Journal of Inflammation Research

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Predictive Value of 5-Methoxytryptophan on Clinical Outcome in Patients with Sepsis Associated Acute Kidney Injury

Xue Sun[1–3], Yang Liu[4], Yan Liu[5], Shaozheng Ai[1–3], Pengli Luo[1,2]

[1]Department of Nephrology, Affiliated Hospital of Qinghai University, Xining, 810000, People's Republic of China; [2]Clinical Research Center for Chronic Kidney Disease in Qinghai Province, Xining, 810000, People's Republic of China; [3]Research Center for High Altitude Medicine, Key Laboratory of High Altitude Medicine(Ministry of Education), Key Laboratory of Application and Foundation for High Altitude Medicine Research in Qinghai Province (Qinghai-Utah Joint Research Key Laboratory for High Altitude Medicine), Qinghai University, Xining, 810000, People's Republic of China; [4]Department of Chest Surgery, Affiliated Hospital of Qinghai University, Xining, 810000, People's Republic of China; [5]Department of Public Health, Qinghai University Medical College, Xining, 810000, People's Republic of China

Correspondence: Pengli Luo, The Affiliated Hospital of Qinghai University, No. 29 Tongren Road, Xining City, 810000, People's Republic of China, Tel +8615297093191, Email qhlpl2108@163.com

Purpose: Our study aims to investigate specific changes in serological 5-MTP expression in sepsis-associated acute kidney injury (SA-AKI) patients and assess its potential as a biomarker for SA-AKI occurrence. Additionally, we seek to evaluate the predictive value of 5-MTP in long-term clinical prognosis following SA-AKI.

Patients and Methods: A prospective cohort study included 31 healthy controls and 78 patients diagnosed with sepsis at the Affiliated Hospital of Qinghai University. Following the collection of serological samples, 5-MTP levels were determined using targeted metabolomics.Additionally, we collected clinical data, including blood routine, biochemical, inflammatory indicators and severity of disease. Spearman correlation, COX regression analysis and Kaplan-Meier curves were used to evaluate the correlation between serum 5-MTP and renal function and the value of prognosis.

Results: The findings revealed that serum 5-MTP levels were significantly elevated in SA-AKI patients compared to both the healthy control and sepsis groups($P<0.05$), and were associated with Scr, BUN, and eGFR levels($P<0.05$). Additionally, 5-MTP was identified as an independent influencing factor for all-cause mortality in patients with sepsis and SA-AKI. Higher levels of 5-MTP were linked to faster recovery of kidney function, while lower levels were associated with increased 90-day all-cause mortality in SA-AKI patients.

Conclusion: 5-MTP may have a protective role in the development of SA-AKI, and an early increase in serological expression of 5-MTP could positively impact the prognosis of sepsis and SA-AKI.

Keywords: sepsis associated acute kidney injury$_1$, 5-methoxytryptophan$_2$, prognosis$_3$, 90-day mortality rate$_4$, biomarker$_5$

Introduction

Worldwide, the number of sepsis cases ranges from 1.9 million to 48.9 million each year.[1] Sepsis-associated acute kidney injury (SA-AKI) is a common and life-threatening complication in hospitalized and critically ill patients.[2] SA-AKI significantly increases in-hospital mortality[3] and triples the risk of chronic kidney disease (CKD).[4] Early detection of SA-AKI is challenging, and current diagnostic criteria rely on elevated serum creatinine and/or decreased urine output, which may lead to delayed dentification.[5,6] Several new biomarkers for SA-AKI, such as plasma and urinary neutrophil gelatinase-associated lipoproteins (NGAL) and urinary interleukin-18 (IL-18) have shown promise in predicting SA-AKI occurrence.[7–9] However, their clinical utility and prognostic value in SA-AKI remain uncertain. Further research is needed to identify reliable biomarkers for SA-AKI, aiding in early prevention strategies and long-term prognosis monitoring.

A recently discovered endogenous tryptophan metabolite, 5-Methoxytryptophan (5-MTP). Alterations in the serum levels of 5-MTP have been noted in different disease states. For instance, a significant decrease in serum 5-MTP concentration was observed in sepsis patients.[10] In kidney diseases, the expression of serum 5-MTP in children with

Received: 20 February 2025
Accepted: 13 May 2025
Published: 28 May 2025

lupus nephritis (LN) was found to be positively correlated with disease activity and prognosis.[11] Moreover, investigations into patients with CKD revealed a decrease in the expression level of 5-MTP in these individuals.[12] According to our previously published data, 5-MTP serological expression levels in sepsis and SA-AKI patients have certain changes, which are correlated with renal function.[13]

However, the association between serum 5-MTP levels and renal function recovery and long-term clinical outcomes in SA-AKI patients remains unknown. Therefore, our study aimed to evaluate the predictive value of 5-MTP in long-term clinical prognostic characteristics after SA-AKI, and to help clinicians to assess the condition of patients early, improve the prognosis of SA-AKI patients.

Materials and Methods

Patients' Cohort

A prospective study was conducted to investigate the association between serum 5-MTP levels, kidney function, and clinical outcomes in individuals suffering from sepsis and SA-AKI.The study included in patients aged 18 to 80 years admitted to the Affiliated Hospital of Qinghai University between March 2023 and February 2024.Participants included a healthy control group and a case group, with the latter diagnosed according to the Sepsis-3 criteria (International Consensus on the Definition of Sepsis and Septic Shock).[14] Patients in the case group who met the diagnostic criteria for acute kidney injury as outlined by the Kidney Disease: Improving Global Outcomes (KDIGO) in 2012[15] were included in the SA-AKI group.Healthy controls were individuals without cancer, acute or chronic kidney failure, liver disease, or neurological disease.Exclusion criteria utilized by the SA-AKI group consist of: 1) Patients with primary or secondary kidney diseases (eg, diabetic nephropathy, cardio-renal syndrome, hypertensive nephropathy); 2) Patients undergoing maintenance renal replacement therapy (peritoneal dialysis, hemodialysis); 3) Patients with autoimmune diseases and malignant tumors; 4) Cases of prerenal azotemia, such as severe blood loss or dehydration; 5) Patients who have undergone continuous hemofiltration therapy or received citric acid anticoagulation; 6) Pregnant women, children, and individuals over the age of 80.For Patient samples, our study complies with the Declaration of Helsinki and approved by the Ethics Committee of the Affiliated Hospital of Qinghai University (No:P-SL-2023–193).Informed consent was obtained from all the patients.

Sample Collection And Storage

Clinicians rigorously evaluate patients admitted to the ICU based on outpatient or emergency test results. Upon diagnosing sepsis, blood samples are promptly collected at the time of admission to prevent any potential errors in experimental results caused by medication or medical procedures during treatment. The medical team extracted 3mL of venous blood and placed it in a collection vessel containing EDTA. Following thorough mixing, the sample was centrifuged for 15 minutes. Post-centrifugation, the samples were visually inspected for signs of hemolysis. To prevent repeated freeze-thaw cycles, the plasma was divided into 100μL aliquots, transferred to labeled frozen tubes using a corresponding pipette, stored for subsequent analysis. Once all samples were collected, they were tested and analyzed together in the same batch to ensure consistency and avoid inter-batch variations.

Clinical Data Collection

General information(gender, age, underlying diseases, comorbidities), hemodynamics[MAP (mean arterial pressure), pressors], severity of the disease [Sequential Organ Failure Assessment(SOFA)score, mechanical ventilation, Acute Physiology and Chronic Health Evaluation(APACHE)II score], blood routine examination[white blood cell(WBC), Neutrophil(NEUT), lymphocyte(LY), Neutrophil-lymphocyte Ratio(NLR)], Inflammatory index [procalcitonin (PCT), IL-6 and C-reactive protein(CRP)], serum biochemical index(bilirubin, albumin), renal function[serum creatinine (Scr), blood urea nitrogen(BUN)].

Study Endpoint

Prospective follow-up was conducted at 1, 2, and 3 months from the date of selection through outpatient visits or telephone interviews. The study had two endpoints: primary endpoint was all-cause death, referring to the death of patients due to any cause, secondary endpoint was the recovery of renal function within 7 days in SA-AKI patients, the criteria of renal function recovery refer to previous literature.[16]

Determination of Plasma 5-MTP

The specific method of serum 5-MTP is described in our previously published protocol.[13] LC-MS/MS analyze was commissioned Shanghai Bioprofile Technology Co., Ltd.

Statistical Analysis

All statistical analyses were conducted using SPSS 28.0 software. Continuous variables with a normal distribution were presented as mean ± standard ($\bar{x} \pm s$) deviation.Two-independent sample *t*-tests were used for group comparisons, while one-way ANOVA was utilized for comparisons across multiple groups. Non-normally distributed data were presented as median (quartile)[M(P25, P75)], with non-parametric tests such as rank sum test used for group comparisons. A significance level of α=0.05 was employed for all tests. Categorical data were expressed as percentages and inter-group comparisons were performed using the chi-square test at α=0.05 level. Spearman correlation analysis was used to assess the relationship between serum 5-MTP levels and inflammatory, renal function, and other biomarkers. Logistic regression analysis was conducted to identify factors influencing renal function, and an ROC curve was generated to assess the predictive value of 5-MTP in SA-AKI. Cox regression analysis was employed to evaluate the impact of 5-MTP levels and related risk factors on renal function recovery and clinical outcomes, with Kaplan-Meier curves constructed for survival analysis. Statistical significance was set at $P < 0.05$.

Results

Comparison of General Information and Laboratory Indexes Among Subject

A total of 546 hospitalized patients admitted to the ICU were initially screened, with 136 patients meeting the diagnostic criteria for sepsis. Following the application of exclusion criteria, 78 sepsis patients were ultimately included, of which 39 met the diagnostic criteria for AKI. Additionally, 35 cases were selected as the healthy control group. After excluding 4 cases with incomplete basic data, a total of 31 cases were included for analysis. Statistical analysis revealed no significant differences in basic data such as age, sex, BMI, and comorbidities among the three groups (P>0.05), indicating comparable data across the groups. Refer to Supplementary Table 1 for more details.WBC, NEUT, LY, NLR, CRP, platelet, 5-MTP, Scr, BUN, eGFR, Cys-C, AST, total bilirubin, direct bilirubin, indirect total bilirubin, TP, albumin, APTT, PT, TT, FIB and D-dimer among subject were significant differences(P<0.05). Refer to Table 1 for detailed information.

Results of Serum 5-MTP Targeted Metabolomics

Figure 1A and B shows the overall distribution of samples. The consistency of the healthy control group was robust, displaying a clear clustering trend. In contrast, the data from the sepsis group and SA-AKI group exhibited slightly more scattered distribution compared to the control group, with some samples overlapping to a certain extent. This variation may be attributed to individual differences resulting from the primary infection focus in each group.

Figure 1C illustrates the results of hierarchical clustering of metabolites across the three groups. Notably, the expression of 5-MTP in the SA-AKI group is markedly higher than in the sepsis and healthy control group.The metabolites of the key comparison are depicted in Figure 1D. The figure illustrates that 5-MTP is up-regulated in the SA-AKI group compared to the sepsis group (Fold Chang value = 1.440426, P<0.001). Among the detected tryptophan metabolites, 5-MTP emerges as the most crucial, with the highest variable importance in the Projection value. Figure 1E illustrates statistical differences in 5-MTP levels among the three groups (P<0.05). These findings, suggest that the change in 5-MTP levels is specific to the SA-AKI group.

Table 1 Comparison of Laboratory Indicators Among the Three Groups

Laboratory index	Control (n=31)	Sepsis (n=39)	SA-AKI (n=39)	*F/H/* χ^2	*P*
WBC (10^9/L)	5.09(4.35,5.98)	10.18(7.21,15.63)*	10.87(7.10,18.45)*	39.547	<0.001
NEUT (10^9/L)	2.68(2.31,3.36)	9.04(5.78,14.84)*	9.61(5.73,15.68)*	52.747	<0.001
LY (10^9/L)	1.92(1.44,2.25)	0.65(0.41,0.87)*	0.56(0.38,0.76)*	52.874	<0.001
NLR	1.57(1.25,1.90)	13.79(8.41,25.15)*	14.22(7.66,32.86)*	51.562	<0.001
Platelet (10^9/L)	195(167,264)	136(94,228)*	119(56,198)*	19.798	<0.001
ALT(U/L)	24(17,35)	22(12,55)	43(15,115)	2.381	0.304
AST(U/L)	22(18,25)	26(16,75)	53(24,103)*	11.866	0.003
TBil (umol/L)	13.3(9.8,17.7)	24.5(14.5,44.6)*	25.6(18.8,57.6)*	19.854	<0.001
DBil (umol/L)	3.1(3.7,5.6)	9.1(4.9,20.6)*	14.3(6.85,32.7)*	29.316	<0.001
IBil (umol/L)	9.1(6.9,12.8)	16(9.2,24)*	13.5(9.15,19.7)*	9.333	0.009
TP(g/L)	65.6(63.6,70.1)	54.5(51.3,57.8)*	53.5(43.35,60.75)*	122.593	<0.001
Albumin (g/L)	42.07±3.154	28.26±4.826*	29.16±7.331*	65.944	<0.001
Globulin (g/L)	24.4(22.4,27.2)	26.4(22.3,28.5)	25.9(22.05,29.4)	0.681	0.712
APTT(s)	27.3(26,29)	28.5(26.6,34.5)	37.2(31.35,44.80)*#	33.360	<0.001
PT (s)	10.39±0.75	13.78±1.671*	16.22±4.295*#	91.380	<0.001
TT (s)	18.86±1.717	15.18±1.372*	16.15±1.796*	65.296	<0.001
FIB (mg/dL)	2.72±0.534	4.93±1.678*	4.61±1.698*	45.295	<0.001
Dimer (mg/L)	0.40(0.40,0.70)	4.30(2.70,8.31)*	7.60(3.32,13.50)*	64.184	<0.001
CRP(mg/L)	3.13(3.13,3.13)	44.98(21.75,130.00)*	122.00(36.11,199.00)*	68.946	<0.001
Scr (umol/L)	58(53,68)	72(60,88)	202(134,359)*#	78.051	<0.001
BUN (mmol/L)	6.3(5.2,7.0)	7.3(5.7,9.2)	17.69(11.2,24.5)*#	63.966	<0.001
eGFR (mL/min)	110.94±17.468	89.88±19.220*	29.49±16.790*#	204.902	<0.001
Cys-C (mg/L)	0.88(0.67,0.97)	1.39(0.99,2.13)*	2.53(1.71,3.74)*#	50.240	<0.001

Note: *Significant difference compared to control group, #Significant difference compared to sepsis group.
Abbreviations: WBC, white blood cell count; NEUT, neutrophil count; LY, lymphocyte count; NLR, Neutrophil lymphocyte ratio; ALT, glutamic-pyruvic transaminase; AST, glutamic oxalacetic transaminase; APTT, activated partial thromboplastin time; PT, prothrombin time; TT, thrombin time; FIB, fibrinogen; CRP, C-reactive protein; Scr, serum creatinine; BUN, serum urea nitrogen; eGFR, estimated glomerular filtration rate; Cys-C, cystatin C; TBil, total bilirubin; DBil, direct bilirubin; IBil, indirect bilirubin; TP, total protein.

Comparison of Primary Morbidity and Severity between Sepsis and SA-AKI Group

Statistical analysis revealed no significant differences in infection source, mechanical ventilation, and APACHEII scores between the sepsis group and SA-AKI group ($P>0.05$). However, there were significant disparities in SOFA score, IL-6 levels, and PCT levels between the two groups ($P<0.05$). The SA-AKI group exhibited higher SOFA score, IL-6 levels, and PCT levels compared to the sepsis alone group, indicating more severe inflammation, organ damage, complications, and overall disease severity in SA-AKI patients. Detailed data can be found in Table 2.

Correlation of 5-MTP with Renal Function and Inflammatory Markers

Figure 2A–C demonstrated a significant correlation between serum 5-MTP and Scr, BUN, and eGFR ($P<0.05$), with correlation coefficients of 0.402, 0.282, and −0.455, respectively. However, no significant differences were observed in cystatin C, PCT, CRP, IL-6, and other indicators ($P>0.05$), as depicted in Figure 2D–G.

Analysis of Influencing Factors of SA-AKI Occurrence

Patients with sepsis were categorized based on the development of AKI, with 0 representing sepsis without AKI and 1 representing SA-AKI patients. Various factors were considered as independent variables in logistic regression analysis. The study findings revealed that PCT, SOFA score, IL-6, PT, APTT, TT, MAP and 5-MTP were significant factors influencing the occurrence of SA-AKI ($P<0.05$), as presented in Table 3. Further multivariate analysis was conducted on clinically relevant indicators identified in the univariate analysis to elucidate the impact of 5-MTP on SA-AKI. The results demonstrated that serum PCT, 5-MTP, PT and APTT were independent influencing factors for the development of

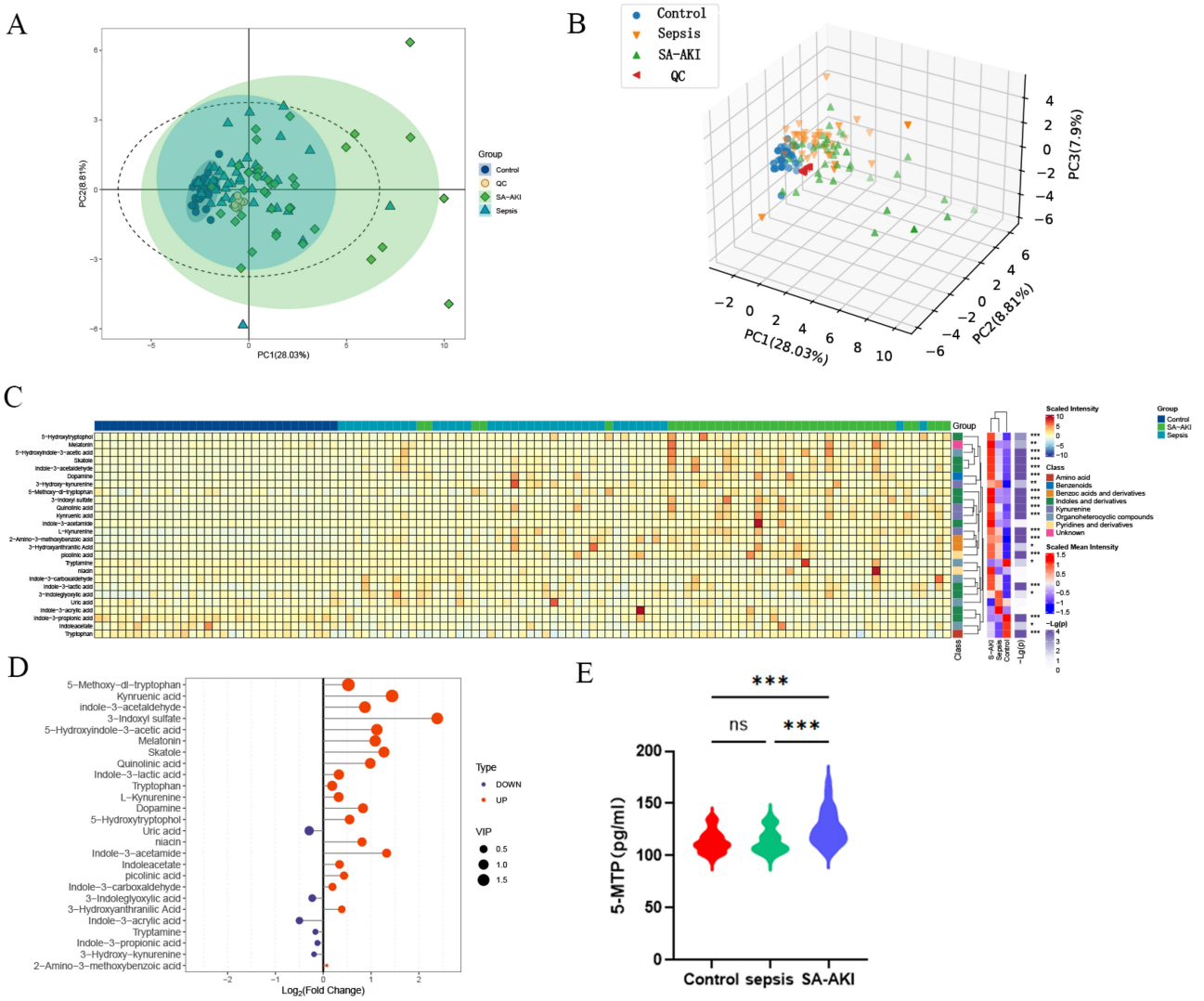

Figure 1 Metabolomic results of 5-MTP. (**A**) Principal component analysis diagram; (**B**) Principal component analysis 3D diagram;(**C**) Heat map;(**D**) metabolite importance analysis;(**E**) Comparison of 5-MTP expression levels among the three groups.*P < 0.05, **P < 0.01, ***P < 0.001 denote statistically meaningful differences among the groups.

SA-AKI, as depicted in Table 4.In Figure 2H, the optimal cut-off value for serum 5-MTP was found to be 110.16 pg/mL. The area under the ROC curve was calculated as 0.736 (95% CI: 0.626–0.846, P<0.001), suggesting that 5-MTP could serve as a valuable biomarker for predicting the onset of SA-AKI.

Comparison of Clinical Data between SA-AKI Patients with Renal Function Recovery and Those without Recovery within 7 Day

To further investigate the impact of 5-MTP on kidney injury, we assessed the recovery time of kidney injury in SA-AKI patients. Patients were categorized into a recovery group and a non-recovery group based on whether their kidney injury resolved within 7 days. A comparison was then made between the two groups in terms of basic data, laboratory indicators, and 5-MTP expression levels that could potentially influence the outcome. No statistically significant variances were observed in APACHEII score, SOFA score, and CRP (P>0.05). However, statistically significant differences were noted in mechanical ventilation, IL-6, PCT, and 5-MTP levels between the two groups (P<0.05). These results suggest that SA-AKI patients with mechanical ventilation are more likely to experience unrecovery in renal

https://doi.org/10.2147/JIR.S524046

Table 2 Comparison of Primary Morbidity and Severity of Sepsis and SA-AKI Between the Two Groups

General Information	Sepsis (n=39)	SA-AKI(n=39)	Z/t/ χ^2	P
Source of infection (n,%)				
Pulmonary infection	21 (53.80)	16 (41.00)	2.550	0.448
Abdominal infection	14 (35.90)	19 (48.70)		
Urinary infection	3 (7.70)	4 (10.30)		
Skin soft-tissue infection	1 (2.60)	0 (0.00)		
Mechanical ventilation (n,%)	20 (51.30)	24 (61.50)	0.834	0.361
APACHEII score	13.0 (10.0, 16.0)	15.0 (12.0, 21.0)	−1.653	0.098
SOFA score	5.0 (4.0, 8.0)	8.0 (5.0, 12.0)#	−2.748	0.006
IL-6 (pg/mL)	136.0 (66.70, 273.0)	691.69 (38.30, 2966.75)#	−2.194	0.028
PCT(ng/mL)	3.0 (0.50, 11.20)	40.0 (5.50, 100.0)#	−4.333	<0.001

Note: #Significant difference compared to sepsis group.
Abbreviations: SOFA, Sequential Organ Failure Assessment; APACHEII, Acute Physiology and Chronic Health Evaluation; IL-6, interleukin-6; PCT, procalcitonin.

function, and a more severe inflammatory response is associated with a lower likelihood of renal function recovery. Conversely, SA-AKI patients exhibiting high levels of 5-MTP expression are more likely to recover from renal injury, as illustrated in Table 5.

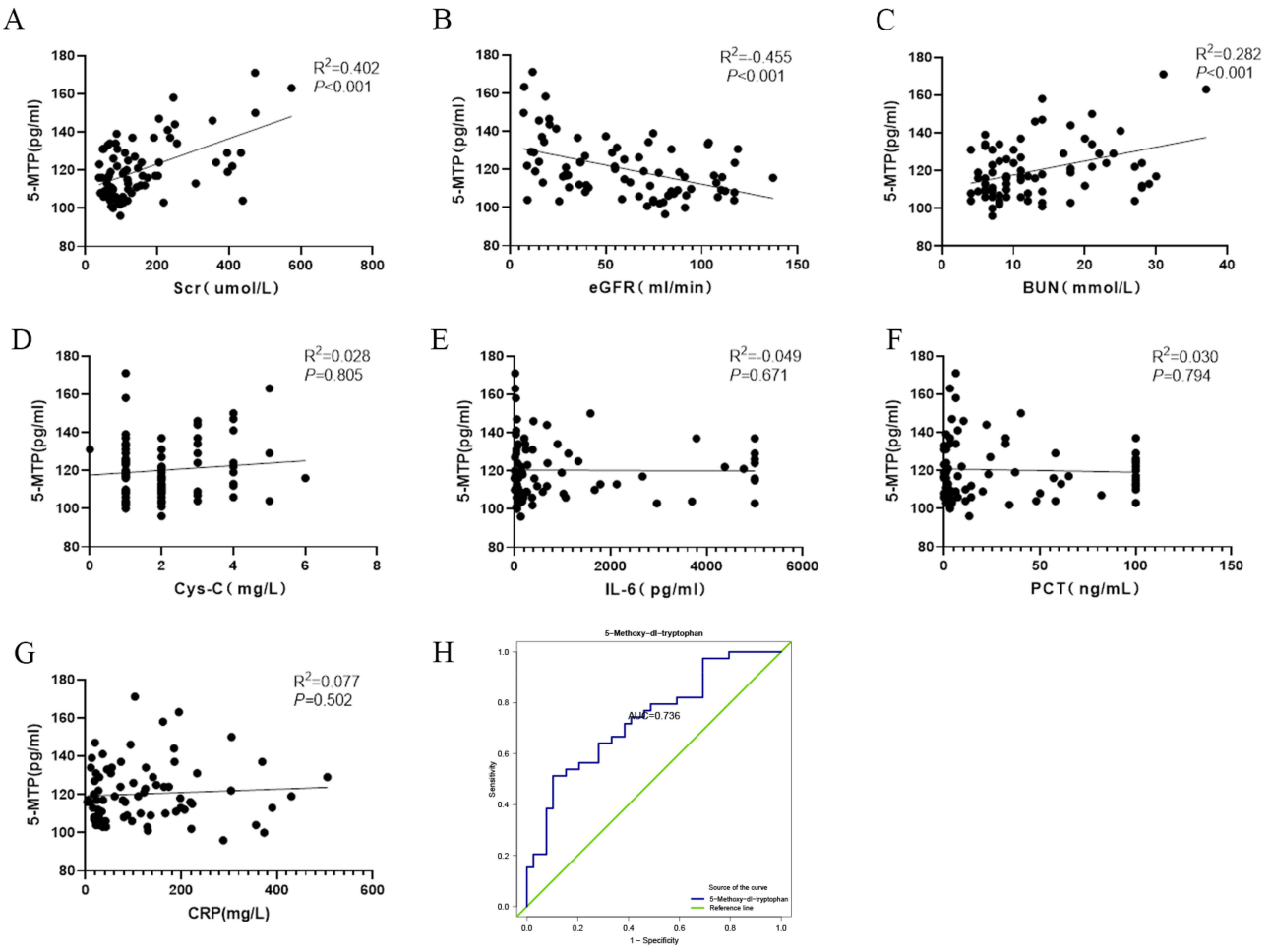

Figure 2 Correlation of 5-MTP with renal function and inflammation and its predictive value for SA-AKI.Correlation between serum 5-MTP and Scr (**A**), eGFR (**B**), BUN (**C**), Cys-C (**D**), IL-6 (**E**), PCT (**F**) and CRP(**G**); (**H**) ROC curve of 5-MTP predicted AKI in sepsis patients(n=78).
Abbreviations: r^2, correlation coefficient; *P*, p value; AUC, Area Under the Curve.

Table 3 Univariate Logistic Regression Analysis

Index	B	BE	Wald	OR	*P*
Age (years)	0.015	0.018	0.669	1.015 (0.980, 1.051)	0.413
Male (n,%)	0.322	0.464	0.481	1.380 (0.555, 3.429)	0.488
MAP(mmHg)	−0.053	0.016	11.059	0.949 (0.920, 0.979)	0.001
Mechanical ventilation	0.419	0.459	0.831	1.520 (0.618, 3.739)	0.362
WBC (10^9/L)	0.036	0.028	1.586	1.036 (0.980, 1.095)	0.208
NEUT (10^9/L)	0.033	0.030	1.232	1.034 (0.975, 1.096)	0.267
LY (10^9/L)	0.265	0.401	0.437	1.304 (0.594, 2.863)	0.509
CRP(mg/L)	0.004	0.002	3.693	1.004 (1.000, 1.009)	0.055
IL-6 (pg/mL)	0.001	0.000	7.462	1.001 (1.000, 1.001)	0.006
PCT(ng/mL)	0.029	0.008	12.661	1.030 (1.013, 1.047)	<0.001
SOFA score	0.117	0.050	5.443	1.124 (1.019, 1.240)	0.020
APACHEIIscore	0.076	0.041	3.360	1.079 (0.995, 1.170)	0.067
APTT(s)	0.162	0.043	14.395	1.176 (1.081, 1.278)	<0.001
PT (s)	0.326	0.115	8.070	1.386 (1.106, 1.735)	0.005
TT (s)	0.413	0.159	6.783	1.512 (1.108, 2.063)	0.009
FIB(mg/dL)	−0.125	0.139	0.819	0.882 (0.672, 1.157)	0.366
Dimer(mg/L)	0.034	0.026	1.727	1.035 (0.983, 1.089)	0.189
5-MTP (pg/mL)	0.066	0.020	10.514	1.068 (1.026, 1.112)	0.001

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC, white blood cell count; NEUT, neutrophil count; LY, lymphocyte count; APTT, activated partial thromboplastin time; PT, prothrombin time; TT, thrombin time; FIB, fibrinogen; CRP, C-reactive protein; IL-6, interleukin-6; PCT, procalcitonin; SOFA, Sequential Organ Failure Assessment; APACHE II, Acute Physiology and Chronic Health Evaluation; MAP, mean arterial pressure; 5-MTP, 5-methoxytryptophan.

Table 4 Multivariate Logistic Regression Analysis

Index	B	BE	Wald	OR	*P*
IL-6 (pg/mL)	0.000	0.000	0.155	1.000 (0.999, 1.000)	0.693
PCT(ng/mL)	0.038	0.015	6.692	1.039 (1.009, 1.069)	0.010
SOFA score	0.141	0.080	3.087	1.151 (0.984, 1.348)	0.079
APTT(s)	0.196	0.072	7.282	1.216 (1.055, 1.402)	0.007
PT (s)	0.444	0.199	4.988	1.559 (1.056, 2.302)	0.026
TT (s)	0.091	0.293	0.096	1.095 (0.616, 1.946)	0.756
5-MTP (pg/mL)	0.088	0.032	7.590	1.092(1.026,1.163)	0.006
MAP(mmHg)	−0.020	0.025	0.630	0.980(0.932,1.030)	0.427

Abbreviations: NEUT, neutrophil count; IL-6, interleukin-6; PCT, procalcitonin; APTT, activated partial thromboplastin time; PT, prothrombin time; TT, thrombin time; SOFA, Sequential Organ Failure Assessment; MAP, mean arterial pressure; 5-MTP, 5-methoxytryptophan.

Table 5 Comparison of Renal Function Recovery and Non-Recovery in SA-AKI Patients

General Information	Recovery (n=21)	Unrecovery(n=18)	Z/t/ $\chi 2$	*P*
Age (years)	63±12	59±14	0.767	0.448
Male (n,%)	9 (42.9)	13 (72.2)	3.399	0.065
Mechanical ventilation	5 (23.8)	10 (55.6)	4.127	0.042
APACHEIIscore	16.0 (13.0, 20.0)	12.0 (12.0, 24.0)	−0.141	0.888
SOFA score	8.0 (6.0, 16.0)	7.0 (5.0, 8.0)	−1.234	0.217
CRP(mg/L)	114.53(34.85,189.75)	156.00(36.57,243.25)	-0.845	0.398
IL-6 (pg/mL)	208.0 (33.10, 1302.4)	1961.0 (547.75, 3935.25)	−2.327	0.020
PCT(ng/mL)	22.0 (4.51, 49)	10.0 (28.80, 100.0)	−2.411	0.016
5-MTP (pg/mL)	132.71±19.184	119.13±8.631	2.919	0.007

Abbreviations: SOFA, Sequential Organ Failure Assessment; APACHE II, Acute Physiology and Chronic Health Evaluation; IL-6, interleukin-6; PCT, procalcitonin; 5-MTP, 5-methoxytryptophan.

https://doi.org/10.2147/JIR.S524046

Table 6 Sepsis Cluster and SA-AKI Cohort Comparison Between Surviving and Dying Groups

Index	Sepsis Squadron			SA-AKI Queue		
	Survival (n=36)	Death (n=42)	*P*	Survival (n=21)	Death (n=18)	*P*
Age (years)	60(52,75)	57(51,69)	0.179	61±15	61±11	0.921
Male (n,%)	19 (52.8)	28 (66.7)	0.211	10 (47.6)	12 (66.7)	0.232
CRP (mg/L)	57.95(20.03,158.58)	111.0(29.6,204.5)	0.083	114.53(34.85,185.25)	131.50(63.73,317.00)	0.260
IL-6 (pg/mL)	119.5(35.23,626.75)	320.0(104.83,2743.44)	0.018	208.0(28.45,1228.15)	2401.0(324.08,4827.5)	0.008
PCT (ng/mL)	5.55(0.58,29.97)	16.81(3.14,100)	0.020	3.48(22,57.5)	83.5(26.24,100)	0.019
5-MTP (pg/mL)	126.11(116.21,137.31)	110.65(104.27,121.28)	<0.001	133.0±17.645	118.79±11.454	0.005
SOFA score	6.0(4.00,8.00)	8.0(5.00,15.0)	0.020	6.0(5.00,9.0)	9.0(7.00,20.00)	0.011
APACHEIIscore	13(10.0,16.00)	16.0(12.0,20.0)	0.026	14.0±4.0	20.0±8.0	0.010
WBC (10^9/L)	11.22(7.79,17.78)	10.08(6.98,15.33)	0.443	10.81(6.85,19.11)	11.5(7.07,19.25)	0.791
NEUT (10^9/L)	9.33(6.51,15.76)	9.25(5.72,13.25)	0.641	12.14±9.549	12.95±8.681	0.464
LY (10^9/L)	0.60(0.39,0.90)	0.60(0.40,0.82)	0.960	0.56(0.33,0.84)	0.59(0.42,0.91)	0.481
NLR	14.02(8.41,27.93)	15.5(8.02,33.0)	0.748	15.84(7.15,40.5)	14.9(10.15,27.11)	0.430

Abbreviations: SOFA, Sequential Organ Failure Assessment; APACHE II, Acute Physiology and Chronic Health Evaluation; IL-6, interleukin-6; PCT, procalcitonin; 5-MTP, 5-methoxytryptophan; CRP, C-reactive protein; WBC, white blood cell count; NEUT, neutrophil count; LY, lymphocyte count; NLR, Neutrophil lymphocyte ratio.

Comparison of Clinically Relevant and Analysis of Influencing Factors indicators in Sepsis and SA-AKI patients with Different Prognoses

The findings revealed no significant variations in age, sex, CRP, WBC, NEUT, LY, and NLR between the survival and death groups in the overall sepsis cohort ($P>0.05$). However, significant differences were observed in 5-MTP, IL-6, PCT, SOFA, and APACHEII scores ($P<0.05$). In SA-AKI queue, significant differences were noted in 5-MTP, IL-6, PCT, SOFA score, and APACHEII score between the survival and death groups($P<0.05$). These results suggest that patients in the death group exhibited more severe disease manifestations, characterized by higher IL-6, PCT levels, SOFA score, and APACHEII score. Notably, the serum levels of 5-MTP were significantly higher in the survival group compared to the death group, indicating that elevated 5-MTP levels were associated with a more favorable prognosis and reduced risk of mortality, as depicted in Table 6.

In order to specifically assess the impact of 5-MTP on the all-cause death of patients with sepsis and SA-AKI, our study utilized univariate and multivariate COX models.The findings revealed that 5-MTP levels were linked to all-cause mortality in sepsis and SA-AKI patients, as depicted in Figure 3A–D. This suggests that 5-MTP plays a crucial role in determining the prognosis of SA-AKI. Subsequently, K-M survival curves were utilized to compare mortality rates in sepsis and SA-AKI based on 5-MTP expression levels. The optimal cutoff value for 5-MTP was determined to be 115.23 pg/mL using the Jorden index. Analysis of the K-M curve demonstrated that lower levels of 5-MTP expression were significantly associated with higher 90-day mortality rates in sepsis patients, as illustrated in Figure 3E and F). Similarly, in the SA-AKI subgroup, lower 5-MTP levels were strongly correlated with increased 90-day mortality, while higher 5-MTP levels were linked to better survival outcomes.

Discussion

In this study, we investigated the relationship between 5-MTP and SA-AKI by analyzing the serological expression level of 5-MTP. We also assessed the correlation between serological 5-MTP expression and the prognosis of patients with sepsis and SA-AKI. Our findings revealed a significant increase in serum 5-MTP expression in patients with SA-AKI, which showed correlations with Scr, BUN, and eGFR. Additionally, 5-MTP was identified as an independent influencing factor for all-cause mortality in patients with sepsis and SA-AKI. Higher levels of 5-MTP were associated with accelerated kidney function recovery, while lower levels were linked to higher 90-day all-cause mortality in SA-AKI

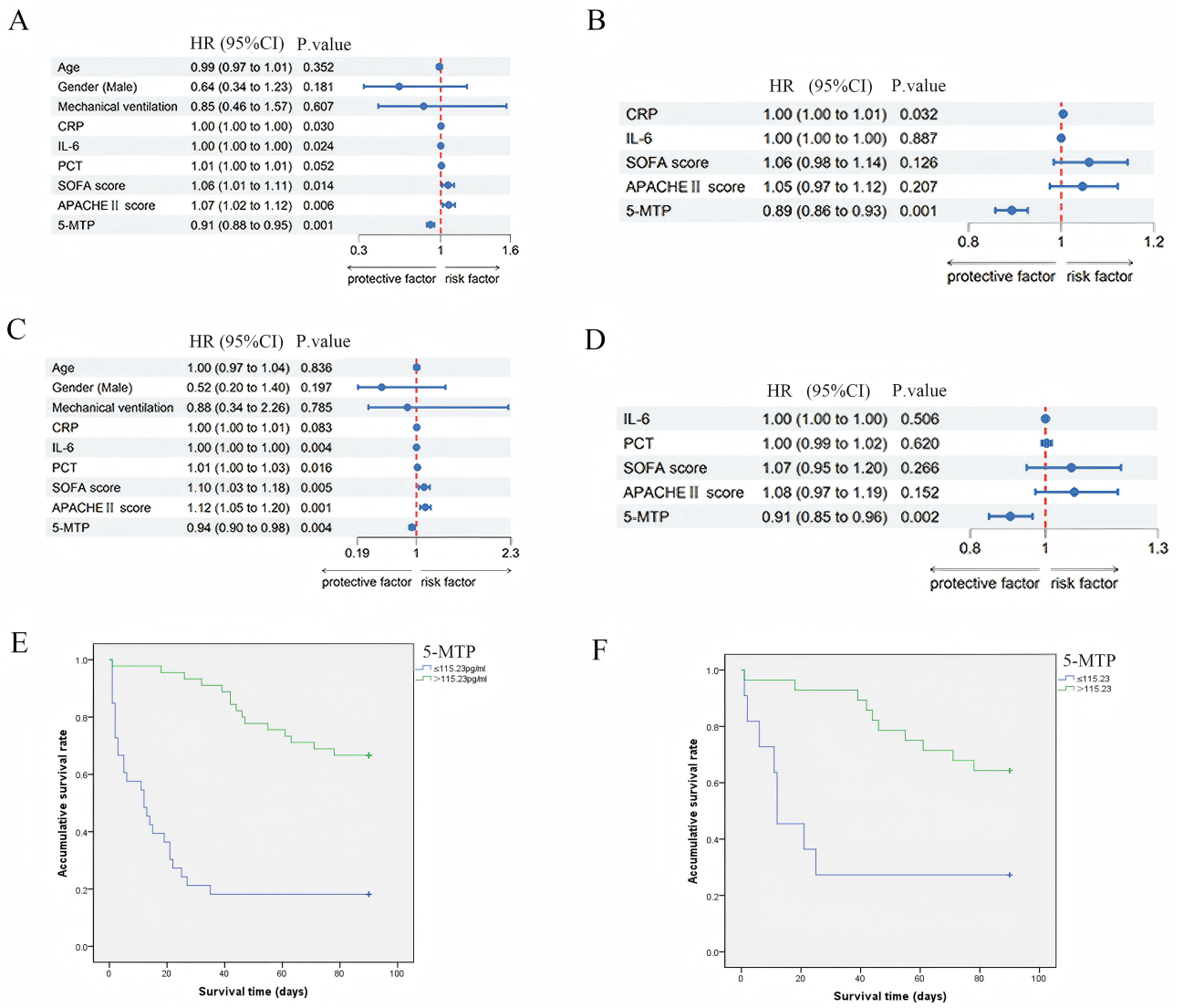

Figure 3 COX regression analysis and survival curves of sepsis group and SA-AKI group. (**A**)Sepsis group single-factor COX regression;(**B**) Sepsis group multi-factor COX regression; (**C**) SA-AKI subgroup single-factor COX regression;(**D**)SA-AKI subgroup multi-factor COX regression; (**E**)Sepsis group K-M survival curve;(**F**) SA-AKI subgroup K-M survival curve.

patients. 5-MTP may have a protective role in the development of SA-AKI, with early increases in serological 5-MTP expression positively impacting the prognosis of sepsis and SA-AKI.

Up to 60% of individuals with sepsis develop AKI.[17] Early detection of kidney injury is crucial for successful intervention and patient prognosis. However, the definition of AKI by KDIGO has limitations, including the need for baseline serum creatinine values for creatinine elevation determination and challenges in establishing pre-AKI baseline serum creatinine without direct data.[18,19] In summary, neither urine volume nor creatinine alone can reliably predict SA-AKI occurrence, nor can they serve as clinical indicators for patient prognosis assessment. In a previous study by our team, it was found that 5-MTP is a crucial metabolic product in sepsis and SA-AKI, showing a significant positive correlation with renal function indicators such as Scr and BUN. This means that as the levels of Scr and BUN increase, serum 5-MTP levels also increase. Previous studies had a limitation in lacking a healthy control group as a baseline. However, upon adding the healthy control group in this study, it was observed that the expression level of serum 5-MTP in the SA-AKI group was higher and related to renal function. These findings suggest that the early elevation of 5-MTP serves as an indicator of renal function impairment in sepsis patients. There are few studies investigating 5-MTP in SA-

https://doi.org/10.2147/JIR.S524046

AKI. However, we have found that melatonin, along with 5-MTP, is an endogenous metabolite produced by the tryptophan metabolic pathway. Melatonin plays a therapeutic role in SA-AKI and is elevated in the disease state,[20] demonstrating a similar trend to that of 5-MTP as discussed in this paper.We propose that in the event of sepsis, an inflammatory outburst should trigger renal to release 5-MTP, which plays a crucial role in regulating the inflammatory response and mitigating kidney damage associated with sepsis. Utilizing the ROC curve, we assessed the impact of 5-MTP on SA-AKI, revealing that 5-MTP possesses a high predictive value for forecasting the occurrence of SA-AKI. Thus, it is suggested that 5-MTP may serve as a valuable tool for predicting AKI occurrence in patients with sepsis.

A retrospective cohort study revealed that a longer recovery time following AKI correlates with a heightened risk of CKD progression.The duration of recovery post-AKI emerges as a crucial predictor for CKD risk.[21] Notably, individuals who experience complete reversal of AKI early in the disease exhibit more favorable clinical outcomes compared to those with persistent AKI.[22] During our patient monitoring throughout hospitalization, we observed that serum 5-MTP expression levels were elevated in AKI patients with renal function recovery within 7 days, as opposed to those who did not recover within this timeframe. This was similar to previous findings in LN[11] and acute myocardial infarction,[23] where increased 5-MTP levels improved patient renal outcomes.This finding suggests a correlation between serological 5-MTP expression and renal function recovery, offering potential for predicting AKI reversal and introducing a novel target for SA-AKI treatment.

Clinical events of death or survival within 90 days were observed as an endpoint for all patients in our study. We discovered that patients with lower baseline concentrations of 5-MTP were more likely to experience adverse events such as death, both in the sepsis cohort and the SA-AKI subgroup cohort analysis. This is consistent with the results of regarding its effects on cardiovascular events.[23] These findings indicate that 5-MTP anti-inflammatory mediators play a significant role in the pathophysiological processes of sepsis patients. High serum levels of 5-MTP early on may inhibit the release of inflammatory factors and responses, leading to a positive impact on patient prognosis.

Our study aims to complement the array of biomarkers for SA-AKI, offering a fresh perspective to enhance outcomes in SA-AKI patients, and to advance the diagnosis and treatment of SA-AKI. However, our study does have limitations. Firstly, we only measured 5-MTP at one time point upon ICU admission, without continuous monitoring during treatment, which hindered a comprehensive evaluation of the impact of 5-MTP level fluctuations on SA-AKI prognosis.Secondly, in some cases, serological samples were not collected again at the conclusion of the 90-day follow-up, preventing a reevaluation of relevant kidney function indicators and the association between these indicators and 5-MTP at the end of the follow-up.

Conclusion

The results of this study suggest that tryptophan metabolic pathway changes significantly during SA-AKI disease, and endogenous 5-MTP is an important factor affecting the prognosis of critically ill patients with SA-AKI. 5-MTP is closely related to kidney function, and high concentrations of 5-MTP are associated with early recovery of kidney function. Low concentrations of 5-MTP increased the risk of death in SA-AKI patients.

Ethics Statement

For Patient samples, our study complies with the Declaration of Helsinki and approved by the Ethics Committee of the Affiliated Hospital of Qinghai University (No:P-SL-2023–193).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the study design, execution, acquisition of data, analysis and interpretation; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted and agree to be accountable for all aspects of the work.

Funding

This research was supported by "2023 Young Scientific Foundation of Qinghai University" (No: 2023-QYY-2); Qinghai Province"Kunlun Talents · High-end Innovative and Entrepreneurial Talents" cultivate leading talents (2022).

Disclosure

The authors report no conflicts of interest in this work.

References

1. Chiu C, Legrand M. Epidemiology of sepsis and septic shock. *Curr Opin Anaesthesiol*. 2021;34(2):71–76. doi:10.1097/ACO.0000000000000958
2. Kindgen-Milles D, Dimski T, Brandenburger T. [Acute kidney injury: epidemiology, pathophysiology, repair mechanisms]. *Anasthesiol Intensivmed Notfallmed Schmerzther*. 2021;56(2):90–100. doi:10.1055/a-1105-0587 Danish
3. Kellum JA, Chawla LS, Keener C, et al. The effects of alternative resuscitation strategies on acute kidney injury in patients with septic shock. *Am J Respir Crit Care Med*. 2016;193(3):281–287. doi:10.1164/rccm.201505-0995OC
4. Coca SG, Yusuf B, Shlipak MG, Garg AX, Parikh CR. Long-term risk of mortality and other adverse outcomes after acute kidney injury: a systematic review and meta-analysis. *Am J Kidney Dis*. 2009;53(6):961–973. doi:10.1053/j.ajkd.2008.11.034
5. Kellum JA, Lameire N, Aspelin P, et al. Kidney disease: improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl*. 2012;2(1):1–138. doi:10.1038/kisup.2012.1
6. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute dialysis quality initiative workgroup. acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the second international consensus conference of the Acute Dialysis Quality Initiative (ADQI) group. *Crit Care*. 2004;8(4):R204–212. doi:10.1186/cc2872
7. Pan HC, Yang SY, Chiou TTY, et al. Comparative accuracy of biomarkers for the prediction of hospital-acquired acute kidney injury: a systematic review and meta-analysis. *Crit Care*. 2022;26(1):349. doi:10.1186/s13054-022-04223-6
8. Zhang A, Cai Y, Wang PF, et al. Diagnosis and prognosis of neutrophil gelatinase-associated lipocalin for acute kidney injury with sepsis: a systematic review and meta-analysis. *Crit Care*. 2016;20:41. doi:10.1186/s13054-016-1212-x
9. Marx D, Metzger J, Pejchinovski M, et al. Proteomics and metabolomics for AKI diagnosis. *Semin Nephrol*. 2018;38(1):63–87. doi:10.1016/j.semnephrol.2017.09.007
10. Wang YF, Hsu YJ, Wu HF, et al. Endothelium-derived 5-methoxytryptophan is a circulating anti-inflammatory molecule that blocks systemic inflammation. *Circ Res*. 2016;119(2):222–236. doi:10.1161/CIRCRESAHA.116.308559
11. Lin TC, Kuo CC, Wu CY, Yeh KW, Kuo ML, Huang JL. The role of 5-methoxytryptophan in pediatric-onset lupus nephritis: a retrospective cohort study. *J Microbiol Immunol Infect*. 2020;53(5):797–802. doi:10.1016/j.jmii.2018.12.003
12. Chen DQ, Cao G, Chen H, et al. Identification of serum metabolites associating with chronic kidney disease progression and anti-fibrotic effect of 5-methoxytryptophan. *Nat Commun*. 2019;10(1):1476. doi:10.1038/s41467-019-09329-0
13. Sun X, Wang H, Liu Y, et al. 5-methoxytryptophan alleviates lipopolysaccharide-induced acute kidney injury by regulating Nrf2-mediated mitophagy. *J Inflamm Res*. 2024;17:9857–9873. doi:10.2147/JIR.S474040
14. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA*. 2016;315(8):801–810. doi:10.1001/jama.2016.0287
15. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin Pract*. 2012;120(4):c179–184. doi:10.1159/000339789
16. Kellum JA, Sileanu FE, Bihorac A, Hoste EAJ, Chawla LS. Recovery after acute kidney injury. *Am J Respir Crit Care Med*. 2017;195(6):784–791. doi:10.1164/rccm.201604-0799OC
17. Bagshaw SM, Lapinsky S, Dial S, et al. Acute kidney injury in septic shock: clinical outcomes and impact of duration of hypotension prior to initiation of antimicrobial therapy. *Intensive Care Med*. 2009;35(5):871–881. doi:10.1007/s00134-008-1367-2
18. Bernier-Jean A, Beaubien-Souligny W, Goupil R, et al. Diagnosis and outcomes of acute kidney injury using surrogate and imputation methods for missing preadmission creatinine values. *BMC Nephrol*. 2017;18(1):141. doi:10.1186/s12882-017-0552-3
19. Doi K, Yuen PST, Eisner C, et al. Reduced production of creatinine limits its use as marker of kidney injury in sepsis. *J Am Soc Nephrol*. 2009;20(6):1217–1221. doi:10.1681/ASN.2008060617
20. Deng Z, He M, Hu H, et al. Melatonin attenuates sepsis-induced acute kidney injury by promoting mitophagy through SIRT3-mediated TFAM deacetylation. *Autophagy*. 2024;20(1):151–165. doi:10.1080/15548627.2023.2252265
21. Bandak G, Grams ME. Kidney-related outcomes after hospital-associated acute kidney injury: even the mildest episodes count. *Am J Kidney Dis*. 2016;67(5):716–718. doi:10.1053/j.ajkd.2016.02.030
22. Yoon SY, Kim JS, Jeong KH, Kim SK. Acute kidney injury: biomarker-guided diagnosis and management. *Medicina*. 2022;58(3):340. doi:10.3390/medicina58030340
23. Huang K, Wen XQ, Zhang W, et al. Predictive value of 5-methoxytryptophan on long-term clinical outcome after PCI in patients with acute myocardial infarction-a prospective cohort study. *J Cardiovasc Transl Res*. 2024;17(5):1036–1047. doi:10.1007/s12265-024-10518-6