Correlation of Urinary Biomarkers (Interleukin-6, Transforming growth factor-β, E-Cadherin, and MCP-1) with Conventional Parameters of Disease Progression in Patients of Posterior Urethral Valves: A Comparative Analysis

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Aims: Posterior urethral valves (PUV) are the leading cause of end-stage renal disease in boys. The study aimed to look at the ongoing renal damage and profibrotic activity by measuring the levels of Interleukin-6 (IL-6), Transforming growth factor-β (TGF-β), E-cadherin, and Monocyte Chemoattractant Protein-1 (MCP-1) and observing trends in subsequent follow-ups and at the same time correlating them with the established parameters of disease progression.

Materials and Methods: This prospective study included 36 consecutive patients of PUV, managed over a period of 18 months. IL-6, TGF-β, E-cadherin, and MCP-1 were measured in urine samples at the time of admission, pre-fulguration and 3 months’ and 9 months’ post fulguration. The observed values were correlated with the conventional parameters used in clinical practice.

Results: All the biomarkers showed statistically significant trends when these values were compared on admission, postoptimization and 3 months’ and 9 months’ postfulguration. None of the biomarkers showed a significant correlation with renal function tests. E-Cadherin and TGF-β showed a positive and a negative correlation with ultrasonography (USG) kidney, ureter, and bladder (KUB) respectively. E-Cadherin showed a positive correlation, whereas IL-6 and TGFβ showed negative correlation respectively with micturating cystourethrogram (MCUG). IL-6 showed statistically a significant negative correlation with dimercapto succinic acid (DMSA). MCP-1 did not show any significant correlation with USG KUB, MCUG and DMSA.

Conclusion: This study concludes that E-Cadherin, IL-6, TGF-β can be promising urinary biomarkers for early detection of the ongoing renal damage in patients of PUV following valve fulguration. MCP-1 may have more complex interactions, with inflammatory markers; which warrants further research.

KEYWORDS: E-cadherin, interleukin-6, monocyte chemoattractant protein-1, posterior urethral valves, transforming growth factor-β

INTRODUCTION

Posterior urethral valves (PUV) are the most common cause of lower urinary tract obstruction in male infants.\(^1\)\(^2\) Despite recent advances, the morbidity and mortality associated with them remain high. This can be attributed to the absence of substantial clinical and laboratory markers, which predict early renal injury in patients of this obstructive uropathy. Tracking changes in patients of PUV is further complicated by renal obstructive uropathy. Tracking changes in patients of PUV is further complicated by renal obstructive uropathy.
functional changes corresponding to normal maturation in developing kidneys.\(^3\)

Along with the renin-angiotensin system (RAS), three cell types play a fundamental role in the pathogenesis and progression of renal damage (1) tubular epithelial cells, (2) infiltrating inflammatory cells, and (3) interstitial fibroblasts. Hence, the components of the RAS and, inflammatory markers may have both diagnostic and prognostic potential. These include proteins like transforming growth factor β (TGF-β), monocyte chemoattractant protein-1 (MCP-1), and interleukin-6 (IL-6) and epithelial markers such as E-cadherin; epidermal growth factor, endothelin-1, urinary tubular enzymes N-acetyl-β-D-glucosaminidase, β2 micro globulins; and integral membrane proteins like aquaporins.\(^4\) Out of the wide array of above mentioned biomarkers, TGF-β, monocyte chemoattractant protein-1 (MCP-1), IL-6 and E-cadherin were chosen for the study; as supporting literature was available, the methodology was relatively simple, the reagents were easily available and were cost-effective, and the results were available within an acceptable time frame. The null hypothesis was that urine biomarkers did not play a role in predicting progression of renal damage in PUV patients.

This study aimed to measure the levels of urinary biomarkers (IL-6, TGF β, MCP-1, E-Cadherin) in patients with PUV; and to study the trends over subsequent follow-ups and to compare them with available conventional clinical, radiological, and biochemical markers.

**Materials and Methods**

This was a prospective study, conducted on a cohort of 36 consecutive patients diagnosed with PUV in the Department of Pediatric surgery, at a tertiary care teaching hospital in India. The study period extended from January 2018 to June 2019. All boys diagnosed with PUV in a single unit were included in the study. Patients who died before the completion of 9 months, after fulguration, those who refused consent or were lost to follow up were excluded.

The protocol was approved by the institutional ethics committee vide letter no INT/IEC/2018/000605, and an informed consent was taken from all patients.

The patients were evaluated, as per institutional protocol for assessment of the status of renal functions, i.e., biochemistry, ultrasonography (USG) of kidney, ureter, and bladder (KUB), micturating cystourethrogram (MCUG), dimercaptop succinic acid (DMSA), urine routine examination and urine culture.

After the clinical and radiological diagnosis was reached, the patients were admitted and stabilized in terms of correction of dehydration, acidosis; per urethral catheterization was done and creatinine levels were monitored. After adequate optimization, the patients were taken up for valve ablation. Per-urethral catheter was placed at the end of the procedure and was removed after 24–48 h.

Renal biochemistry, USG KUB and MCUG were done at 3 months after transurethral fulguration (TUF). If there was a poor resolution of symptoms, worsening in hydronephrosis on USG, or non-normalization of the posterior urethra in the MCUG, patients were taken up for check cystoscopy and redo TUF if required. This subset of patients was analyzed separately. Renal biochemistry, USG KUB were repeated at 3 and 9 months postoperatively. DMSA was done at 3 months’ and 9 months’ postfulguration to assess renal function and resolution or appearance of scars and pyelonephritic changes.

Ultrasound findings were assessed in terms of hydrourteronephrosis, hydronephrosis, echotexture of kidneys, bladder thickness, and postvoid residual urine volume. Results were categorized into:

1. Mild improvement (persistence but downgrading of hydrourteronephrosis and hydronephrosis)
2. Moderate improvement (persistence of minimal pyelectasis or minimal hydronephrosis with normal bladder and ureters)
3. Significant improvement (normalization of ultrasound findings)
4. The urinary biomarkers– IL-6, TGF-β, E-cadherin, and MCP-1 were measured in urinary samples of these patients at 4 different intervals.
   1. At time of admission;
   2. After stabilization with IV fluids and post catheterization, before taking up the patient for TUF, (pre-operative optimized value)
   3. Post fulguration: 3 months; and at 9 months.

Midstream urine directly voided in a sterile container and stored at -80°C\(^5\) till the analysis was done. To account for sample differences in urine concentration and osmolarity, urinary biomarker concentration was corrected for urinary creatinine concentration (pg/mg creatinine).

For MCP-1, Diaclone\®; precoated, 12 × 8 strips, 96 wells; was used for analysis; whereas solid phase enzyme-linked immunoassay (ELISA) 96 well kit based on sandwich principle from DRG\® was used for TGF β analysis. Double-antibody sandwich ELISA precoated, 12 × 8 strips, 96 wells, kit from Qaybee-bio life
science® was used for analysis of E-Cadherin and solid phase sandwich ELISA kit containing 96 wells from Diaclone® was used for analysis of IL-6.

**Statistical analysis**
The statistical analysis was carried out using IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp. The analysis included qualitative variables frequency table, association of variables based on Chi-square test and if any cell frequency was < 5, then Yates corrections were used for $2 \times 2$ contingency table or method pooling and Fisher’s exact test was used (for higher order than $2 \times 2$ table).

All quantitative variables were estimated using measures of central location (mean and median) and measures of dispersion (standard deviation). For normally distributed data, for paired wise comparison using t-test, repeated measure ANOVA and Wilcoxon signed-rank test, and Friedman test were used. All statistical tests were seen at two-tailed level of significance ($P \leq 0.01$ and $P \leq 0.05$).

**RESULTS**

**Conventional parameters**
In this study, the mean age was 1.2 years. Antenatal diagnosis was present 31% patients ($n = 11$) Stream was satisfactory for 44% ($n = 16$) patients; while it was poor for 56% ($n = 20$) patients. Straining at micturition was present for all patients except for one patient.

Mean serum urea and serum creatinine as measured on admission, pre-fulguration, and 3 months and 9 months’ postfulguration was 33.99 mg/dl, 26.50 mg/dl, 23.33 mg/dl, 22.89 mg/dl and 0.90 mg/dl, 0.59 mg/dl, 0.43 mg/dl, and 0.35 mg/dl, respectively. The decreasing trends were statistically significant till 3 months’ postfulguration. No statistically significant trend was observed in the values 3 months’ and 9 months’ postfulguration for both serum urea (P = 1) and serum creatinine ($P = 0.517$).

After 3 months of fulguration, 22% ($n = 8$) patients had mild, 53% ($n = 19$) patients had moderate and 25% ($n = 9$) had significant improvement in USG findings. At 9 months of follow up 22% ($n = 8$) patients had mild improvement, 36% ($n = 13$) patients had moderate improvement and 42% ($n = 15$) patients had significant improvement. Statistically significant trends were seen in USG findings done at the predecided timelines.

All patients underwent DMSA scan at 3 months’ and 9 months’ postfulguration. Outcomes were analyzed in terms of resolution or appearance of new scars or pyelonephritic changes. 31% patients ($n = 11$) showed improvement in serial DMSA scans whereas there was no significant change for 69% ($n = 25$) patients. This change was statistically significant.

MCUG findings were compared in terms of normalization of posterior urethra and resolution of vesicoureteral reflux (VUR). Out of 36 patients, 53% ($n = 19$) patients had normal MCUG after 3 months of fulguration, and out of remaining 47% ($n = 17$); 14% ($n = 5$) patients had normal MCUG after 9 months of fulguration; whereas VUR persisted for 33% ($n = 12$) patients even after 9 months of fulguration. Statistically significant correlation was found between MCUG findings on admission and at 3 months and 9 months post fulguration.

On the basis of clinical response and USG and MCUG findings, 13.8% ($n = 5$) patients were taken up for check cystoscopy and redo fulguration.

**Biomarkers**
Values of E-Cadherin, Monocyte Chemoattractant Peptide-1 (MCP-1), IL-6, TGF β were measured on admission, prefulguration, and 3 months and 9 months post fulguration [Figure 1a-d].

E-Cadherin, MCP-1, IL6, TGF β levels at time of admission, prefulguration, 3 months and 9 months postfulguration values were compared and results are shown in Table 1. All the subsets were found statistically significant with relation to each other.

**Correlation of biomarkers with conventional parameters**

**Correlation of biomarkers with ultrasonography findings**
Spearman’s Rho test between E-Cadherin and USG KUB was found statistically significant; with a positive correlation ($r = 0.598$). Similarly, statistical significance was observed between TGF β and USG KUB; with a negative correlation ($r = -0.585$). No statistically significant correlation was found between USG KUB and; MCP-1 and IL-6.

**Correlation of biomarkers with micturating cystourethrogram findings**
$t$-test was applied and relation between E-Cadherin levels, IL-6 levels, TGF β levels and MCUG findings was statistically significant; with $P = 0.0001$, 0.004, 0.015 respectively. No statistically significant correlation was found between MCUG and MCP-1 ($P = 0.147$).

**Correlation of biomarkers with dimercaptosuccinic acid findings**
$t$-test was applied and correlation between IL-6 levels and DMSA was found statistically significant ($P = 0.015$). However, no statistically significant correlation was observed DMSA findings and; E-Cadherin, MCP-1 and TGF β ($P = 0.131$, 0.95, 0.856 respectively).
Correlation of biomarkers with renal function tests

Pearson correlation was applied to study correlations between renal function tests (urea and creatinine) and MCP-1, IL-6, TGF β, and E-Cadherin levels. However, no statistically significant correlation was found between renal function tests and MCP-1, IL-6, TGF β, and E-Cadherin levels [Table 2].

Comparison of trends in levels of biomarkers on the basis of requirement of REDO fulguration

Two groups namely Group A (n = 31 – not requiring redo fulguration) and Group B (n = 5 requiring redo fulguration) were made and trends amongst the biomarkers were studied. Statistically significant correlation was observed in values of E-cadherin and TGF-β at 3 months and 9 months’ post fulguration [Table S1].

Discussion

As early as 1988, Parkhouse et al. reported, that the prognosis of renal function in patients with PUV is poor, with one-third of the patients developing renal failure by early adulthood.[6] This may attribute to changes in stroma and alterations in RAS and scaffolding transmembrane epithelial proteins.[6] We were able to establish data comparable to contemporary literature and in addition, came up with interesting observations.

Serum urea and serum creatinine may serve as a sensitive marker for following short-term course. However, their value tends to plateau quite early; whereas renal parenchymal changes continue to evolve by 2 years of life. Moreover, our study validates the same, as no statistically significant trends were observed between values at 3 months’ and 9 months’ post fulguration. This itself demands a marker which retains its sensitivity for following long term disease progression. Moreover, relatively low serum concentration of urea and creatinine and their greater tubular reabsorption leads to a lack of precision in its measurement in infants as compared to older children and infants.[7-9]

We observed statistically significant trends in USG KUB between prefulfuration findings and findings at 3 months’ and 9 months’ post fulguration. Hence, it is an effective and easily available tool to follow the temporal profile of PUV. However, its inability to predict ongoing renal damage and subjective interpretations, hampers its use for defining disease progression.

Renal scars and VUR are associated with poor prognosis in patients with PUV. In a study conducted by Haecker et al., primary dysplastic renal malformations were found in 80% of patients with PUV.[10] Renal scarring represents an advanced stage of renal damage, including tubular ischemia and destruction of the proximal tubules. These patients are likely to have more active tubulointerstitial fibrogenesis and RAS activation.[11] This study was done with an intent to try to establish alternative methods like urinary biomarkers, which may detect these changes at a relatively early stage.

These biomarkers when incorporated in the routine investigation panel may potentially aid better prognostication and early institution of therapeutic measures namely Angiotensin-converting enzyme (ACE1) inhibitors; before hypertension and renal scars set in. We came out with results which were well supported by available literature too.

Renal parenchymal injury and fibrosis are marked by a defect in epithelial integrity and loss of polarity. This
in turn leads to loss of E-Cadherin. In other words, increase in levels of E-Cadherin, reflects the recovery of renal parenchymal injury. Our results showed a significant increase in levels of E-Cadherin following successful fulguration. There was a positive correlation of E-Cadherin levels with USG and MCUG findings, further validating its value. Statistically significant correlation was observed between-group requiring redo fulguration and group not requiring the same in the values prefulguration, 3 months’ and 9 months’ post fulguration; substantiating its role further. To the best of our knowledge, we believe that ours is one of the first few studies which have tried to correlate conventional markers with intercellular adhesion molecules like E-Cadherin in patients with PUV.

MCP-1 is a powerful chemotactic and activator factor for monocytes and plays a role in channelizing monocytes to the renal interstitium. Various studies have revealed, increased MCP-1 levels in obstructive uropathies. In the current study, a statistically significant and a continuous decline were observed in the MCP-1 levels in all patients after adequate valve ablation. Our results are studies conducted by Madsen et al., Bartoli et al., Taranta-Janusz et al., and Mohammadjafari et al.[11‑16] However, MCP-1 excretion did not significantly correlate with the nuclear scans, MCU, USG KUB, and renal function tests; hence, questioning the use of the urinary level of this chemokine as a diagnostic and prognostic marker. This can probably be ascribed to a small sample size and relatively short follow-up as ours was a time-bound study. We recommend further studies are required to assess whether it can be used optimally as a urinary biomarker in patients with PUV.

IL-6 is a well-known marker of inflammation. In our study, the levels of urinary IL-6 showed a progressive decline in all patients after adequate valve ablation, which was statistically significant. The downwards trend in urinary IL-6 level indicates that these patients responded well to valve ablation and that there was a gradual downregulation of inflammatory response following removal of the bladder outlet obstruction. Mandelia et al. did not observe any significant trend in IL-6 levels before and after fulguration.[11] Haraoka et al. found that IL-6 levels were not elevated in children with VUR.[17] Gokce et al. found that urine IL-6 and IL-8 concentrations were significantly higher in children with renal scarring and VUR and in children with VUR than in the control group.[18] Tramma et al. reported that there were no statistically significant differences between urinary IL-6 levels in children with and without VUR.[19] It was observed that there was a significant correlation between IL-6 levels and changes in MCUG and DMSA; hence, substantiating its role as an effective biomarker.

TGF-β is a profibrotic cytokine and its pivotal role in the pathogenesis of progressive renal failure has been elucidated by many studies.[20] In our study, we measured urinary TGF-β levels in PUV patients and our results are consistent with those of MacRae Dell et al.[21] who studied urinary TGF-β excretion in 14 children.

### Table 1: Pairwise comparisons of E-cadherin, monocyte chemoattractant protein-1, interleukin-6, transforming growth factor-β levels on admission, prefulguration, 3 months and 9 months post fulguration

| E-Cadherin (pg/mg creatinine) | Mean difference | SE  | P        |
|------------------------------|-----------------|-----|----------|
| On admission                 |                 |     |          |
| Prefulguration               | -47.528*        | 6.072 | 0.0001** |
| 3 months                     | -237.056*       | 14.015 | 0.0001** |
| 9 months                     | -365.722*       | 18.833 | 0.0001** |
| Prefulguration               |                 |     |          |
| 3 months                     | -189.528*       | 12.525 | 0.0001** |
| 9 months                     | -318.194*       | 17.938 | 0.0001** |
| 3 months                     |                 |     |          |
| 9 months                     | -128.667*       | 14.120 | 0.0001** |
| MCP-1 (pg/mg creatinine)     |                 |     |          |
| On admission                 |                 |     |          |
| Prefulguration               | 0.408*          | 0.049 | 0.0001** |
| 3 months                     | 1.031*          | 0.069 | 0.0001** |
| 9 months                     | 1.581*          | 0.100 | 0.0001** |
| Prefulguration               |                 |     |          |
| 3 months                     | 0.622*          | 0.043 | 0.0001** |
| 9 months                     | 1.172*          | 0.082 | 0.0001** |
| 3 months                     |                 |     |          |
| 9 months                     | 0.550*          | 0.054 | 0.0001** |
| IL-6 (pg/mg creatinine)      |                 |     |          |
| On admission                 |                 |     |          |
| Prefulguration               | 0.486*          | 0.039 | 0.0001** |
| 3 months                     | 0.997*          | 0.046 | 0.0001** |
| 9 months                     | 1.561*          | 0.058 | 0.0001** |
| Prefulguration               |                 |     |          |
| 3 months                     | 0.511*          | 0.032 | 0.0001** |
| 9 months                     | 1.075*          | 0.045 | 0.0001** |
| 3 months                     |                 |     |          |
| 9 months                     | 0.564*          | 0.035 | 0.0001** |
| TGF β (pg/mg creatinine)     |                 |     |          |
| On admission                 |                 |     |          |
| Prefulguration               | 0.481*          | 0.035 | 0.0001** |
| 3 months                     | 1.156*          | 0.062 | 0.0001** |
| 9 months                     | 1.839*          | 0.087 | 0.0001** |
| Prefulguration               |                 |     |          |
| 3 months                     | 0.675*          | 0.050 | 0.0001** |
| 9 months                     | 1.358*          | 0.077 | 0.0001** |
| 3 months                     |                 |     |          |
| 9 months                     | 0.683*          | 0.045 | 0.0001** |

*P<0.05, **P<0.001. Value are expressed as mean difference±SE. SE: Standard error, IL-6: Interleukin-6, TGF-β: Transforming growth factor-β, MCP-1: Monocyte chemoattractant protein-1
with PUV and reported that urinary TGF-β excretion was significantly greater in patients with PUV than in healthy controls. Our results are also in agreement with other studies which have examined urinary TGF-β expression in patients with congenital obstructive uropathy. The level of urinary TGF-β in all patients showed a steady decline, after adequate valve ablation, indicating that our patients responded well to surgical therapy. A sustained downregulation of RAS, following removal of the bladder outlet obstruction, was observed. Statistically significant correlations were observed between TGF-β levels and USG findings, MCU and DMSA; making it a promising biomarker. Statistical significant correlation was observed between-group requiring redo fulguration and group not requiring the same in the values 3 months’ and 9 months’ post fulguration; substantiating its role further. However, no significant correlation was observed between renal function tests and TGF-β levels.

Biomarkers continued to show statistically significant trends at the time (i.e., 3 months’ and 9 months’ postfulguration) when renal function tests lost statistical significance. This substantiates their role in predicting on going renal damage. However, these biomarkers did not correlate well with serum urea and serum creatinine. Here, we would like to emphasize that our study was done on catheterized patients. Further studies where trends between biomarkers and renal function tests are studied in patients with pristine urethras could be of immense help. As this will typify the patients into low-risk and high-risk groups.

In the light of our observations, we would also like to hypothesize that even the most accurate measure of whole kidney Glomerular filtration rate (GFR), cannot account for loss of some nephrons, as the developing kidney is simultaneously adapting to dynamic changes till at least 2 years of life. This questions the role of estimated GFR in prognostication of these patients. However, further studies and longer follow-up are required to prove the same.

This study was aimed to measure the levels of these biomarkers in patients of PUV and to correlate them with established conventional parameters. Apart from short follow-up, another limitation of our study was a small size; as patients undergoing vesicostomy were excluded.

The scope of further study includes doing a case–control study to assess the baseline values and find out cut off values when ACE1 inhibitors can be initiated; which further can be correlated with renal recovery. Further studies with a longer follow-up are also needed to find out the time required to return these biomarkers to baseline values and this will further help in assessing the sensitivity and specificity of these biomarkers.

### Table 2: Pearson correlations of urinary biomarkers with renal function tests

| Biomarkers                        | Urea (mg/dl)-9 months | Creatinine (mg/dl)-9 months | E-Cadherin (pg/mg creatinine)-9 months | MCP-1 (pg/mg creatinine)-9 months | IL-6 (pg/mg creatinine)-9 months | TGF-β (pg/mg creatinine)-9 months |
|----------------------------------|-----------------------|-----------------------------|----------------------------------------|-----------------------------------|---------------------------------|----------------------------------|
| **Pearson correlation**          | Urea                  | Creatinine                  | E-Cadherin                             | MCP-1                             | IL-6                            | TGF-β                            |
| **Pearson correlation**          | 1                     | 0.685**                     | 0.061                                  | −0.053                            | 0.044                           | −0.043                           |
| **P**                            | 0.000                 | 0.723                       | 0.760                                  | 0.798                             | 0.804                           | 0.804                            |
| **Pearson correlation**          | 0.685**               | 1                           | −0.223                                 | 0.040                             | 0.233                           | 0.080                            |
| **P**                            | 0.000                 | 0.191                       | 0.818                                  | 0.171                             | 0.642                           | 0.642                            |
| **Pearson correlation**          | 0.061                 | −0.223                      | 1                                      | −0.431**                          | −0.566**                        | −0.516**                         |
| **P**                            | 0.723                 | 0.191                       | 0.009                                  | 0.171                             | 0.642                           | 0.642                            |
| **Pearson correlation**          | −0.053                | 0.040                       | −0.431**                               | 1                                 | 0.652**                         | −0.219                           |
| **P**                            | 0.760                 | 0.818                       | 0.009                                  | 0.171                             | 0.642                           | 0.642                            |
| **Pearson correlation**          | 0.044                 | 0.233                       | −0.566**                               | 0.652**                           | 1                               | 0.160                            |
| **P**                            | 0.798                 | 0.171                       | 0.000                                  | 0.000                             | 0.352                           | 0.352                            |
| **Pearson correlation**          | −0.043                | 0.080                       | −0.516**                               | −0.219                            | 0.160                           | 1                                |
| **P**                            | 0.804                 | 0.642                       | 0.001                                  | 0.200                             | 0.352                           | 0.352                            |

**IL-6:** Interleukin-6, **TGF-β:** Transforming growth factor-β, **MCP-1:** Monocyte chemoattractant protein-1, **Correlation is significant at 0.01 level (2 tailed), *Correlation is significant at 0.05 level (2 tailed)
This study disproves the null hypothesis that urine biomarkers did not play a role in predicting the progression of renal damage in PUV patients. Long-term studies are needed to study the sensitivity and specificity of individual biomarker. Till that time, a combination of biomarkers can be of immense help when incorporated in routine investigation panel; as they continue to show a significant change, when values of other markers have plateaued. This can be a game-changer in the scenario of PPUV patients as this will not just aid in prognostication, but will also improve our preparedness to deal with these patients in terms of issues inherent to CKD.

**Conclusion**

We conclude that E-Cadherin, IL-6, TGF-β may be promising urinary biomarkers to follow the 1st year outcomes of patients of PUV undergoing valve fulguration and have a potential to be incorporated into routine investigation panel. MCP-1 may have more complex interactions with other pro and anti-inflammatory markers which warrant further research. Large prospective multicenter studies with follow-up from fetal life through adulthood are need of the hour.

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**Conflicts of interest**

There are no conflicts of interest.

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| Biomarker | Timing       | Group A (n=31) pg/mg creatinine | SD   | Group B (n=5) pg/mg creatinine | SD   | P    |
|-----------|--------------|---------------------------------|------|-------------------------------|------|------|
| E-Cadherin| On admission | 811.90                          | 80.28| 800.00                        | 78.18| 0.77 |
|           | Prefulguration| 880.84                          | 75.38| 806.80                        | 72.24| 0.05*|
|           | 3 months     | 1154.06                         | 120.32| 996.40                        | 109.32| 0.01*|
|           | 9 months     | 1372.71                         | 152.51| 1174.20                       | 132.41| 0.01*|
| MCP-1     | On admission | 8.07                            | 1.03 | 7.76                          | 1.02 | 0.53 |
|           | Prefulguration| 7.65                            | 1.02 | 6.76                          | 1.01 | 0.08 |
|           | 3 months     | 7.02                            | 0.79 | 7.20                          | 0.77 | 0.64 |
|           | 9 months     | 6.43                            | 0.64 | 5.88                          | 0.59 | 0.08 |
| IL-6      | On admission | 5.17                            | 0.64 | 4.66                          | 0.60 | 0.10 |
|           | Prefulguration| 4.69                            | 0.62 | 4.10                          | 0.63 | 0.06 |
|           | 3 months     | 4.17                            | 0.61 | 3.64                          | 0.62 | 0.08 |
|           | 9 months     | 3.61                            | 0.60 | 3.08                          | 0.63 | 0.07 |
| TGF-β     | On admission | 7.21                            | 1.22 | 6.44                          | 1.19 | 0.19 |
|           | Prefulguration| 6.70                            | 1.20 | 6.16                          | 1.21 | 0.19 |
|           | 3 months     | 6.01                            | 1.23 | 7.79                          | 1.90 | 0.01*|
|           | 9 months     | 5.30                            | 1.17 | 6.50                          | 1.40 | 0.04*|

*P<0.05. Values are expressed as mean±SD in Group A (n=31) and Group B (n=5). IL-6: Interleukin-6, TGF-β: Transforming growth factor-β, MCP-1: Monocyte chemoattractant protein-1, SD: Standard deviation