The diagnostic and prognostic value of heme oxygenase 1 in sepsis-induced acute kidney injury: a cross-sectional observational study

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Research article

Keywords: Heme oxygenase 1; Sepsis; Acute kidney injury

Posted Date: August 23rd, 2019

DOI: https://doi.org/10.21203/rs.2.13523/v1

Abstract

Background Sepsis patients suffer from severe inflammatory and poor prognosis. Local inflammation resulted from sepsis is found to trigger organ injury, such as acute kidney injury (AKI). We conducted a cross-sectional observational study to examine the diagnostic and prognostic role of serum heme oxygenase 1 (HO-1) on sepsis-induced AKI. Methods The 83 enrolled patients were initially divided into two groups with no AKI (NAKI) and sepsis-induced AKI group (SAKI) based on whether had AKI. Then the patients were concretely divided into four groups: septic shock and AKI group (SS+AKI group), sepsis-induced AKI group (S+AKI group), septic shock group (SS group), and sepsis group (S group. The venous blood was sampled within 24 hours after diagnosis of sepsis. We detected the serum HO-1 and laboratory indicators by enzyme-linked immunosorbent assay. The 28-day survival status was observed between the HO-1 high- and low-level patients grouped by the median of HO-1 concentration 41.33U/L. Results We found that there were statistically significant results of SOFA score and admission time between SAKI and NAKI group ($p<0.05$). The level of HO-1 in SAKI group was obviously elevated as compared with NAKI group ($p<0.05$). It was remarkable to show that HO-1 level was remarkably higher in SS+AKI group than that in other three groups ($p<0.05$). In All groups, HO-1 positively correlates with SOFA score, Scr, Hb, APTT, Urea, and TnI ($p<0.05$). In SS+AKI group, HO-1 was positively associated with SOFA score, Scr, AKI stage, γ-GT, and FDP ($p<0.05$). In S+AKI, HO-1 level was positively related to the level of Scr, AKI stage, and ALP ($p<0.05$). In SS group, SOFA score was in negative correlation to HO-1 ($p<0.05$). The AUC of HO-1 and serum creatinine was 0.824 (95% CI: 0.703-0.944) and 0.778 (95% CI: 0.658-0.919) separately. The AUC of combined with HO-1 and serum creatinine was 0.864 (95% CI: 0.761-0.968). The survival analysis showed that sepsis patients with high HO-1 level had a higher mortality rate compared with patients with low HO-1 expression. Conclusions The findings from this study make contributions to clinical value of HO-1, suggesting that HO-1 plays a diagnostic and prognostic role in sepsis-induced AKI.

Background

The occurrence of bacterial sepsis can result in millions of deaths each year[1,2]. There is evidence that sepsis enables the switch from initial systemic inflammation to acute local inflammation of multi-organ, which finally leads to organ failure, such as acute kidney injury (AKI)[3]. Sepsis complicated with AKI has been thought of as a key factor of high mortality. AKI represents a tough task to address among clinical practices in intensive care unit all over the world[4]. A considerable amount of literature has been published on the pathogenesis of AKI, however, the mechanisms underlying the progression of sepsis-induced AKI have remained unclear. Once organism has response to the pathological stimulation, the oxidative stress and inflammatory exert mutual reinforcement and give further influence on body[5,6]. Recent evidence has shown that the role of oxidative stress in the development of AKI is increasingly being recognized[7,8]. Several attempts have been made to indicate that heme oxygenase-1 (HO-1) play an antioxidant role in the progression of acute organ injury[9-11]. The aim of this study is to explore the diagnostic and prognostic significance of HO-1 in sepsis-induced AKI.

HO-1 is one functional isoform of heme oxygenase which is the rate limit enzyme of heme catabolism in mammalian cells. The metabolic products of heme are generated after the upregulation of HO-1, which is mainly found in liver, spleen and lung[12-14]. It is necessary here to clarify that HO-1 plays an important cytoprotective role in the inflammatory response to organ injury[15,16]. The regulation of HO-1 expression and secretion is a protective response in the forms of AKI[17,18].

The present study seeks to obtain data which will help to estimate the role of HO-1 in sepsis-induced AKI. Patients for this study were collected from the First Affiliated Hospital of Dalian Medical University. Based on the analysis between different sepsis groups, this study was conducted in the form of clinical information and laboratory results with the statistic approach in order to address the correlation between HO-1 and laboratory indicators in sepsis. The findings suggest that HO-1 plays a diagnostic and prognostic role in sepsis-induced AKI.

Methods

Subjects and study design. The sepsis patients of this study were conducted in the First Affiliated Hospital of Dalian Medical University, China, from June 2018 to Jan 2019. The 109 sepsis patients were collected at early stage of this study. Those patients who died within 24 hours (n=9), had no blood test within 24 hours (n=6), chronic nephropathy (n=8) and malignancy (n=3) were excluded from the present study. Criterion for selecting sepsis patients was diagnostic criteria for sepsis 3.0. The total of 83 sepsis patients fulfilled inclusion criteria including sepsis-induced AKI patients (SAKI, n=36) and sepsis patients with no AKI (NAKI, n=47). According to the definition of septic shock and global kidney diagnostic criteria in Kidney Disease: Improving Global Outcomes (KDIGO), the patients were recruited and divided into four distinct groups: septic shock and AKI group (SS+AKI group, n=18), sepsis-induced AKI group (S+AKI group, n=18), septic shock group (SS group, n=20), and sepsis group (S group, n=27). This study was approved by the Ethics Review Committee of the First Affiliated Hospital of Dalian Medical University. It was identified that the institutional committee of the First Affiliated Hospital of Dalian Medical University had approved this study, including all relevant details. It’s confirmed that all experiments were performed in accordance with relevant guidelines and regulations.

Laboratory measurements. Venous blood of patients was obtained within 24 hours after the diagnosis of sepsis. Blood samples were placed at room temperature for 15 minutes. After centrifugation, aliquots of serum were stored at -80°C while waiting for subsequent assay. HO-1 level of serum samples was routinely measured by enzyme-linked immunosorbent (ELISA) assay. The ELISA assay was evaluated using two different cutoff values. The physiological parameters were applied for the routine check of sepsis patient admitted to hospital.

Statistical analysis. Statistical data was generated by using SPSS (22.0, IBM SPSS Statistics, USA). Data are expressed as mean ± standard deviation, or median (25th-75th percentile). We used Mann-Whitney U test to evaluate the variables between SAKI patient group and NAKI patient group. The Kruskal-wallis test was set out to examine the variables in SS+AKI group, S+AKI group, SS group, and S group. The difference of indicators between groups were studied with ordinal logistic regression mode. The Spearman test was used to assess the correlation of variables. Receiver operating characteristic (ROC) curve was drawn to predicted incidence of sepsis-induced AKI with calculate area under curve (AUC). Survival curve was generated by Kaplan–Meier survival curve. $P<0.05$ was considered statistically significant.

Results

Clinical characteristics and laboratory data of sepsis patients. Table 1 presented the characteristics of 83 sepsis patients, among whom SAKI was 36 (43.4%) and NAKI was 47 (56.6%). As shown in Table 1, SOFA sore and time of ICU stay differed significantly between SAKI patients and NAKI patients ($p<0.05$). Table 2 provided the remarkable difference of HO-1, CK-MB, TnI, Urea, MYO, PCT and APTT between SAKI patients and NAKI patients ($p<0.05$). None of other differences were statistically significant ($p>0.05$).

The sepsis patients were categorized as four groups based on sepsis, shock, AKI, and their combinatorial relationship as described in method. It can be seen from Table 3 that a total of 7 parameters changed significantly between these four groups ($p<0.05$), including ALP, Urea, MYO, Scr, PCT, APTT, and PT.

Profile analysis of HO-1 level among different sepsis groups. To assess the characteristic role of HO-1 in sepsis, the concentration of HO-1 was examined and compared between distinct sepsis groups. In Fig. 1 A, we observed that HO-1 level in SAKI group was higher significantly than that in NAKI group ($p = 0.001$). We also detected HO-1 level in SS+AKI group compared with the level in each one of other three groups, and the significant results are presented in Fig.1 B ($p<0.05$). However, no significant differences were found between S+AKI, SS, and S groups ($p>0.05$).

Correlation analysis of HO-1 with laboratory data of sepsis patients. In an attempt to analyze the correlation between HO-1 and laboratory data, Spearman correlation test was employed to examine whether HO-1 was significantly associated with laboratory indicators. The results obtained from the analysis were summarized in Table 4 and 5. In all sepsis patients, HO-1 had a positive relation to Hb, TnI, Urea, Scr, APTT and SOFA sore ($p<0.05$). In SS+AKI group, HO-1 had obviously a positive relation to SOFA score, AKI grade, Scr, γ-GT and FDP ($p<0.05$). In S+AKI group, HO-1 was significantly correlated with AKI grade, Scr and ALP, respectively ($p<0.05$). In SS group, there was a negative correlation between HO-1 and SOFA score. In sepsis group, however, HO-1 had significant relation to neither SOFA score ($p=0.625$) nor Scr ($p=0.146$).

Potential prognosis value of HO-1 and survival analysis. It was presented from Fig.2 that the AUC of incidence for HO-1 and Scr were 0.824 (95%CI: 0.703-0.944) and 0.788 (95%CI: 0.658-0.919) respectively. When the cutoff value of HO-1 was 40.96U/L, the sensitivity of HO-1 prognosis value was 76.9%, and the specificity of HO-1 prognosis value was 79.4%. The AUC of combination with these two indicators was 0.864 (95%CI: 0.761-0.968). The sensitivity was 92.3%, and the specificity 73.5%.

The overall survival analysis was set out to evaluate the survival outcomes of sepsis patients. High/low HO-1 level group was divided by the median of serum HO-1 level (41.33U/L). The Fig.3 demonstrated that the mortality was increased in high level of HO-1 group than that in low level of HO-1 group.

Discussion

The present cross-sectional study showed that level of HO-1 was significantly higher in sepsis-induced AKI compared with sepsis without AKI. The combined role of HO-1 and Scr was significantly more likely to predict the occurrence of AKI during sepsis than either of the two indicators. In both SS+AKI and S+AKI group, HO-1 concentration was positively associated with AKI grade, suggesting that HO-1 level had a strong relationship with the severity of AKI, especially organ injury.

This study provides clinical evidence of diagnostic and prognostic value of HO-1 during the progression of sepsis. It is now well established from a variety of studies, that HO-1 can be induced by hemin, which may further cause oxidative stress and inflammation, especially in the progression of acute organ injury[19,20]. Heme, as a ubiquitous compound of human tissue, is involved in physiology and metabolism. Once heme is released from cell, the oxidation reaction would occur to free heme. Subsequently, free heme is certainly converted to the ferric state, namely hemin. HO-1 acts as a stress response protein in the reticuloendothelial system, therefore decomposing heme into iron, biliverdin and carbon monoxide. The induction of HO-1 plays an antioxidant-derived cellular protective role during oxidative stress. A positive relationship between oxidative stress and AKI has been reported in the literature[7,21]. Evidence has showed that one characteristics of AKI is tubular epithelial cell oxidative stress, which further causes microvascular dysfunction and inflammation[22,23]. The present study clearly showed that increased serum HO-1 is a positive factor to predict the extent of AKI.

In this observational study, we clearly demonstrated that HO-1 concentration had a significant relationship with Scr level in the SS+AKI group and S+AKI group. In other two groups, however, HO-1 was not correlated with Scr. According to KDIGO consensus group, Scr has an increase of $\geq$0.3 mg/dl or >50% of baseline within a 48-hour period during AKI, which has standardized the identification of AKI. Based on the analysis of area under ROC curve, HO-1 and Src in sepsis patients were 0.824 and 0.788, respectively. The area under ROC curve of combination between HO-1 and Src was 0.864. The combination analysis of HO-1 and Scr contributed to a more effective approach for the prediction of AKI than each of them in AKI. It was observed from the ROC curve that HO-1 was by itself performed as a predictive value in the early stage of sepsis-induced AKI. As presented in the statistical analysis of HO-1 and Scr, it can thus be

suggested that HO-1 could be regared as a clinical putative marker in the pathogenesis of renal injury, especially sepsis-induced AKI.

Sepsis is a common condition that contributes to the emergence of systemic inflammation, resulting in the hemolytic lesion[24,25]. It is widely known that there are several mechanisms underlying hemolysis[26-28]. The occurrence of hemolysis could result from some toxins released by pathogens and fibrin chain emerging in intravascular coagulation. The complement system intervenes the activity of red blood cell during sepsis[29,30]. It was interestingly found in this study that HO-1 concentration had a positive relation to Hb level, which was consistent with the phenomenon described above. This finding indicated that hemolytic reaction released the heme with the final induction of HO-1 expression, suggesting HO-1 detection would contribute to the improvement of hemolytic index.

Prior studies have certified the protective role of HO-1 in renal dysfunction, which is conducive to survival rate[31,32]. It had been established in previous research that Toll like receptor (TLR) played an important role in autophagy to protect renal tissue[33]. In sepsis animal model, deletion of TLR2 not TLR4 aggravated the renal insufficiency and tissue damage. When the $TLR2^{+}$ $TLR4^{-}$ mice was treated with cisplatin, HO-1 expression was increased in heme plus group, which group was found that renal function was improved. There was no similar phenomenon occurred in $TLR4^{-}$ group. This result may be explained by the fact that the HO-1 was involved in the promotion of renal function recovery. Our result of survival cure showed that there was a high mortality rate in patients with elevated HO-1 level. This result might be somewhat limited by activity of TLR signal pathway, which lead to a deficiency of HO-1 protective function. This is an important issue for further research of HO-1 and TLR function.

There are several limitations in this study. First, the current research was a single-center study with limited sample size in each group. Further work is required to collect more participants to replenish adequate data. Second, the blood collection was conducted within 24 hours, which might be relatively large for a time-limited window of the ICU case.

Conclusions

Our present study set out to examine the HO-1 level in sepsis-induce AKI and evaluate the correlation between HO-1 and laboratory indicators. The investigation of HO-1 has shown that its concentration was increased in sepsis-induced AKI, especially in septic shock and AKI group. The correlation between HO-1 and Scr was determined using statistic methods, indicating that both of them have predictive value in disease evolution and prognosis of sepsis with AKI. Continued efforts are needed to conduct more investigation and experiments to make HO-1 more accessible to the pathogenesis of AKI. The evidence from this study suggests that high serum HO-1 is a putative index to contribute to the diagnosis and prognosis of sepsis-induced AKI.

Abbreviations

HO-1: heme oxygenase 1; AKI: Acute kidney injury; SAKI: Sepsis-induced AKI; SSAKI: Septic shock and AKI; ELISA: Enzyme-linked immunosorbent assay; RBC: red blood cell; HB: hemoglobin; HCT: hematocrit; WBC: white blood cell; ALB: albumin; ALT: alanine aminotransferase; AST: glutamic oxaloacetic transaminase; ALP: alkaline phosphatase; γ-GT: γ-glutamyl transpeptidase; TBil: total bilirubin; CK-MB: creatine kinase isoenzyme; TnI: hypersensitive troponin; Urea: urea; MYO: myoglobin; Scr: serum creatinine; PCT: procalcitonin; AMY: amylase; Lipase: lipase; APTT: activated partial thromboplastin time; PT: prothrombin time; FIB: fibrinogen; FDP: fibrinogen degradation products.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Review Committee of the First Affiliated Hospital of Dalian Medical University and conducted in accordance with the principles of the Declaration of Helsinki. All the information was de-identified in the downloaded dataset. Thus, the ethical approval statement and the need for informed consent were waived for this manuscript.

Consent for publication

Not applicable.

Availability of data and material

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Competing interests

The authors declare that they have no competing interests.

Funding

This work was supported by the grant from Dalian Science & Technology Innovation Fund (No.2018J13SN099), and partially supported by the grants from National Natural Science Foundation of China (No. 81703871) and Doctoral Start-up Foundation of Liaoning Province (No. 20170520408). No additional funding sources for this study. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Author Contributions

Research idea and study design: N.L., Data acquisition: M.Z., N.W., H.C., Data analysis/interpretation: S.X., H.L., Statistical analysis: S.X., M.Z., Supervision or mentorship: S.X., H.L., N.L. All authors have read and approved the manuscript.

Acknowledgements

Not applicable.

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Tables

Table 1 Clinical characteristics of 83 enrolled sepsis patients

Variable	Total	Acute kidney injury		p value
		Yes(n=36)	No(n=47)	
Age (years	65.55±17.77	66.59±17.88	74.73±17.88	0.571
Male,n (%)	47(56.6	20(55.6	27(57.4	0.983
SOFA score	5.69±3.06	7(5-10)	4(3-5	0.001
Sepsis focus				0.46
Respiratory,n (%)	24(28.9)	10(27.8)	14(29.8)	
Abdominal,n (%)	22(26.5)	13(36.2)	9(19.1)	
Urinary,n (%)	4(4.8)	3(8.3)	1(2.1)	
Skin,n (%)	22(26.5)	2(5.5)	20(42.6)	
Others,n (%)	11(13.3)	8(22.2)	3(6.4)	
MV,n (%)	61(73.5)	29(80.6)	32(68.1)	0.56
Length of ICU stay (days)	27±31	20±18	32±25	0.023
ICU mortality,n (%)	49(59.03)	24(66.67)	23(48.93)	0.093

SOFA Sequential Organ Failure Assessment, MV mechanical ventilation, ICU intensive care unit

Table 2 Laboratory data of 83 enrolled sepsis patients

Variable	Total	Acute kidney injury		p value
		Yes(n=36)	No(n=47)	
HO-1 (U/L)	41.15(34.66-48.27)	203.5(40.16-240.39	37.45(27.65-42.69)	0.001
RBC (10^9/L)	3.78±0.93	3.92±0.96	3.66±0.91	0.279
HB (g/L)	115.48±28.56	118.66±31.11	113±26.52	0.442
HCT (%)	35.6(26.9-40)	37.05(28.03-42.55)	34.1(26.5-38.45)	0.243
WBC (10^9/L)	13.38(9.54-17.43)	13.3(10.87-17.23)	13.41(8.28-17.8)	0.63
ALB (g/L)	29.97±7.16	30.63±7.98	29.46±6.5	0.541
ALT (U/L)	40(29.5-90.5)	40.5(29.25-99.75)	40(29-89.5)	0.99
AST (U/L)	58(31-104.5)	49(34-158.5)	59(30-104.5)	0.626
ALP (U/L)	76(51-105.5)	81.5(66.5-112.25)	67(46-86)	0.09
r-GT (U/L)	39(18-87)	31(20.25-85)	41(17.5-99.5)	0.708
TBil (μmol/L)	20(11.8-31.8)	18.45(10.4-38.6)	20(12.45-27.95)	0.7
CK-MB (U/L)	2.7(1-7.1)	4.68(1.75(11.51)	1.71(0.78-5.45)	0.007
TnI (ug/ml)	0.17(0.028-0.58)	0.302(0.097-0.785)	0.097(0.023-0.392)	0.048
Urea (μmol/L)	10.81(7.21-17.61)	17.61(11.35-24.04)	7.63(5.58-10.41)	0.001
MYO (ng/ml)	227.61(92.84-625.62)	476.26(194.72-872.43)	165.11(66.43-364.66)	0.001
Scr (μmol/L)	104(70-162)	184.5(123-253)	72(58-91)	0.001
PCT (ng/ml)	2.05(0.81-7.74)	7.34(1.58-32.93)	1.36(0.5-2.83)	0.001
AMY (U/L)	80(53.5-155)	67(49.5-169)	84(53.5-155)	0.673
Lipase (U/L)	94(29.5-268.5)	99(31.25-489.5)	89(27.5-197)	0.742
APTT (s)	33.2(26.75-44.3)	37.4(29.53-53.53)	31.4(25.8-36.65)	0.04
PT (s)	14.2(12.7-16.3)	14.65(13.13-18)	13.8(12.25-15.25)	0.049
FIB (g/L)	3.56(2.43-5.08)	3.79(2.79-5.28)	3.48(2.14-4.99)	0.609
FDP (mg/L)	15.49(7.93-46.56)	23.54(8.8-56.77)	15.03(6.64-43.03)	0.448
D-dimer (μg/L)	5270(2660-17970)	5130(2855-17920)	5410(2570-18105)	0.597

Table 3 Laboratory data from four groups of sepsis patients

Variable	SS+AKI	S+AKI	SS	S	p value
RBC (10^9/L)	4.03±0.98	3.8±0.95	3.41±0.93	3.84±0.86	>0.05
HB (g/L)	125.53±33.19	110.87±27.6	108.76±28.98	116±24.83	>0.05
HCT (%)	36.25(30.20-43.70)	37.25(30.88-39.63)	33.50(24.28-40.18)	34.7(29.90-38.5)	>0.05
WBC (10^9/L)	12.91(9.82-17.71)	14.78(10.68-17.22)	2.93(7.57-19.05)	13.06(8.61-17.56)	>0.05
ALB (g/L)	29.82±8.69	31.55±7.29	27.61±5.49	30.77±6.95	>0.05
ALT (U/L)	43(30.5-150)	38(22-68)	36(27-109)	40.5(31-75)	>0.05
AST (U/L)	64(33-224.5)	45(34-78)	59(26.5-92)	56.5(31.25-108.75)	>0.05
ALP (U/L)	74(47-113.5)	83(75-110)	66.5(36.5-77)	78(60-99)	0.043
r-GT (U/L)	30(21.5-89.5)	40(17-86)	21(13.5-83.5)	50(28.5-126)	>0.05
TBil (μmol/L)	21.1(12-40.85)	13.5(8.7-28.2)	20.6(14.75-36.25)	19.2(11.28-24.18)	>0.05
CK-MB (U/L)	3.69(1.38-12.37)	5.57(2.36-12.63)	1.98(0.99-4.85)	1.6(0.66-5.96)	0.05
TnI (ug/ml)	0.33(0.13-0.99)	0.26(0.05-0.77)	0.14(0.04-0.58)	0.069(0.02-0.36)	>0.05
Urea (μmol/L)	15.54(9.7-19.06)	19.11(12.61-29.3)	9.31(5.59-12.56)	7.22□5.94-9.93□	<0.001
MYO (ng/ml)	570.45(178.50-819.46)	471.01(194.76-1003.98)	199.7(81.52-450.65)	137.42(46.75-306.67)	0.002
Scr (μmol/L)	160.5(120-227.25)	214(128-294)	81.5(69.5-99.75)	69(57-88)	<0.001
PCT (ng/ml)	9.25(0.73-31.39)	5.68(2.57-35.9)	1.05(0.4-2.4)	1.38(0.59-3.2)	0.008
AMY (U/L)	67(51-125.5)	67(47-225)	82(39.5-170)	86.5(54-149.75)	>0.05
Lipase (U/L)	68(18.5-271.5)	106(35-748)	89(26-141)	78.5(33-255.25)	>0.05
APTT (s)	36.3(30.15-51.25)	38.5(28.4-56.7)	33.8(27.15-89.5)	29.49±7.64	<0.05

PT (s)	15.8(14.45-18.4)	13.2(12.55-15.05)	15(13.15-17.68)	12.7(11.8-14.9)	0.002
FIB (g/L)	3.48(2.45-4.43)	4.55(2.77-6.35)	3.15(1.5-4.54)	3.48(2.25-6.5)	>0.05
FDP (mg/L)	27.4(17.15-61.7)	11.22(4.85-23.76)	15.1(5.93-78.2)	14.5(6.56-41.98)	>0.05
D-dimer (μg/L)	12160(4125-18335)	3630(2290-9130)	5410(2570-19895)	5370(2345-14412.5)	>0.05

Table 4 Correlation between laboratory indicators and HO-1 in patients with sepsis

Variable	HO-1 concentration	
	r	p
Hb	0.247	0.024
TnI	0.246	0.025
Urea	0.295	0.008
Scr	0.489	<0.001
APTT	0.233	0.035
SOFA score	0.494	<0.001

Table 5 Correlation between laboratory indicators and HO-1 in the four groups of sepsis

Variable	HO-1 concentration	
	r	p
SS+AKI		
SOFA score	0.548	0.018
AKI grade	0.736	0.001
Scr	0.561	0.016
r-GT	0.528	0.024
FDP	0.709	0.001
S+AKI		
SOFA score	0.118	0.641
AKI grade	0.548	0.019
Scr	0.566	0.014
ALP	0.49	0.046
SS		
SOFA score	-0.722	<0.001
Scr	0.359	0.12
S		
SOFA score	-0.099	0.625
Scr	-0.406	0.036

Figures

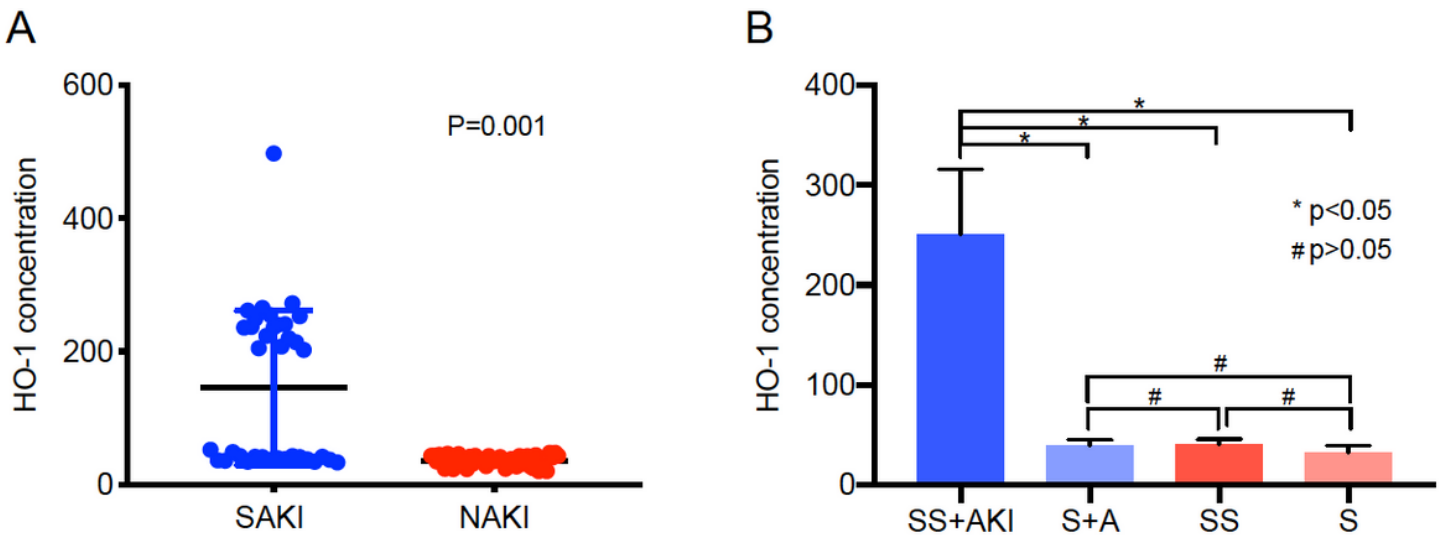

Figure 1

The comparison of HO-1 in distinct sepsis groups. A. The concentration of HO-1 in SAKI group and NAKI group. B. The concentration of HO-1 in SS+AKI group, S+AKI group, S+S group, and S group. *p<0.05, #P>0.05.

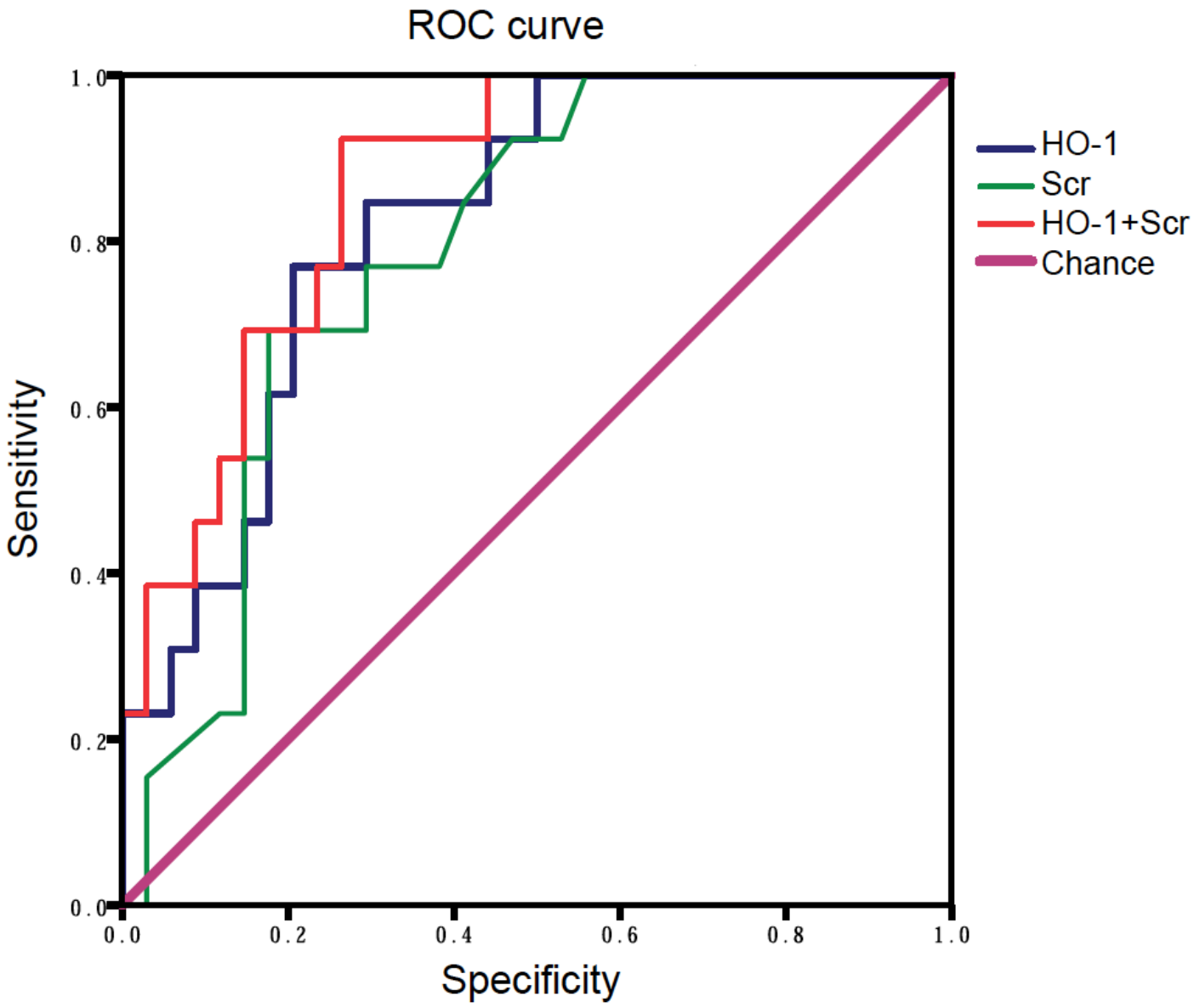

Figure 2

ROC curve for HO-1 level in sepsis-induced AKI. ROC curve of HO-1, Scr, and both of them in sepsis-induced AKI group. The AUC of HO-1=0.824 (95%CI: 0.703-0.944). The AUC of Scr=0.788 (95%CI: 0.658-0.919). The AUC of HO-1 and Scr=0.864 (95%CI: 0.761-0.968).

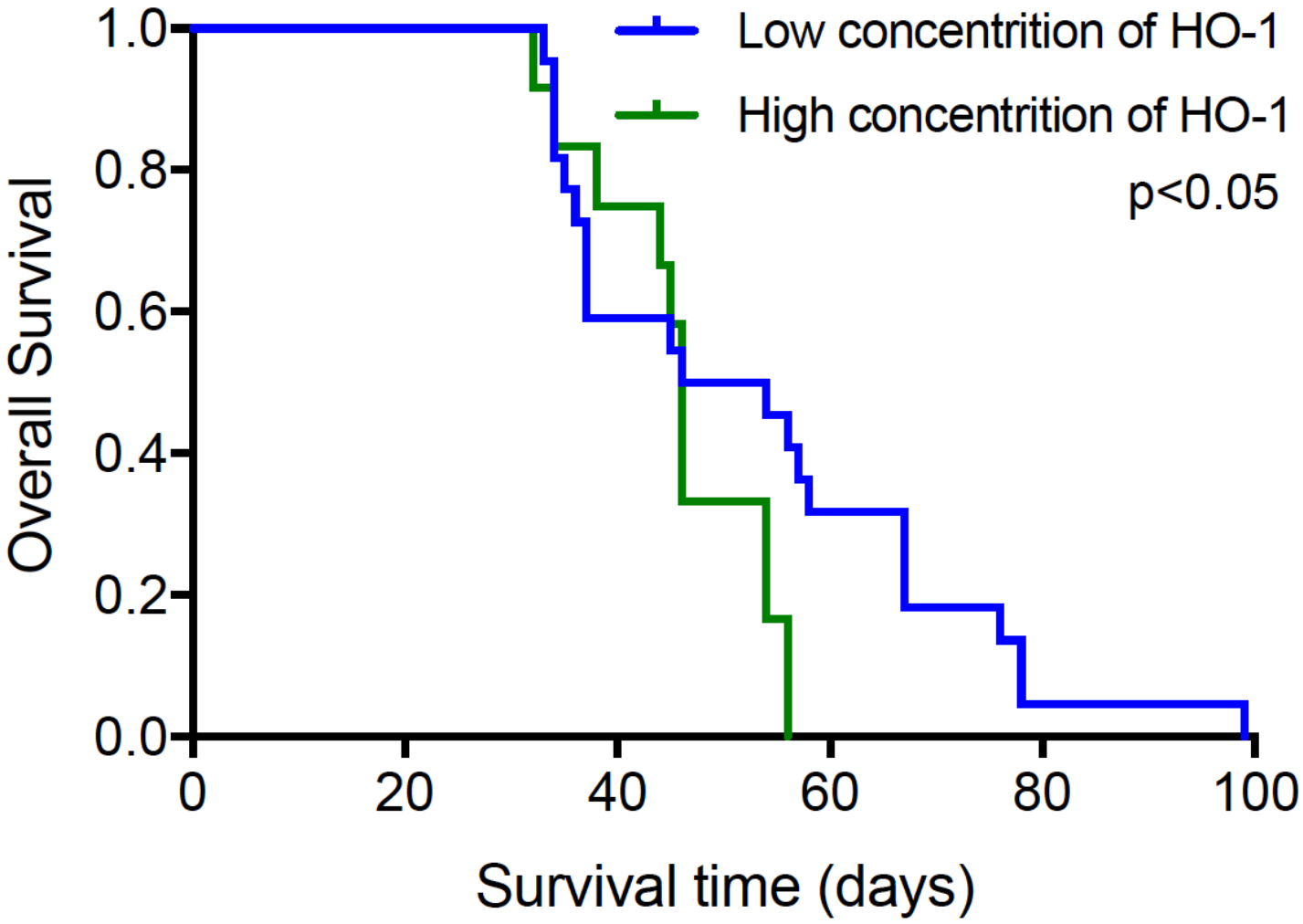

Figure 3

Kaplan–Meier survival curve of 83 sepsis patients with high/low HO-1 expression.