Journal of Clinical & Experimental Cardiology
ISSN: 2155-9880

Maravic-Stojkovic et al., J Clin Exp Cardiolog 2014, 5:4
DOI: 10.4172/2155-9880.1000307

Research Article Open Access

# Levels of Presepsin and Midregion-Proadrenomedullin in Septic Patients with End-Stage Renal Disease after Cardiovascular Surgery: 1-Year Follow Up Study

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## Abstract

**Background:** Procalcitonin (PCT) is a marker for sepsis diagnosis, identification of bacterial infection and monitoring of antibiotic therapy. It has been shown that PCT is not a good choice in patients with hemodialysis. Therefore, we have explored two biomarkers: a) presepsin, and, b) midregion-proadrenomedullin (MR-proADM) in patients having End-Stage Renal Disease (ESRD).

**Patients and Methods:** We prospectively enlisted 20 patients, who underwent cardiovascular surgery and had been on dialysis. The diagnosis of sepsis has been established clinically and confirmed by PCT. Blood samples were taken before and after dialysis. Additionally, plasma and sera of 10 healthy blood donors without any complications were used as controls.

**Results:** Presepsin plasma concentrations (4368 ± 3088 *vs*. 694.1 ± 239.1 pg/mL) were significantly higher in patients with sepsis compared with controls ($p<0.0001$), but without significance between survivors and non-survivors ($p=0.77$). Circulating levels of MR-proADM (4.15 ± 2.72 *vs*. 0.294 ± 0.03 nmol/L) were also elevated in ESRD patients ($p>0.05$) with no significance between alive and deceased ($p=0.53$) patients. Adjustments have shown that the difference for MR-proADM level is due to the random sampling variability ($p=0.989$), whereas difference for presepsin remained highly significant ($p<0.001$).

**Conclusions:** Our results indicate that the accuracy of new biomarkers is equal to that of PCT in patients with ESRD. Presepsin might be as good marker in repeated measurements, before and after dialysis, as it is PCT.

**Keywords:** Cardiac surgery; End-stage renal disease; Midregion-proadrenomedullin; Presepsin; Sepsis

## Introduction

According to epidemiological information the incidence of sepsis is increasing markedly from year to year [1,2]. Despite the efforts to define and recognize sepsis in early stage of the disease sepsis remains a serious condition. Hospital mortality due to sepsis has ranged from 25 to 80% over the last few decades [3,4]. The cost of treating patients with acute myocardial infarction is lower than treating patients with sepsis [4]. Mortality of sepsis is a serious problem especially in surgical Intensive Care Units (ICUs) whose patients underwent emergent, urgent, or elective operations.

Surgical interventions trigger endotoxin and cytokine release [5,6]. Several biomarkers have been investigated for their accuracy to diagnose sepsis, to provide a prognosis and to monitor successfulness of antimicrobial therapy. Procalcitonin (PCT) is one among them and it is widely used from ninety's [7]. We have previously reported our experience with PCT monitoring in patients who underwent cardiac surgery but the efficiency of PCT is still under discussion in some situations [8]. There is a subgroup of patients with End-Stage Renal Disease (ESRD), on chronic dialysis, scheduled for elective cardiac surgery. Cardiovascular diseases are predominant cause of death in these patients. Mortality rate of the patients with ESRD after cardiac surgery is between 13-67% [9]. PCT is a small protein with molecular weight of 12.7 kDa [10]. Due to its small size it is reported to be eliminated during dialysis. Thereafter, PCT as a marker is under doubt when supervising antibiotic efficiency in patients on dialysis.

The usefulness of presepsin as a diagnostic marker of sepsis has been reported [11-13]. Presepsin is a soluble subunit of the CD14 molecule, expressed on monocytes and other cell lines [14]. The physiological role of the sCD14 subunit is yet unknown but 2 mechanisms of its production are described: first, it is released from monocytes, and second, it is secreted *via* a signaling pathway [11,15]. However, as the level presepsin increases within 2-3 h after the sepsis development it is reasonable to conclude that presepsin is more likely to be released than secreted. The soluble fraction of CD14 exists in 2 forms, a 49 kDa form and a 55 kDa form [16].

Kitamura et al. described and specified a new protein with hypotensive properties from human pheochromocytoma, and named it Adrenomedullin (ADM) [17]. Its preprotein, a more stable mid-regional fragment of proadrenomedullin (MR-proADM) is suitable for measuring in the peripheral circulation, and it was identified in plasma of patients with septic shock [18]. Its molecular mass is not well defined yet [19].

In this study we compared the usefulness of 2 new biomarkers against PCT: a) presepsin, i.e. soluble CD14 molecule subtype (sCD14-

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**Received** March 20, 2014; **Accepted** April 15, 2014; **Published** April 30, 2014

**Citation:** Maravic-Stojkovic V, Lausevic-Vuk L, Jovic M, Filipovic M, Bojic Milinovic T, et al. (2014) Levels of Presepsin and Midregion-Proadrenomedullin in Septic Patients with End-Stage Renal Disease after Cardiovascular Surgery: 1-Year Follow Up Study. J Clin Exp Cardiolog 5: 307. doi:10.4172/2155-9880.1000307

ST), and, b) MR-proADM in patients with ESRD having sepsis during their post-operative course.

## Patients and Methods

### Patients

This study was a prospective, observational, trial in ESRD patients with sepsis, on chronic dialysis, following cardiac surgery. After obtaining approval from the Ethics Committee and written informed consent from each patient, this study included 20 consecutive patients (5 women, 15 men; aged 33 to 73 years; mean 62.4 ± 43.4) scheduled to undergo open heart surgery. We assessed patients who were selected for elective cardiac surgery from December/2011 until June/2012 at the 200-bed academic tertiary care hospital having ESRD. The criterion for inclusion in the study was the type of the operation: Coronary Artery Bypass Grafting (CABG) surgery, valve reconstruction, combined CABG and valve procedures, thoracic aortic surgery, abdominal aortic aneurysm, reoperation, and radiofrequent ablations. Entry criteria for investigation included patients admitted to the ICU, who were diagnosed as having sepsis (n=20), according to the guidelines of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee [5]. Nine patients submitted to surgical procedure were on chronic hemodialysis program, whereas 11 of them developed acute renal dysfunction and were dialyzed for the first time after surgery. ESRD patients on dialysis without sepsis (according to ACCP/SCCM Consensus Conference) were excluded [5]. Ten healthy volunteers from the Department of Transfusion without any complains were included as a control group.

Thereafter, we monitored patients from admission to ICU, and the entire hospital stay. The clinical investigation, including body temperature, microbiologic examinations and chest radiograph, was performed daily until ICU discharge. The Sequential Organ Failure Assessment (SOFA) score and Acute Physiology and Chronic Health Evaluation (APACHE II) were routinely obtained at the first postoperative day, and was repeated once daily at 5:00 AM until discharge from ICU. Microbiologic examinations such as sputum, blood, and urine samples for culture were performed routinely on patients when infection, bacteriemia, or sepsis was suspected. Details on the length of ICU stay, the hospital stay, and the mortality rates were obtained from the hospital admission database.

### Procedure for hemodialysis (HD)

All patients accepted for an elective operation underwent dialysis on the day before the operation, and all patients had intraoperative hemofiltration on Cardiopulmonary Bypass (CPB). The target value for perioperative hemoglobin concentration was 10 g/L or higher. For myocardial protection, patients received antegrade hypothermic (4°C) crystalloid (St. Thomas cardioplegia), and CPB performed at moderate systemic hypothermia (25°C to 32°C). Post-operatively, the dialysis was started after hemodynamic stabilization. In the case of acute exacerbation of chronic renal failure, in order to be stabilized hemodynamically, patients received continuous veno-venous hemodiafiltration [20].

### Assays

Blood samples were collected before induction of dialysis and 1 h after the HD session. Blood was taken from the cannulated fistula and immediately centrifuged for 20 min. Serum was divided into 2 aliquots for biochemical analysis and for measurement of inflammatory parameters. Leukocyte and platelet count was determined using a Coulter counter HmX (Coulter Electronics, Luton, England).

PCT concentrations in serum were measured by Time-Resolved Amplified Cryptate Emission (TRACE) assay with the commercially available PCT test (B.R.A.H.M.S Diagnostic Gmbh, Henningsdorf/Berlin, and Germany). A PCT level of 2.0 ng/mL was considered as a proof of sepsis [6].

C-reactive protein (CRP) levels were measured by quantitative immuno-turbidimetric method for high sensitivity CRP (hsCRP) (BIOKIT, Barcelona, Spain).

Whole blood or EDTA plasma was used for presepsin measurement on the PATHFAST immunoanalyzer (Mitsubishi Chemical Medience Corp., Tokyo, Japan) by Chemiluminiscent Enzyme Immunoassay (CLEIA). The recommended *cut off* level for sepsis was 600 pg/mL [14].

MR-proADM was detected in EDTA plasma using TRACE assay with the commercially available MR-proADM test (B.R.A.H.M.S Diagnostic Gmbh, Henningsdorf/Berlin, Germany). For the diagnosis of sepsis reference range from 0.72 to 25.4 nmol/L was recommended [18].

On the basis of serum PCT concentrations, the use of antibiotics was encouraged or discouraged, with *cut off* level of 0.5 ng/mL [20]. No antibiotic therapy was administrated routinely in the absence of clinical signs of infection or positive bacteriology.

### Statistical analysis

Statistical analysis was performed by using SPSS 11.0 software (SPSS, Chicago, IL). Data were presented as mean ± standard deviation. If continuous data were not normally distributed, data were expressed as a median (minimum-maximum) and the Kolmogorov-Smirnov test was used. Intergroup differences were assessed by two-way ANOVA if continuous data were normally distributed and by Mann Whitney Rank Sum test if continuous data were not normally distributed. Statistical significance was accepted at $p<0.05$ two-tailed.

## Results

Table 1 shows the baseline characteristics of the patients. The operative data are shown in Table 2. Of all the patients with ESRD, 35% underwent isolated coronary artery bypass grafting, 25% had replacement or reconstruction of one or more valves, 25% underwent combined procedures CABG and valve, and 15% had vascular surgery, radiofrequency ablation, or complicated cardiac interventions.

All these patients developed sepsis during peri-operative period. Figure 1 shows the mean values of PCT, presepsin, MR-proADM and hsCRP in patients with ESRD who developed sepsis after cardiovascular surgery, compared with healthy controls. There was a significant difference for presepsin (4368 ± 3088 *vs.* 694.1 ± 239.1 pg/mL; P<0.001), whereas for MR-proADM level (4.15 ± 2.72 *vs.* 0.294 ± 0.03 nmol/L; P=0.989) the difference was attributed to random sampling variability (P>0.05). The same was found for PCT (P=0.902) and hsCRP (P=0.902). Laboratory data are shown in Table 3. We did not find significant differences between survivors and non-survivors concerning biomarker levels: PCT (9.66 ± 17.55 *vs.*14.93 ± 20.54; $p$=0.42), presepsin (4184.1 ± 3039.5 *vs.* 4593.5 ± 3316.2; $p$=0.77), MR-proADM (3.84 ± 2.07 *vs.* 4.47 ± 3.5; $p$=0.53), hsCRP (122.4 ± 89.3 *vs.* 123.07 ± 87.5; $p$=0.67) and BNP (819.4 ± 473.1 *vs.* 1860.6 ± 1701.5; $p$=0.16). Table 4 has shown the overview of the distribution of presepsin, MR-proADM, PCT and hsCRP values in patients with sepsis after ESRD and cardiovascular surgery.

Figure 2 shows the mean values of presepsin and MR-proADM levels measured before and after dialysis in patients with sepsis, proven

| Demographic factor | Total (*n* = 20) |
|---|---|
| Male sex, *n* (%) | 15 (75) |
| Age (years) | 62.4 ± 43.4 |
| LV function (%) | 37.8 ± 26.0 |
| Systolic blood pressure (mm/Hg) | 138.3 ± 43.2 |
| Diastolic blood pressure (mm/Hg) | 88.1 ± 61.5 |
| Heart rate (bpm) | 80 ± 56 |
| NYHA classification, *n* (%) | |
| II | 5 (25) |
| III | 10 (50) |
| IV | 5 (25) |
| **Operations** | |
| Elective, *n* (%) | 10 (50) |
| Urgent, *n* (%) | 10 (50) |
| **Cardiac risk factors** | |
| Arterial hypertension, *n* (%) | 20 (100) |
| Diabetes mellitus, *n* (%) | 8 (40) |
| Hyperlipoproteinemia, *n* (%) | 14 (70) |
| Previous cardiovascular diseases, *n* (%) | 20 (100) |
| History of smoking, *n* (%) | 8 (40) |
| Obesity, *n* (%) | 10 (50) |
| Family history, *n* (%) | 9 (45) |
| **Preoperative events** | |
| Myocardial infarction, *n* (%) | 9 (45) |
| Repeat myocardial infarction, *n* (%) | 2 (10) |
| Myocardial infarction after PCI x2, *n* (%) | 1 (5) |
| Cerebrovascular insult, *n* (%) | 2 (10) |
| Pulmonary oedema, *n* (%) | 1 (5) |
| Angina pectoris, *n* (%) | 4 (20) |
| Coronary revascularization, *n* (%) | 1 (5) |
| Valve replacement, *n* (%) | 1 (5) |
| Atrial fibrillation, *n* (%) | 1 (5) |
| Thoracoabdominalis aortic aneurysm, *n* (%) | 4 (20) |
| **End-Stage Renal Disease** | |
| Chronic program of dialysis, *n* (%) | 9 (45) |
| Duration of dialysis (months) | 46 ± 31.8 |
| Acute renal insufficiency, *n* (%) | 11 (55) |

**Table 1:** Preoperative Status of Patients with End-Stage Renal Disease. Data are mean ± standard deviation for continuous variables or *n* (%) for categorical variables. LV: Left Ventricle; NYHA: New York Heart Association: PCI: Percutaneous Coronary Intervention.

by PCT. Although we have found decrease in PCT and MR-proADM levels following HD, there were not found statistical differences in plasma concentrations of all three biomarkers measured before and after dialysis sessions.

Type of surgery and mortality rate during the study period are given in Table 2. Postoperative stay at the ICU was 19.6 ± 16.4 (range, 2 to 57) days and total hospital stay 26.5 ± 20 (range, 6 to 80) days. The in-hospital mortality rate was 35% (7/20); one patient passed away with diagnosis of cardiac arrest upon assystolia and 6 patients died due to *institio cordis*, multiorgan dysfunction and sepsis. Four patients (20%) died within 30 days, 4/20 (20 %) died within 6 months, and 1/20 (5%) died 1 year after the operation. Two patients died due to cardiac events, one patient 3 months and another 8 months after discharge.

## Discussion

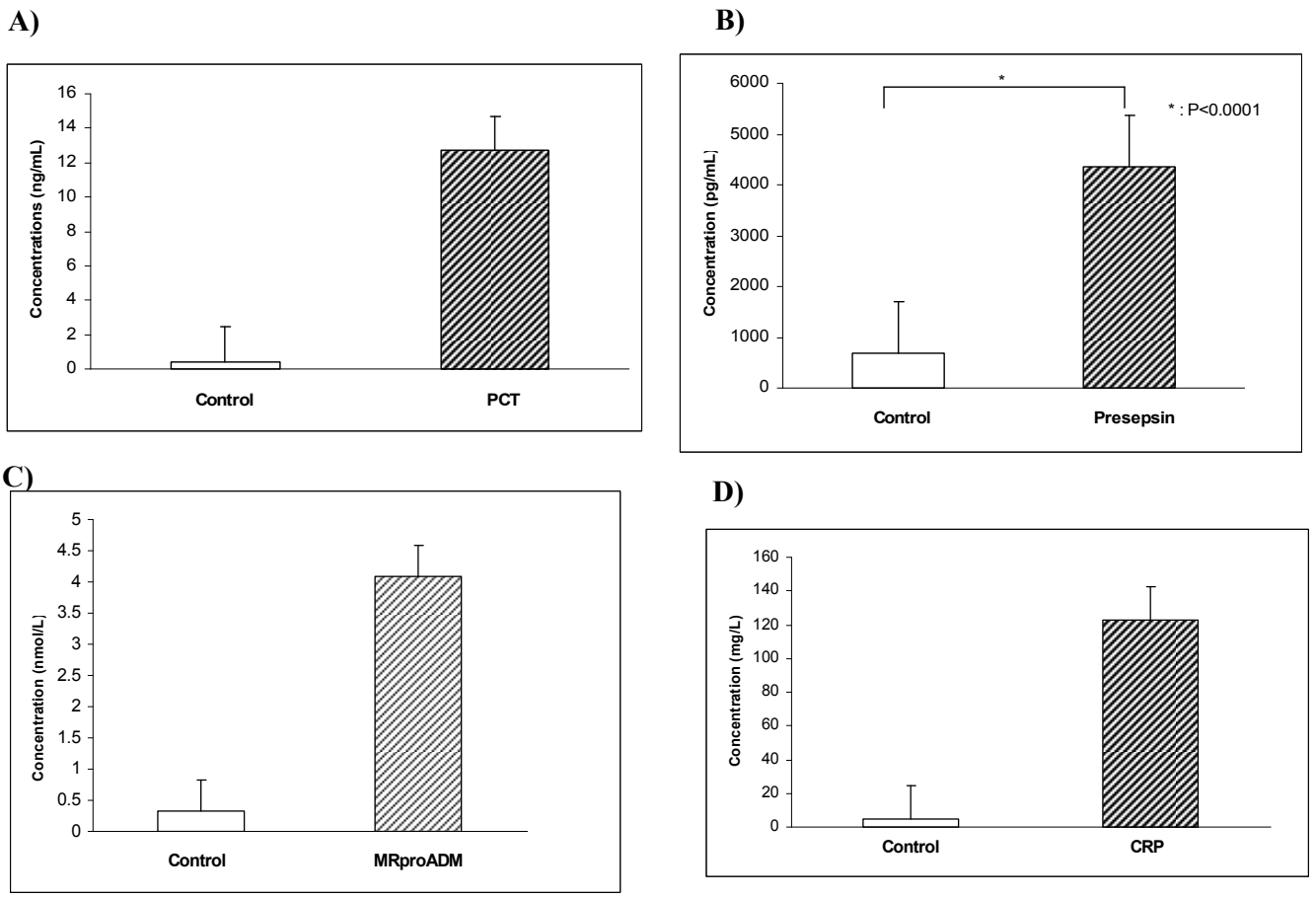
Cardiac surgery provokes an inflammatory response that contributes to the renal insult [21,22]. Endotoxin and circulating inflammatory cytokines peak 4-24 h after CPB and have been directly associated with acute renal injury [23,24]. Acute renal dysfunction is a major medical problem occurring in 5% of all patients admitted to the hospital and 30% of those admitted to an ICU [25]. Furthermore, acute renal injury remains a common, serious complication of cardiac surgery[26]. Unfortunately, typical characteristics (older age, history of atherosclerotic vascular disease) of those presenting for cardiac surgery make them generally a group at high renal risk [26].

In patients treated by haemodialysis, cardiovascular complications and infections are the main causes of morbidity and mortality [27]. Biological markers of inflammation: PCT, CRP, and interleukin (IL)-6, have been shown to be predictive of death in ESRD patients [28-30]. In patients on dialysis, PCT has been extensively studied and several studies have reported that PCT decreased after a hemodialysis session [30,31]. In contrast, CRP and IL-6 levels do not differ after dialysis compared with pre-haemodialysis levels. The cause of this might be due to PCT clearance by dialysis, because of its low molecular weight or it may be absorbance by the filter membrane [29,31,32]. Moreover, Nishokura et al. specified that the PCT clearance seems to become constant at 2.3 to 3.4 mL/min during a 5 to 24 h haemodialysis session [32]. Akbulut et al. found that PCT level fell from 2.13 to 1.8 ng/mL after dialysis, whereas CRP levels were almost unchanged [31]. Paradoxically, the kidneys are exposed to exotoxins and endotoxins and are also most vulnerable organs for infections. Once renal injury occurs, it takes several weeks to resolve and inflammation is permanent or enhanced [33]. However, the decrease in serum PCT after a haemodialysis session reduces the sensitivity of PCT [28]. Therefore, we explored the usefulness of 2 new biomarkers in septic patients.

The findings from Spanuth and Endo indicate that presepsin is a promising marker for the diagnosis and prognosis of sepsis, particularly in predicting 30-day mortality rate [10,11]. Presepsin is a molecular fragment derived from sCD14 and serves as a receptor for complexes of Lipopolysaccharide (LPS) and LPS binding protein (LBP) activating the toll-like receptor 4 on monocytes/phagocytes. Based on enzyme inhibitor experiments it seems that sCD14-Subtype is of 13 kDa molecular weight but this is still debated [14]. The plasma half-life of presepsin was reported to be 4-5 h, and mechanisms of production are related to the phagocytosis and cleavage from membrane. One could assume that presepsin constantly appears in plasma of septic

| Procedure | No. of Patients | No. of Deaths 30 Days | No. of Deaths 6 Months | No. of Deaths 1 Year |
|---|---|---|---|---|
| Isolated CABG (x2) | 2 | 1 | | |
| Isolated CABG (x3) | 4 | | 1 | 1 |
| Isolated CABG (x4) | 1 | | | |
| AVR and MVR | 1 | | | |
| AVR and MVR and Tricuspid valve reconstruction | 2 | 1 | | |
| MVR and Tricuspid valve reconstruction | 2 | | | |
| Redo MVR and Tricuspid valve reconstruction | 1 | | 1 | |
| Bentall and CABG (x1) | 1 | 1 | | |
| Bentall and Redo CABG (x1) | 1 | | 1 | |
| AVR, MVR and CABG (x2) | 1 | | | |
| AAA | 1 | | 1 | |
| RF ablation | 1 | | | |
| Miscellaneous | 2 | 1 | | |
| Total | 20 | 4 | 4 | 1 |

**Table 2:** Operative Procedures and Perioperative Mortality. CABG: Coronary Artery Bypass Grafting; AVR: Aortic Valve Replacement; MVR: Mitral Valve Replacement; AAA: Abdominal Aortic Aneurysm; RF: Radiofrequent; Redo: Reoperation.




Mann-Whitney Rank Sum Test A) P=0.902, B) P<0.0001, C) P=0.989, and D) P=0.902.
ESRD: End-stage renal disease; hsCRP: High sensitivity C-reactive protein; MR-proADM: Mid region proadrenomedullin; PCT: Procalcitonin.

**Figure 1:** Concentrations of (A) PCT, (B) Presepsin, (C) MR-proADM, and (D) hsCRP in ESRD Patients with Sepsis after Cardiovascular Surgery vs. control group.

patients even during dialysis process. Although the kinetics of the soluble forms of the CD14 molecule, as well as sCD14-ST subunit, is under observation, in our study we compared the levels before and after dialysis. We have found that presepsin appeared to be a reliable diagnostic marker for identifying sepsis and that it is a more accurate marker to monitor antibiotics treatment in patients with ESRD, than PCT.

MR-proADM is a stable peptide produced in stoichiometric amounts to ADM, representing the true level of the ADM in plasma [18,34]. ADM and related peptides are synthesized and secreted from vascular smooth muscle and endothelial cells. The half-life of ADM is 22 ± 1.6 minutes and it has potent and long-lasting vasodilatory effects on several vascular systems, but also metabolic and bactericidal properties [17,35]. Hirata et al. reported that the plasma concentrations of ADM increased in patients with sepsis complicated with acute renal disease, which declined following improvement of renal function [36]. The plasma ADM concentration has been shown to be increasing in correlation with serum creatinine in patients with chronic renal failure. Eto has shown that ADM decreases cardiac preload and afterload and improves cardiac contractility and diuresis in patients with heart failure and hypertension [37]. All our patients were in NYHA III or IV class with hypertension lasting for years. In our study, probably the MR-proADM concentrations measured reflect compensatory mechanisms due to heart failure, or renal failure, but the further confirmation of the present findings should be done.

Since many hormones or small fragments of peptides are known to be metabolized in the kidneys, the possibility of a decreased clearance of ADM in renal failure patients cannot be excluded as an explanation for the elevated plasma level. Washimine et al. reported a marked increase in the plasma ADM level in patients with ESRD who had been receiving maintenance haemodialysis [38]. In their comparison between plasma concentrations before and after the hemodialysis, they found that the increased plasma ADM was slightly reduced by dialysis, but the difference was not significant despite the reduction of the fluid volume. In our study we have found a similar trend of a drop of the MR-proADM levels measured after dialysis. It is in agreement with the findings of others who reported that plasma levels of ADM were not altered immediately by hemodialysis but decreased significantly 14-20 h after dialysis [39-41]. Montuenga et al. found that ADM has a molecular weight of 22 kDa and it has to be considered that that the organs producing high levels of ADM could also be included in the clearance of the peptide, especially if it is not a smaller molecule than the diameter of the dialyzer's aperture [19].

Limitation of our study is that other important markers such are IL-6, B-type natriuretic peptide and A-type natriuretic peptide, were not measured. IL-6 has been reported as an inflammatory marker with

| Hematology | Total (n = 20) |
|---|---|
| WBC (10x$^9$/L) | 14.9 [6.1-28.8] |
| Hemoglobin (g/L) | 92.7 [77-115] |
| Platelets (10x$^9$/L) | 172 [85-215] |
| **Biochemistry** | |
| Sodium (mmol/L) | 138.6 [132 -152] |
| Serum creatinine (µmol/L) | 438.7 [104 - 989] |
| Serum urea (mmol/L) | 20 [6.6 – 50.4] |
| **Biomarker level** | |
| PCT (ng/mL) | 3.86 [0.4 – 58.8] |
| Presepsin (pg/mL) | 3145 [1374 – 11237] |
| MR-proADM (nmol/L) | 3.76 [0.5 – 11.12] |
| CRP (mg/L) | 104.4 [8.02 – 271.0] |
| BNP (ng/L) | 1767 [58 – 4752] |
| **Clinical scoring systems** | |
| APACHE II | 19 [14 – 35] |
| SOFA | 14 [4 – 21] |

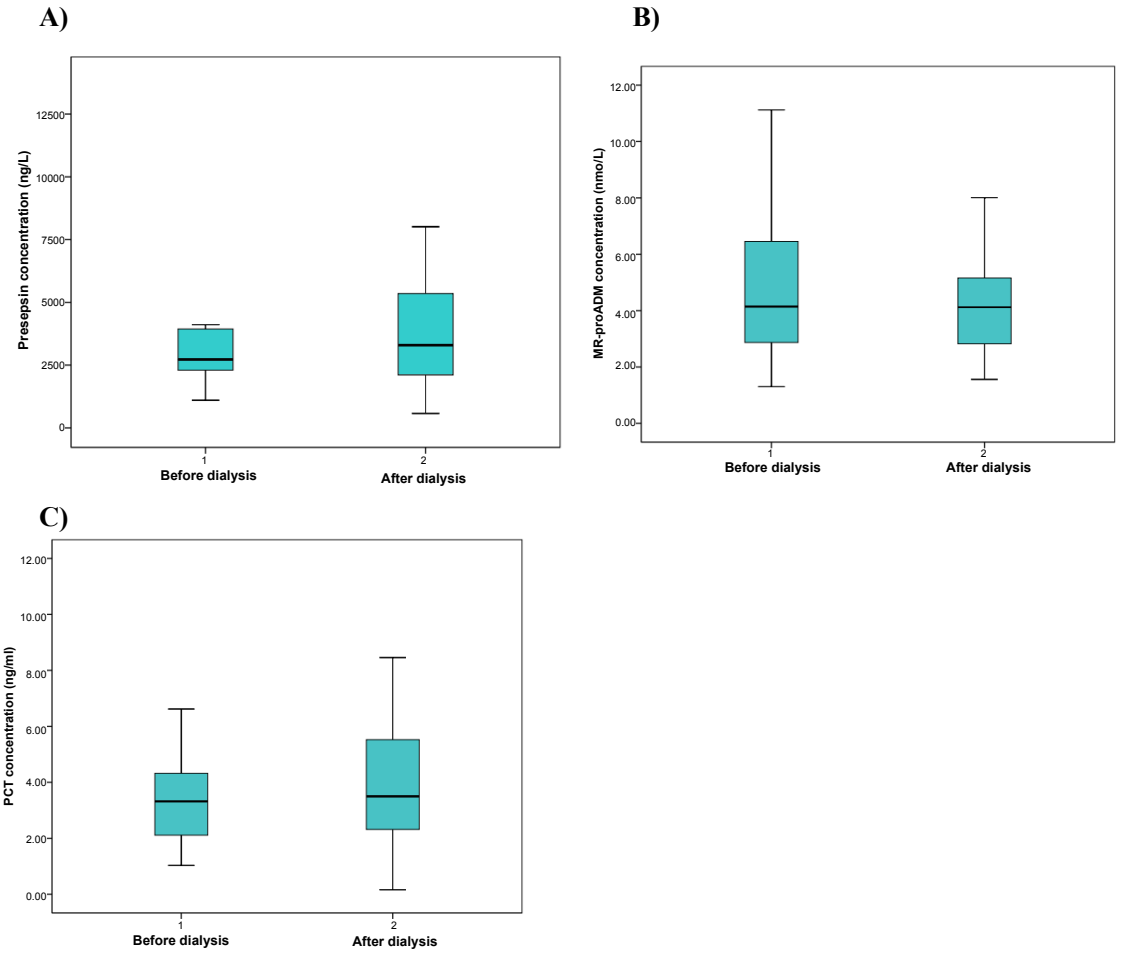
**Table 3:** Laboratory data on the day of sepsis appearance taken before dialysis. Data are expressed as median (minimum-maximum). APACHE II: Acute Physiology And Chronic Health Evaluation II; BNP: B-Type Natriuretic Peptide; Hscrp: High Sensitivity C-Reactive Protein; MR-Proadm: Mid-Region Proadrenomedullin; PCT: Procalcitonin; SOFA: Sequential Organ Failure Assessment; WBC: White Blood Cells.

| | Presepsin | MR-proADM | PCT | hsCRP |
|---|---|---|---|---|
| Kolmogorov-Smirnov coefficient | 0.277, P<0.0001 | 0.111, P>0.05 (0.2) | 0.316 P<0.0001 | 0.167 P>0.05 (0.174) |
| Skewness coefficient | 1.355 | 0.735 | 1.809 | 0.574 |
| Kurtosis | 0.636 | 0.577 | 2.020 | -0.994 |

**Table 4:** Overview of the Distribution of Presepsin, MR-proADM, PCT and hsCRP Values in Patients with Sepsis after ESRD and Cardiovascular Surgery. ESRD: End-Stage Renal Disease; Hscrp: High Sensitivity C-Reactive Protein; MR-Proadm: Mid-Region Proadrenomedullin; PCT: Procalcitonin.

genetic association in patients having acute renal injury after heart surgery. B- and A-type natriuretic peptide, both of whom have been associated with greater rises of proadrenomedullin levels, should be tested in those patients also. The main limitation is the small number of patients, but there are very limited studies concerning ESRD, cardiac surgery and sepsis. We believe that similar investigations are needed to attract attention to this issue. Septic patients are highly heterogeneous population and further scientific work is of broader interest for clinicians and scientific workers.

In conclusion, our results indicate that the diagnostic accuracy of new biomarkers is equal to that of PCT in patients with ESRD. Presepsin might be as good marker in repeated measurements, before




HD: Hemodialysis; MR-proADM: Mid-region proadrenomedullin; n.s: No significant differences.

**Figure 2:** Plasma concentrations of presepsin (A) MR-proADM (B) and procalcitonin (C) in patients with end-stage renal disease before and after hemodialysis (HD) following cardiovascular surgery.

and after dialysis, as it is PCT. Preliminary results have shown that the measurement of presepsin is useful for monitoring antibiotic therapy of sepsis in patients with ESRD.

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