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The relationship of severity of inflammation with the incidence of acute kidney injury in septic patients in the intensive care units: Review of C-reactive protein and interleukin-6

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Abstract

***Objective*: To know the relationship between the occurrence of acute kidney injury (AKI) in patients with sepsis concerning the severity of inflammation. In this study, interleukin-6 (IL-6) and C-reactive protein (CRP) markers represented the severity of inflammation. Furthermore, the researchers wanted to see whether this inflammatory marker in the serum of septic patients in the intensive care unit (ICU) could predict the occurrence of AKI in the future.**

***Design*: This study was a prospective cohort nested-case control study, namely a case-control study conducted in a cohort population.**

***Setting*: This research has been carried out in the ICU of Dr. Wahidin Sudirohusodo Hospital Makassar and Hasanuddin University Hospital. Serum IL-6 examination was carried out in the Hasanuddin University Hospital laboratory.**

***Patients and participants*: This study's samples were septic patients treated in the ICU of Dr. Wahidin Sudirohusodo Hospital Makassar and Hasanuddin University Hospital Makassar starting from January 2021. The sample selection was carried out consecutively, namely the selection of respondents based on the arrival of patients treated in the ICU until fulfilled.**

***Measurement and results*: We used the Mann-Whitney test for data analysis in this study. There was a significant difference in serum IL-6 and CRP levels between the two groups on day 0 and day 3 of ICU admission and changes from day 0 to day 3, whereas changes in CRP levels from day 0 to day 3 were a good predictor of AKI, with a cut-off value of 17.75 mg/l.**

***Conclusions*: In this study, CRP and IL-6 levels could be used to predict AKI. IL-6 and CRP had an essential role in the inflammatory response and helped to predict clinical outcomes in patients with AKI.**

Key words: CRP, interleukin-6, sepsis, AKI, inflammation.

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Introduction

Sepsis remains a significant health problem worldwide and a leading cause of death and critical illness. Approximately 30% of patients develop sepsis on admission or during intensive care unit (ICU) stay. The mortality rate in the ICU is 16.2% in the entire population and 25.8% in patients with sepsis in the ICU. (1) Sepsis is a life-threatening organ dysfunction resulting from an uncontrolled response to infection. Organ dysfunction can be identified by an acute change condition associated with infection of at least 2 points on the Sequential Organ Failure Assessment (SOFA) score, increasing the mortality rate by 10%. (2)

Sepsis is a systemic inflammatory disease mediated by the host immune response. Stimuli recognized by

the immune system can be pathogen-associated molecular patterns (PAMPs) such as bacterial endotoxins and viral deoxyribonucleic acid (DNA) and danger-associated molecular patterns (DAMPs) such as tissue damage due to trauma and reactive oxygen species. This inflammatory response is regulated by releasing cytokines including tumor necrosis factor α (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β). At the systemic level, acute inflammation triggers fever and the release of acute-phase protein secretion by the liver, including C-reactive protein (CRP). CRP is a critical inflammatory protein whose levels are elevated in trauma, infection, and inflammation. (3,4)

Acute kidney injury (AKI) is a complication of organ failure that is often found in sepsis. The current incidence of AKI is 40-50% in critically ill patients with sepsis, which increases the risk of death by six to eight times. (5,6) Sepsis-associated AKI has a high incidence in critically ill patients admitted to the ICU. Sixty-four-point-four percent of patients with sepsis in the ICU experienced early AKI, i.e., AKI that occurred within 24 hours of the initial onset of hypotension. Of this 64.4% of patients, 6.3% were patients included in the risk criteria, 29.4% in the injury criteria, and 18.7% in the failure criteria, based on the risk, injury, failure, loss, and end-stage renal disease (RIFLE) criteria for the severity AKI. (7)

Current evidence suggests that the origin of most cases of AKI is multifactorial and that several concurrent mechanisms may be at work. The mechanisms include inflammation, heterogeneous disruption of microvascular flow at the peritubular and glomerular levels, and disturbances at the mitochondrial level. Inflammation is now believed to play a significant role in the pathophysiology of AKI. It is hypothesized that in ischemia, sepsis, and nephrotoxic models, the initial disturbance causes morphological or functional changes in vascular endothelial cells or tubular epithelium. Then, leukocytes infiltrate the injured kidney, including neutrophils, macrophages, natural killer cells, and lymphocytes. Injury induces the generation of inflammatory mediators such as cytokines and chemokines by tubular and endothelial cells that contribute to leukocyte recruitment to the kidney. Thus, inflammation has an essential role in the initiation and extension phases of AKI. (8)

Based on the background above, the researchers wanted to know the relationship between the occurrence of AKI in patients with sepsis concerning the degree of inflammation. In this study, interleukin-6 and C-reactive protein markers represented the degree of inflammation. Furthermore, the researchers wanted to see whether this inflammatory marker in the serum of septic patients could predict the occurrence of AKI in the future of patients in the ICU.

Materials and methods

Research design

This study was a prospective cohort nested-case control study, namely a case-control study conducted in a cohort population.

Place and time of research

This research has been carried out in the ICU of Dr. Wahidin Sudirohusodo Hospital Makassar and Hasanuddin University Hospital. Serum IL-6 examination was carried out in the Hasanuddin University Hospital laboratory, while plasma C-reactive protein examination was carried out in the respective hospital laboratories. The research has been carried out since January 2021 until the sample was fulfilled.

Sample and research population

This study's sample was septic patients treated in the ICU of Dr. Wahidin Sudirohusodo Hospital Makassar and the ICU of Hasanuddin University Hospital Makassar starting from January 2021. The sample selection was carried out consecutively, namely the selection of respondents based on the arrival of patients treated in the ICU until fulfilled. Inclusion criteria: Patient age >18 years, patients diagnosed with sepsis (quick SOFA criteria), and patients/family of patients willing to be included. Exclusion criteria: Patients with AKI before ICU admission, patients with chronic kidney disease (CKD) or diseases of the urinary tract system, patients with comorbid hypertension, patients with comorbid coronary heart disease, and patients with comorbid diabetes. Drop out criteria: Patients discharged from the ICU for less than three days of hospitalization.

Data collection

The data taken consisted of primary data, which included demographic data, patient clinical data, and laboratory data, including data on C-reactive protein levels. Data on AKI occurrence was obtained by observing the AKI markers in the patient's serum, namely creatinine values and urine production. The data on IL-6 levels were taken from data recording in the hospital laboratory of Hasanuddin University.

Data analysis

Mann-Whitney test was used for data analysis in this study.

Ethical approval
This research was conducted with the approval of the Ethics Committee for Biomedical Research in Humans, Faculty of Medicine, Hasanuddin University Makassar, with the number of 110/UN4.6.4.5.31/PP36/2021.

Results

Characteristics of the research sample
The research sample consisted of 88 total samples divided into two groups, namely the group with AKI and those without AKI, composed of 44 models (**Table 1**).
In terms of age and body mass index (BMI), there was no difference between AKI and non-AKI groups. The mean±standard deviation (SD) of age in the AKI and non-AKI groups were 50.16±15.79 years and 45.41±15.06 years, respectively. The median (min-max) BMI in the AKI group was 23.59 (18.37-33.30) and in the non-AKI group, the mean±SD was 22.98±3.34 (**Table 1**).

Comparison of variables between groups on day 0 in ICU
Table 2 shows statistically significant differences in IL-6 and CRP levels between the two groups using the Mann-Whitney non-parametric test.

Comparison of variables between groups on day 3 in ICU
Table 3 shows differences in IL-6 and CRP levels, statistically significant, between the two study groups through the Mann-Whitney non-parametric test.

Comparison of variables between groups from admission to ICU on day 3
Table 4 shows the difference in the increase in IL-6 in the two groups, which was statistically significant through the Mann-Whitney test ($p<0.05$). Meanwhile, CRP levels in the AKI group tended to increase, while in the non-AKI group, they decreased, which was statistically significant through the Mann-Whitney test ($p<0.001$).

ICU care receiver operating characteristic (ROC) curve analysis on day 0
Table 5 and **Figure 1** show the variables that can be considered predictors of AKI incidence during treatment. CRP levels can be used as a relatively good predictor of AKI (area under the curve [AUC] 79.5%) with a sensitivity of 70.5%, specificity of 75.0%, and a cut-off value of 87.45 mg/l. IL-6 levels can be a good predictor of AKI incidence (AUC 76.0%) at a cut-off value of 524.2 pg/ml with a sensitivity of 61.5% and a specificity of 81.8%.

ICU treatment ROC curve analysis on day 3
Table 6 shows that day 3 CRP levels were good predictors of AKI (AUC 91.0%) with a sensitivity of 81.8% and a specificity of 74.1%, whereas its cut-off value was 93.3 mg/l. IL-6 levels on day 3 can also be used as a predictor of AKI incidence (AUC 87.1%) at a cut-off value of 308.5 pg/ml with a sensitivity of 90.9% and a specificity of 70.5%.

ROC curve analysis of variable changes from admission to ICU day 3
Table 7 shows that the change in CRP levels was a good predictor of AKI (AUC 74.1%) with a sensitivity of 65.9% and a specificity of 81.8% and a cut-off value of 17.75 mg/l. Changes in IL-6 levels can also be a good predictor of AKI incidence (AUC 67.0%) at a cut-off value of 121.5 pg/ml with a sensitivity of 59.1% and a specificity of 81.8%.

Discussion

Sepsis-associated AKI is a complication in critically ill patients, which increases the risk of developing chronic comorbidities and has a very high mortality rate. Sepsis and AKI are related to each other. Sepsis is the most common contributing factor to developing AKI, and AKI of various origins is associated with a higher risk for the severity of sepsis. (9)

Characteristics of research subjects
There was no statistical difference between age and BMI in AKI incidence in this study. However, the subjects of the AKI group had a higher median age than the group without AKI. Sang et al. in their research reported that there was a relationship between age and the occurrence of AKI in critically ill patients with coronavirus disease 2019 (COVID-19). (10,11) BMI in the two groups in this study did not show a statistically significant difference. However, the median BMI of the AKI group was slightly higher than that of the non-AKI group. Another study found that the BMI of patients with AKI and non-AKI showed that BMI was significantly higher in AKI patients compared to non-AKI patients. (12) In addition, the clinical parameter of fluid balance in the septic patient group who had AKI had a higher median, especially on day 3. This study showed a significant difference in fluid balance between the AKI and non-AKI groups on day 3. These results aligned with the survey by Payen et al. who reported an association between positive fluid balance and an increased risk of AKI. (13) Fluid overload is associated with the development of AKI and poor outcomes. (14) It was further explained that

fluid overload and inflammation are independent solid risk factors for worsening outcomes in renal patients. (15)

In this study, another clinical parameter used was the SOFA score. It was found that there was a statistically significant difference, where the SOFA score was higher in the AKI group than in the non-AKI group. This study was in line with Wang et al.'s study which stated that a subgroup analysis showed that SOFA scores were associated with 28-day and 90-day mortality in patients with AKI undergoing continuous renal replacement therapy (CRRT). (16)

Comparison of variables on day 0 and day 3 in the ICU

Previous studies have shown that biomarkers of inflammation and endothelial cell activation were elevated in sepsis and that sepsis was a significant cause of AKI. In our research, it was revealed that there was a substantial difference in IL-6 levels between the AKI and non-AKI groups both on day 0 and day 3 of ICU treatment. The ability of IL-6 at ICU admission as a predictor of short-term renal function was also demonstrated by Shimazui et al. It was found that serum IL-6 levels at ICU admission predict short-term renal function (associated with urine production and possibly anuria >12 hours). This study demonstrated that patients with higher serum IL-6 levels at the time of ICU admission had higher 90-day mortality in the hospital, lower urine output, and a higher incidence of anuria during the first 72 hours of ICU. Patients in the higher IL-6 group had a significantly higher proportion of septic AKI. (17)

CRP is an acute reactant produced by the liver and many inflammatory cells. (18) CRP via the CD32/64 receptor triggers AKI by activating its downstream pathways, including nuclear factor (NF)-κB and transforming growth factor (TGF)/Smad3 to cause kidney inflammation. Macrophage activation induces G1 cell cycle arrest while inhibiting autophagy. (18,19)

Comparison of changes between groups from day 0 to day 3 in the ICU

The change level of each research variable from the time of admission to the ICU until the 3rd day of ICU care showed a statistically significant difference in the increase of IL-6 in the two groups. In addition, CRP levels in the AKI group tended to increase while, in the non-AKI group, they tended to decrease, which was statistically significant. The result was in line with the study of Cosentino et al., which explained that high sensitivity-CRP levels measured at hospital admission in patients with acute myocardial infarction (AMI) was independently associated with the risk of AKI, its severity, and clinical outcomes in the hospital. High-sensitivity CRP significantly increased accuracy for predicting AKI when added to serum creatinine at admission and a variable found to predict AKI independently during multivariate analysis. (20) Meanwhile, IL-6, based on Chae et al. research, described an independent relationship between preoperative serum IL-6 levels with the occurrence of AKI after liver transplant procedures and a significant relationship between higher serum IL-6 levels and the occurrence of AKI. (21)

Another similar study also demonstrated that the severity of AKI was significantly higher in the group with higher IL-6 levels. Higher IL-6 (per tertile) was significantly associated with a higher 90-day in-hospital mortality rate. (17) The role of IL-6 is more widely known to also have a role in the systemic response after the occurrence of AKI. IL-6 is the primary mediator of hepatic neutrophil gelatinase-associated lipocalin (NGAL) production, which can also be used as a biomarker of AKI. (22) Research by Su et al. showed a strong correlation between IL-6 expression and AKI. (23)

Results of the analysis of ROC curve IL-6 and CRP levels

Figure 1 is the ROC curve of changes in IL-6 and CRP levels on day 0 of ICU treatment. **Table 5** is the result of the analysis of cut-off values, sensitivity, specificity, and AUC from **Figure 1**. Through the data above, it is possible to determine variables that can be considered predictors of AKI incidence at the time of admission to the ICU (day 0). CRP can be used as a fairly good predictor of AKI (AUC 79.5%) with a sensitivity of 70.5% and specificity of 75.0% with a cut-off value of 87.45 mg/l. IL-6 levels can be used as a predictor of AKI incidence (AUC 76.0%) at a cut-off value of 524.2 pg/ml with a sensitivity of 61.5% and a specificity of 81.8%.

Figure 2 shows the ROC curve for IL-6 and CRP levels on day 3 of hospitalization in the ICU. **Table 2** is the result of the analysis of cut-off values, sensitivity, specificity, and AUC from **Figure 2**. Through the data above, it is possible to determine variables that can be considered predictors of AKI incidence on day 3 in the ICU. Day 3 CRP level was a good predictor of AKI (AUC 91.0%) with a sensitivity of 81.8% and a specificity of 74.1% with a cut-off value of 93.3 mg/l. IL-6 levels on day 3 can also be used as a predictor of the incidence of AKI (AUC 87.1%) at a cut-off value of 308.5 pg/ml with a sensitivity of 90.9% and a specificity of 70.5%.

Figure 3 is the ROC curve for changes in IL-6 and

CRP levels from day 0 to day 3 of ICU treatment. **Table 3** is the result of the analysis of cut-off values, sensitivity, specificity, and AUC from **Figure 3**. Through the data above, variables can be determined that can be considered predictors of the incidence of AKI during treatment. Changes in CRP levels were good predictors of AKI (AUC 74.1%) with a sensitivity of 65.9% and specificity of 81.8% with a cut-off value of 17.75 mg/l. Changes in IL-6 levels can also be used as a predictor of AKI incidence (AUC 67.0%) at a cut-off value of 121.5 pg/ml with a sensitivity of 59.1% and a specificity of 81.8%.

IL-6 is an inflammatory cytokine that plays an essential role in the inflammatory response and helps predict clinical outcomes in patients with AKI. In this study, CRP and IL-6 levels could be used to predict AKI. It was in line with the research conducted by Murashima et al., which stated that CRP was a predictor of AKI and a mediator of mortality after AKI. (24) The study of Shimazui et al. also indicated that serum IL-6 at the time of ICU admission could predict short-term renal function and mortality in AKI patients and was associated with renal recovery in survivors. (17)

Conclusion

There was a significant difference in serum IL-6 and CRP levels between the two groups on day 0 and day 3 of ICU admission and changes from day 0 to day three. Changes in CRP levels from day 0 to day 3 were a good predictor of AKI, with a cut-off value of 17.75 mg/l.

Table 1. Characteristics of the research sample

Variable	AKI (n=44) Mean±SD/Median (min-max)	Non-AKI (n=44) Mean±SD/Median (min-max)
Age (years)	50.16±15.79*	45.41±15.06*
BMI (kg/m^2)	23.59 (18.37-33.30)	22.98±3.34*
IL-6 levels D0 (pg/ml)	831.00 (53.7-9935.9)	278.9 (16.50-2167.00)
IL-6 levels D3 (pg/ml)	1141.50 (113.7-9230.0)	179.00 (25.10-1175.00)
CRP levels D0 (mg/l)	130.00 (11.06-282.00)	46.60 (1.80-187.20)
CRP levels D3 (mg/l)	156.75 (38.20-478.10)	34.40 (2.30-374.80)
Changes in IL-6 levels (pg/ml)	186.65 (-2015.80 - 5227.40)	2.80 (-1463.40 - 985.20)
Changes in CRP levels (mg/l)	42.50±91.69*	-7.59 (-129.90 - 198.60)
Fluid balance D0 (ml)	133.27±714.23	70±446.16
Fluid balance D3 (ml)	948±1447.59	-110.47±1163.44
SOFA score D0	7.73±4.14	3.03±2.44
SOFA score D3	9.21±4.84	2.33±3.32

Legend: BMI=body mass index; IL-6=interleukin-6; D0=day 0; D3=day 3; CRP=C-reactive protein; SOFA=Sequential Organ Failure Assessment; AKI=acute kidney injury; SD=standard deviation.
*Data normally distributed with the Shapiro-Wilk test.

Table 2. Comparison of variables between groups on day 0 in the ICU

Variable	AKI (n=44) Median (min-max)	Non-AKI (n=44) Median (min-max)	p-value
Interleukin-6 (pg/ml)	831.00 (53.7-9935.9)	278.9 (16.50-2167.00)	<0.001*
CRP (mg/l)	130.00 (11.06-282.00)	46.60 (1.80-187.20)	<0.001*

Legend: ICU=Intensive Care Unit; CRP=C-reactive protein; AKI=acute kidney injury.
*Significant with the Mann-Whitney test ($p<0.05$).

Table 3. Comparison of variables between groups on day 3 in ICU

Variable	AKI (n=44) Median (min-max)	Non-AKI (n=44) Median (min-max)	p-value
Interleukin-6 (pg/ml)	1141.50 (113.7-9230.0)	179.00 (25.10-1175.00)	<0.001*
CRP (mg/l)	156.75 (38.20-478.10)	34.40 (2.30-374.80)	<0.001*

Legend: ICU=Intensive Care Unit; CRP=C-reactive protein; AKI=acute kidney injury.
*Significant with the Mann-Whitney test ($p<0.001$).

Table 4. Comparison of changes in research variables between groups from admission to ICU treatment on day 3

Variable	AKI (n=44) Median (min-max)	Non-AKI (n=44) Median (min-max)	p-value
Changes in IL-6 levels (pg/ml)	186.65 (-2015.80 - 5227.40)	2.80 (-1463.40 - 985.20)	0.006*
Changes in CRP levels (mg/l)	36.5 (-146.20 - 270.70)*	-7.59 (-129.90 - 198.60)	<0.001*

Legend: ICU=Intensive Care Unit; IL-6=interleukin-6; CRP=C-reactive protein; AKI=acute kidney injury
*Significant with the Mann-Whitney test ($p<0.05$).

Table 5. Results of ROC curve analysis of interleukin-6 and CRP levels of ICU treatment on day 0

	Cut-off	Sensitivity	Specificity	AUC
Interleukin-6	524.2 pg/ml	61.4%	81.8%	76.0%
CRP	87.45 mg/l	70.5%	75.0%	79.5%

Legend: ROC=receiver operating characteristic; CRP=C-reactive protein; ICU=Intensive Care Unit; AUC=area under the curve.

Table 6. Results of ROC curve analysis of interleukin-6 and CRP on day 3 of the ICU treatment

	Cut-off	Sensitivity	Specificity	AUC
Interleukin-6	308.5 pg/ml	90.9%	70.5%	87.1%
CRP	93.3 mg/l	81.8%	74.1%	91.0%

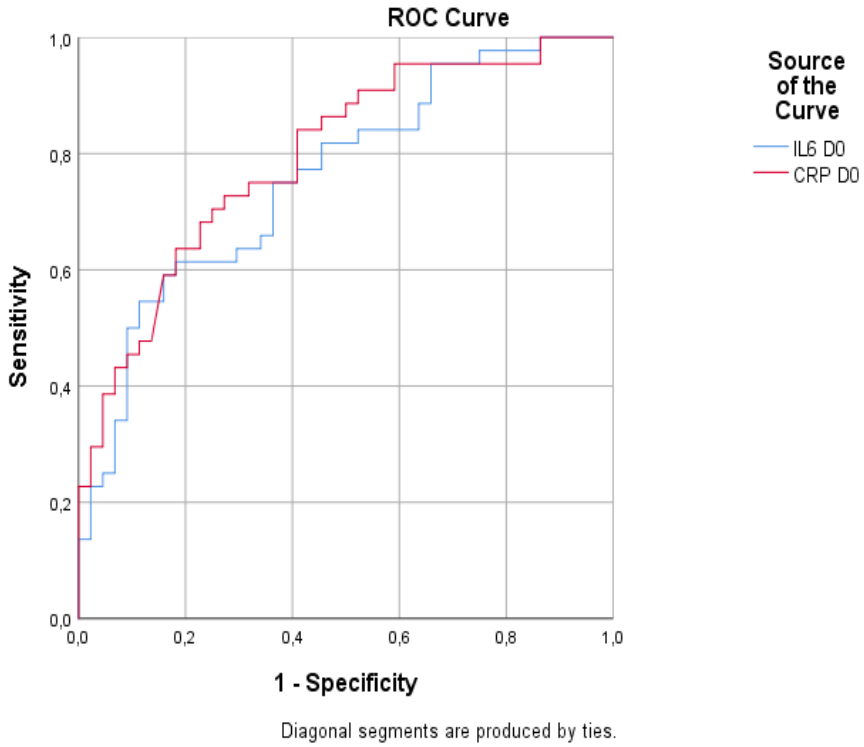
Legend: ROC=receiver operating characteristic; CRP=C-reactive protein; ICU=Intensive Care Unit; AUC=area under the curve.

Table 7. Results of ROC curve analysis of the changes in interleukin-6 and CRP

	Cut-off	Sensitivity	Specificity	AUC
ΔInterleukin-6	121.5 pg/ml	59.1%	81.8%	67.0%
ΔCRP	17.75 mg/l	65.9.%	81.8%	74.1%

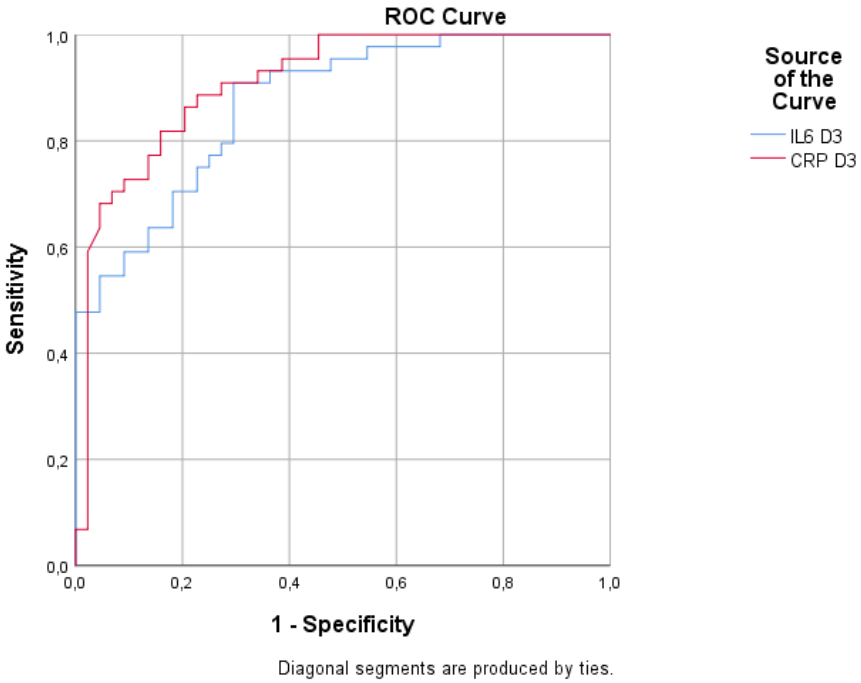
Legend: ROC=receiver operating characteristic; CRP=C-reactive protein; AUC=area under the curve.

Figure 1. ROC of IL-6 and CRP levels on day 0 of ICU treatment



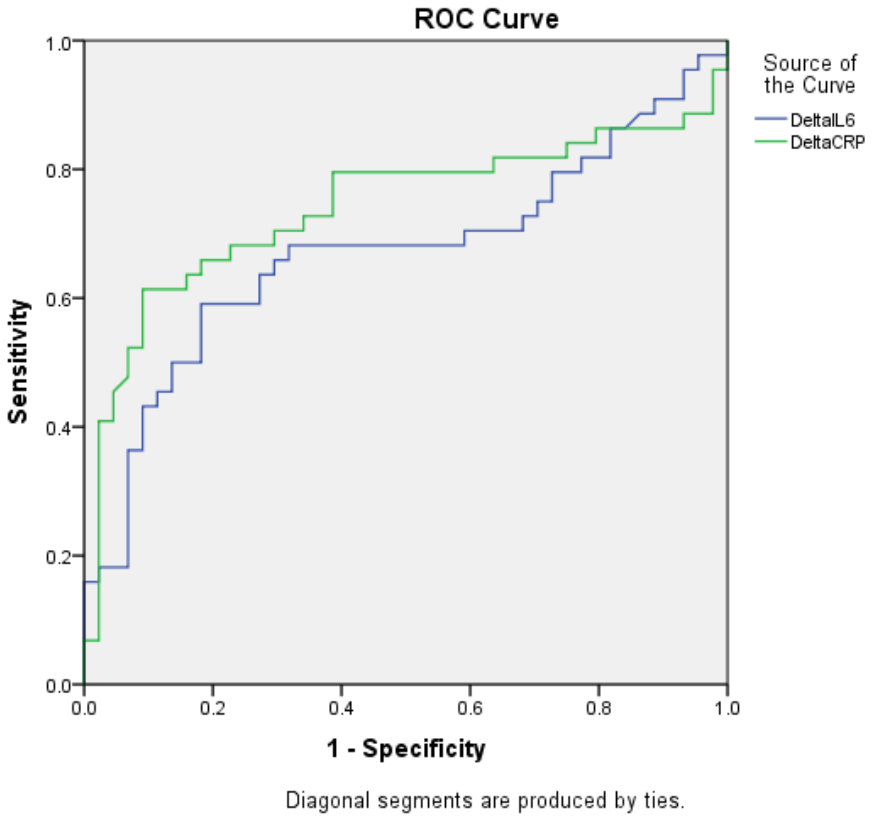
Legend: ROC=receiver operating characteristic; IL-6=interleukin-6; CRP=C-reactive protein; ICU=Intensive Care Unit; D0=day 0.

Figure 2. ROC of IL-6 and CRP levels on day 3 of ICU treatment



Legend: ROC=receiver operating characteristic; IL-6=interleukin-6; CRP=C-reactive protein; ICU=Intensive Care Unit; D3=day 3.

Figure 3. ROC changes in IL-6 and CRP levels



Legend: ROC=receiver operating characteristic; IL-6=interleukin-6; CRP=C-reactive protein.

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