documented, and blood samples were taken before RRT onset to assess DcR3 via ELISA assay. Concurrently, we engaged the human monocytic cell line (THP-1), exposing it to 100ng/ml lipopolysaccharide (LPS) stimulation for 24 hours to analyze mRNA levels of TNFRSF6B and related inflammatory cytokines. SiRNA was utilized to ascertain the impact of DcR3 blockade following LPS stimulation.

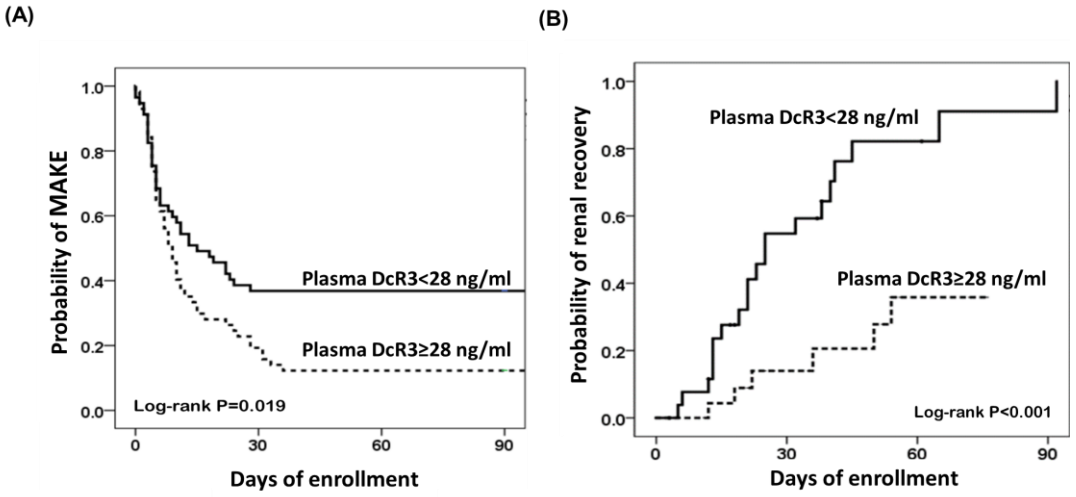
Clinical characteristics	Overall (n=114)	Renal recovery (n=26)	Renal non-recovery (n=88)	*P* value
Age, years	71.54±16.85	67.58±19.72	72.70±15.84	0.174
Male, n (%)	74 (64.9)	19 (73.1)	55 (62.5)	0.321
Body mass index, kg/m^2	23.49±4.83	24.22±5.03	23.27±4.77	0.381
Charlson comorbidity score	7.78±3.52	6.69±3.48	8.1±3.48	0.073
APACHE II score	**25.21±7.48**	**22.04±7.63**	**26.15±7.21**	**0.013***
SOFA score	10.97±3.66	9.88±2.96	11.3±3.8	0.084
Respiratory failure, n (%)	74 (64.9)	17 (65.4)	57 (64.8)	0.954
Shock, n (%)	**36 (31.6)**	**4 (15.4)**	**32 (36.4)**	**0.043**
Heart failure, n (%)	38 (33.3)	9 (34.6)	29 (33.0)	0.875
Liver decompensation, n (%)	19 (16.7)	3 (11.5)	16 (18.2)	0.425
ECMO use, n (%)	14 (12.3)	1 (3.8)	13 (14.8)	0.136
Baseline SCr, mg/dl	2.01±1.56	2.00±1.29	2.01±1.62	0.975
Albumin, g/dL	3.02±0.65	3.37±0.5	2.87±0.66	0.165
CRP, mg/dl	**21.53±5.74**	**19.19±5.63**	**22.22±5.62**	**0.017**
SCr at dialysis initiation, mg/dl	5.49±2.66	5.52±2.36	5.49±2.76	0.961
DcR3, ng/ml	**36.29±38.23**	**19.14±13.16**	**41.36±41.65**	**<0.001**

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; ECMO, extracorporeal membrane oxygenation; SCr, serum creatinine; CRP, C-reactive protein; DCR, decoy cell receptor

Results

We enrolled 114 patients with SA-AKI, with an overall survival rate of 54%. The presence of shock, a higher APACHE II score, and elevated levels of serum DcR3 and CRP were associated with a lack of renal recovery **(Table)**. Interestingly, while serum DcR3 levels did not significantly correlate with mortality, higher levels of DcR3 were linked to an increased likelihood of long-term dialysis dependency among survivors. Specifically, patients with DcR3 levels of 28 ng/ml or higher were found to have poorer renal recovery compared to those with levels below 28 ng/ml **(Figure 1)**. Additionally, in vitro experiments showed that lipopolysaccharide (LPS) stimulation of THP-1 cells resulted in increased mRNA expression of TNFRSF6B and pro-inflammatory cytokines, such as IL-6 and TNF-α **(Figure 2)**. Applying siRNA to inhibit DcR3 expression attenuated these effects, suggesting that DcR3 plays an upstream regulator of cytokine production associated with sepsis.

Figure 1. Kaplan-Meier curves comparing the cumulative probabilities of major adverse kidney events (MAKE) (A) and renal recovery (B), with patients grouped according to the DcR3 levels.



Discussion

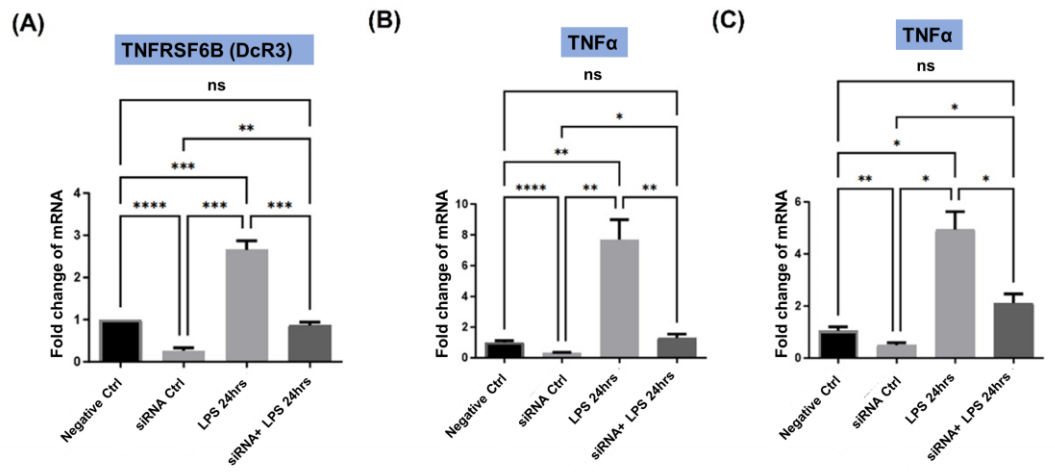
The main findings:

1. Higher serum DcR3 levels correlate with an increased likelihood of long-term dialysis dependency among SA-AKI survivors.
2. DcR3 acts as an upstream regulator in IL-6 and TNF-α associated with SA-AKI

Further research:

- What are the clinical implications of serum DcR3 levels in SA-AKI survivors for managing their kidney dysfunction?
- How does DcR3 contribute to the pathophysiology of SA-AKI and the potential for targeting inflammatory pathways in treatment?
- How does DcR3 compare with other inflammatory markers like CRP, lactate, and procalcitonin in predicting outcomes in SA-AKI?

Figure 2. LPS stimulation caused an increase in the mRNA levels of TNFRSF6B (A), TNF-α (B), and IL-6 (C) in THP-1 cells. However, these increases were reversed by the application of siRNA.



Conclusions

Elevated serum DcR3 levels in patients with SA-AKI may increase the risk of long-term dialysis dependency. Considering its central role in cytokine storms, targeting DcR3 offers a potential immunomodulatory strategy for managing SA-AKI.

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