Midkine as an Early Biomarker of Contrast-induced Acute Kidney Injury in Chronic Kidney Disease Patients Undergoing Percutaneous Coronary Intervention for Acute Coronary Syndrome: A Single-center Prospective Study

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Abstract

BACKGROUND: Contrast-induced acute kidney injury (CI-AKI) is an important complication of percutaneous coronary intervention (PCI).

AIM: We aimed to study the role of serum midkine (MK) as an early biomarker of CI-AKI.

METHODS: We conducted a prospective observational cohort study. It includes 100 chronic kidney disease patients with an estimated glomerular filtration rate ≤60 ml/min/1.73 m². All patients were undergoing PCI for acute coronary syndrome (ACS). We measured serum MK before, 2 and 24 h after PCI.

RESULTS: The mean age of the patients was 70.3 years, 74% of males. Twenty-seven patients developed CI-AKI. The CI-AKI group has a history of diabetes mellitus and/or dyslipidemia, history of diuretics, metformin, and/or angiotensin-converting enzyme inhibitors/angiotensin receptor blockers use. The CI-AKI patients have low left ventricular ejection fraction (EF < 45%) and low creatinine clearance before PCI. The CI-AKI received more contrast volume, had a longer duration of PCI, and had high Mehran risk score after PCI. Comparison between the two studied groups regarding serum MK showed that there was a statistically significant difference regarding serum MK level at 2 h after PCI. Receiver operating characteristic curve analysis for serum MK measured 2 h after PCI was statistically significant to predict CI-AKI.

CONCLUSION: An early serum MK after PCI can be used as an early predictor of CI-AKI in ACS patients.

Introduction

Contrast-induced acute kidney injury (CI-AKI) is an iatrogenic renal injury that follows the intravascular administration of radio-opaque contrast media in susceptible individuals. CI-AKI is defined as a 25% relative increase, or a 0.5 mg/dL absolute increase, in serum creatinine (SCR) within 72 h of contrast exposure, in the absence of an alternative explanation [1]. CI-AKI is responsible for almost a third of all hospital-acquired acute kidney injury (AKI) and occurs most frequently in patients undergoing coronary angiography and percutaneous coronary intervention (PCI). CI-AKI is associated with an increased risk of in-hospital and long-term mortality, development of end-stage renal failure (ESRD), and a new requirement for dialysis, recurrent myocardial infarction (MI), bleeding, and development of heart failure and stroke [2]. It is likely that the renal injury begins immediately after contrast media administration and that sensitive early biomarker could detect the kidney injury very soon, and to this effect, much effort has been made in recent years to identify early, specific biomarkers to allow early diagnosis of CI-AKI and hopefully improve the patients' outcome [3]. Midkine (MK) is a growth factor that regulates cell growth, cell survival, and migration and has an antiapoptotic activity in nephrogenesis. In the kidney, MK is expressed in both proximal tubular cells, distal tubular epithelial cells, and to a lesser extent in endothelial cells and is induced by oxidative stress. The pathophysiological roles of MK are diverse, ranging from the occurrence of AKI to the progression of chronic kidney disease (CKD) [4]. Investigation of MK as a renal biomarker has been undertaken with respect to CI-AKI in patients undergoing PCI due to stable...
angina, using the iso-osmolar contrast agent. It was observed that MK was significantly higher in patients with CI-AKI [5]. The development of novel biomarkers such as MK is promising and may enable more rapid detection of CI-AKI before the expected rise in SCR and give a diagnosis in hours rather than days [5]. However, more studies are necessary to affirm the potential of this molecule.

Methods

Study design and patient's population

The aim of the study was to investigate the role of serum MK as an early biomarker of CI-AKI in patients undergoing PCI for acute coronary syndrome (ACS). It is a prospective observational cohort study that conducted on 100 CKD patients with an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m². All the patients were undergoing PCI for ACS with the exclusion of ESRD patients on chronic renal replacement therapy, patients received a total volume of contrast >350 mL (or >4 mL/kg) and/or previous contrast exposure within 72 h, any documented episode of hypotension (MAP <65 mmHg) within 48 h before or after exposure to the contrast, and patients known with chronic heart failure (New York Heart Association [NYHA] III/IV or recent pulmonary edema), malignancies, sepsis, or a prior kidney transplant.

All patients received the same non-ionic, low-osmolar contrast media, and the same pre- and post-PCI hydration with intravenous (i.v.) isotonic saline (0.9%) according to the recent European Society of Cardiology guidelines on myocardial revascularization with the following regimen:

- Patients presented with non-ST-segment elevation ACS (NSTE-ACS) received 1 mL/kg/h of isotonic saline (0.9%) for 12 h before PCI and continued for 24 h after the PCI (0.5 mL/kg/h if the left ventricular ejection fraction [LVEF] ≤35% or NYHA >2).
- Patients presented with ST-elevation MI (STEMI) received 1 mL/kg/h of isotonic saline (0.9%) for 24 h after the PCI (0.5 mL/kg/h if LVEF ≤35% or NYHA >2).

Data collection

All patients were subjected to full history taking and clinical examination, electrocardiogram (ECG), echocardiography, abdominal ultrasound, assessment of kidney function (creatinine clearance [CrCl] and/or eGFR) according to the Cockcroft-Gault formula, simplified modification of diet in renal disease (MDRD), and CKD epidemiology collaboration (CKD-EPI) equations, full routine laboratory tests, measurement of serum MK: before, 2 and 24 h after PCI using enzyme-linked immunosorbent assay (ELISA) of the commercially available kits, and the MK level will be expressed as ng/mL (assay range: 0.005–1.5 ng/mL), assessment of SCR and blood urea: Before PCI, 24 and 48 h after the procedure, and estimation of risk of CI-AKI after PCI: Using Mehran risk score for the prediction of CI-AKI.

Quantitative determination of serum MK

Test principle

The kit used a double-antibody sandwich ELISA to check the level of MK in the samples. Standards and samples are added to a microplate well pre-coated with monoclonal anti-human MK antibody, with MK antibodies labeled with biotin and combined with streptavidin-horseradish peroxidase to form an immune complex. After 1 h of incubation, washing off the remaining conjugate is allowed to react with substrate solution (chromogen solution A and B). This reaction is stopped by addition of an acidic solution and the optical density (OD) of the resulting yellow product is measured. Furthermore, the OD value is proportional to the concentration of MK. A standard curve is constructed by plotting OD value against concentrations of standards and concentrations of the unknown samples are determined using a standard curve.

Sample collection and storage

The blood samples were collected under aseptic technique, centrifuged and the supernatant serum removed and kept in sterile labeled tubes. The serum samples stored below −20°C. Moreover, repeated freeze-thaw cycles were avoided.

Endpoints

The primary outcome was the occurrence of CI-AKI. The included patients were divided into two groups according to the occurrence of CI-AKI which was defined as a 25% relative increase, or a 0.5 mg/dL absolute increase, in SCR within 48–72 h of contrast exposure, in the absence of an alternative explanation.

Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. Qualitative data were described using the number and percent. Quantitative data were described using range (minimum and maximum), mean, standard deviation (SD), and median. Significance of the obtained results was judged at the 5% level. The used
tests were Chi-square test, Fisher's Exact or Monte Carlo correction, Student's t-test, Mann–Whitney U-test, receiver operating characteristic (ROC) curve, sensitivity, specificity, positive predictive value, negative predictive value, and accuracy.

Results

**Patient's population and baseline characteristics**

The mean age of the studied patients was 70.32 ± 3.62 years; male sex was 74%. The demographic and clinical characteristics of the patients are illustrated in Table 1. A total of 27 patients developed CI-AKI. The current study showed that the CI-AKI group has a history of DM and/or dyslipidemia (p < 0.001 and 0.015, respectively), has a history of diuretics, metformin, and/or angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARBs) use (p = 0.002, <0.001, and 0.005, respectively). The CI-AKI group admitted with anterior and/or lateral ST-T wave ECG changes (p = 0.041), low LVEF (EF <45%) (p = 0.001), anemia (hematocrit <39% in males or 36% in females) (p = 0.004), and low CrCl before PCI (p = 0.013) (Table 1). The CI-AKI group received more contrast volume (p < 0.001), had a longer duration of PCI (p = 0.025), had a larger number of drug-eluting stent (DES) use (p = 0.001), had lesion(s) anatomy of LCX only, LAD only, and/or LCX + LAD (p = 0.004, 0.008, and 0.004, respectively), and after PCI had a high Mehran risk score (p < 0.001) (Table 2).

**Table 1: Demographic and clinical characteristics of the patient**

| Variables                  | Total (n = 100) | Occurrence of CI-AKI p-value |
|----------------------------|----------------|-----------------------------|
| Sex                        | N (%)          | CI-AKI (n = 27)              |
| Male                       | 74 (74.0)      | 16 (60.3)                   | 0.126 |
| Female                     | 26 (26.0)      | 11 (41.1)                   |
| Age in years (mean ± SD)   | 70.32 ± 3.62   | 70.70 ± 3.56                | 0.086 |
| BMI in kg/m² (mean ± SD)   | 26.15 ± 3.58   | 26.13 ± 3.84                | 0.941 |
| Diagnosis                  | N (%)          | Non-CI-AKI CI-AKI            |
| UA                         | 72 (72.0)      | 57 (76.1)                   | 0.255 |
| NSTEMI                     | 17 (17.0)      | 14 (19.2)                   |
| STEMI                      | 11 (11.0)      | 6 (8.2)                     |
| Risk Factors               | N (%)          | Non-CI-AKI CI-AKI            |
| HTN                        | 83 (83.0)      | 59 (80.8)                   | 0.549 |
| DM                         | 45 (45.0)      | 21 (28.9)                   | <0.001|
| Dyslipidemia               | 58 (58.0)      | 37 (50.7)                   | 0.005 |
| Smoker                     | 37 (37.0)      | 25 (34.2)                   | 0.348 |
| IHD                        | 62 (62.0)      | 47 (64.4)                   | 0.419 |
| Drug history               | N (%)          | Non-CI-AKI CI-AKI            |
| Diuretics                  | 17 (17.0)      | 13 (19.6)                   | 0.002 |
| Metformin                  | 12 (12.0)      | 9 (13.3)                    | <0.001|
| ACEI/ARBs                  | 55 (55.0)      | 34 (46.6)                   | 0.005 |
| ECG (ST-T wave changes)    | N (%)          | Non-CI-AKI CI-AKI            |
| Anterior                   | 26 (26.0)      | 15 (20.5)                   | 0.041 |
| Inferior                   | 23 (23.0)      | 15 (20.5)                   | 0.338 |
| Posterior                  | 7 (7.0)        | 4 (5.5)                     | 0.384 |
| Lateral                    | 28 (28.0)      | 15 (20.5)                   | 0.041 |
| Low LVEF                   | 11 (11.0)      | 8 (11.0)                    | 1.000 |
| (EF <45%)                  | 28 (28.0)      | 14 (19.2)                   | 0.001 |
| Anemia                     | 40 (40.0)      | 23 (31.5)                   | 0.004 |
| Creatinine clearance and/or eGFR | N (%) | Non-CI-AKI CI-AKI            |
| Cockcroft                  | 41.95 ± 8.11   | 43.16 ± 8.32                | 0.013 |
| Gault formula (mean ± SD)  | 45.01 ± 10.00  | 46.15 ± 10.01               | 0.060 |
| MDRD equation (mean ± SD)  | 42.66 ± 9.74   | 43.77 ± 9.81                | 0.061 |

**Table 2: Procedural and post-procedural characteristics of the patients**

| Variables                  | Total (n = 100) | Occurrence of CI-AKI p-value |
|----------------------------|----------------|-----------------------------|
| Type of PCI                | n %            | CI-AKI (n = 27)              |
| Non-primary                | 89 (89.0)      | 67 (91.8)                   | 0.161 |
| Primary                    | 11 (11.0)      | 6 (8.2)                     |
| Contrast volume (mL)       | Mean ± SD      | 191.0 ± 47.34               | <0.001|
| Duration PCI (minutes)     | Mean ± SD      | 63.80 ± 36.01               | 0.025 |
| Number of DES              | Mean ± SD      | 1.40 ± 0.62                 | 0.74 ± 0.53 |
| Number of lesions          | N (%)          | Non-CI-AKI CI-AKI            |
| 1 vessel                   | 75 (75.0)      | 56 (76.7)                   | 0.230 |
| 2 vessels                  | 21 (21.0)      | 13 (17.8)                   | 0.296 |
| 3 vessels                  | 4 (4.0)        | 4 (5.5)                     | 0.00 |
| Lesion's anatomy           | N (%)          | Non-CI-AKI CI-AKI            |
| LCX only                   | 4 (4.0)        | 0 (0.0)                     | 4 (14.8) |
| RCA only                   | 28 (28.0)      | 18 (24.7)                   | 10 (37.0) |
| LAD only                   | 55 (55.0)      | 46 (63.0)                   | 9 (33.3) |
| LAD + LCX                  | 4 (4.0)        | 0 (0.0)                     | 4 (14.8) |
| LAD + RCA                  | 9 (9.0)        | 9 (12.3)                    | 0.00 |
| Mehran risk score (mean ± SD) | 6.82 ± 2.60 | 5.89 ± 1.93                | <0.001|

**Primary outcomes**

Comparison between the two studied groups showed that there was a statistically significant difference regarding serum MK 2 h and 24 h after PCI (p < 0.001) (Figure 1).

Figure 1: Comparison between the two studied groups regarding serum Midkine before PCI, 2 h and 24 h after PCI showed that there was a statistically significant difference regarding serum MK 2 h and 24 h after PCI (p < 0.001). CI-AKI: Contrast induces-acute kidney injury, PCI: Percutaneous coronary interventions

ROC curve analysis for serum MK is done and showed that the serum MK 2 h after PCI is an early predictor of CI-AKI as evidenced by a leftward and upward shift of the curve (p = 0.004). In addition, the
best cutoff value of serum MK 2 h after PCI to predict CI-AKI is >0.59 ng/mL (Figure 2 and Table 3).

![Figure 2: ROC curve analysis for serum Midkine before PCI, 2 h and 24 h after PCI done and showed that the serum Midkine 2 h after PCI is a good early predictor of CI-AKI as evidenced by a leftward and upward shift of the curve, AUC of 0.689, a p = 0.004, sensitivity of 70.37% and specificity of 61.64%. Also, the best cut off value of serum Midkine 2 h after PCI to predict CI-AKI is >0.59 ng/mL. ROC: Receiver operating characteristic, PCI: Percutaneous coronary intervention, CI-AKI: Contrast induced-acute kidney injury, AUC: Area under the curve.](image)

### Discussion

The present study is a prospective observational cohort study aimed to study the serum MK as an early predictor of CI-AKI and elucidate the main predictors of CI-AKI in 100 patients who underwent PCI for ACS.

In the current study, the incidence of CI-AKI was 27%, which was considered to be relatively high, and we can contribute this to all patients being CKD with eGFR <60 mL/min/1.73 m². This was in agreement with that reported by Tsai et al. [6] who studied incidence, predictors, and outcomes of AKI of 985,737 patients who underwent PCI and reported that the incidence of CI-AKI after PCI was 26.6% in patients with severe CKD at baseline, compared with 5.2% in patients with normal baseline renal function.

We found that there was no statistical significance between the two studied groups (CI-AKI and non-CI-AKI) regarding the demographic data (age, sex, and BMI). This is in concordance with results obtained by Watabe et al. [7] who studied the association of CI-AKI with long-term cardiovascular events in ACS patients who underwent emergent PCI. A total of 1059 patients were enrolled in the study, 368 (34.7%) had CKD and CI-AKI occurred in 164 (15.5%) patients. He concluded that CI-AKI was a significant incremental predictor of cardiovascular events at each stage of CKD in ACS patients. In contradiction to our findings, the study by Ji et al. [8] who studied a total of 805 patients underwent PCI and developed a new post-PCI CI-AKI risk score based on a retrospective study of the risk factors for CI-AKI. He reported that the CI-AKI group was statistically significant older and obese (p < 0.001 and 0.001, respectively) but there was no significance regarding the gender. Moreover, Yuan et al. [9] who studied risk factors and incidence of CI-AKI in a total of 1061 Chinese patients underwent emergency PCI, found that the incidence of CI-AKI was 22.7% and that female gender was a statistically significant predictor for CI-AKI group (p < 0.001). This contradiction could be explained by a limited study population in our study.

In the current study, we found that there was no statistical significance between the two studied groups according to the diagnosis on admission (STEMI, NSTEMI, or UA). This was in agreement with the study by Uzunhasan et al. [10] who studied the predictors of CI-AKI and long-term prognosis in patients with ACS underwent PCI. One thousand and eighty-three patients were enrolled, the study concluded that the patients who developed CI-AKI had worse prognosis at long-term follow-up. This agreement could be explained by the similarity of inclusion and exclusion criteria between our study and that reported by Uzunhasan et al. [10].

On the contrary, Tsai et al. [6] reported that the clinical presentation of the patients (UA, NSTEMI, and STEMI) was statistically significant between the studied groups (p < 0.001). He concluded that the clinical factors such as STEMI presentation, the severity of CKD, and cardiogenic shock were the statistically significant independent factors associated with the development of CI-AKI and that CI-AKI development was strongly associated with in-hospital mortality. This contradiction could be explained by a difference in inclusion and exclusion criteria and study population between both studies.

In the present study, there was statistical significance in the comparison between the two studied groups regarding diabetes mellitus (DM) as a risk factor (p < 0.001). The same was reached by Uzunhasan et al. [10] who reported that DM was statistically significantly associated with CI-AKI (p = 0.001). However, Watabe et al. [7] reported that there was no statistical
significance regarding DM between the two studied groups (CI-AKI and non-CI-AKI). This contradiction could be explained by a difference in duration, control, and type of DM between the study population which was not mentioned in the different studies.

In the current study, there was no statistical significance in the comparison between the two studied groups regarding hypertension (HTN) as a risk factor. The same was reached by Watabe et al. [7]. This was not in agreement with the study by Celik et al. [11] who studied the association between contrast media volume-eGFR ratio and CI-AKI after primary PCI in a total of in 597 patients. He reported that only HTN was statistically significant between the two studied groups (CI-AKI and non-CI-AKI). Furthermore, he concluded that contrast volume-eGFR ratio was significantly associated with CI-AKI after primary PCI. This contradiction could be explained by a limited study population in our study and relatively to the difference in duration and control of HTN between the study population which was not mentioned in the different studies.

We found that there was statistical significance between the two studied groups regarding ACEI/ARBs use (p = 0.005). The same was reached by Zaki et al. [12] who studied the clinical predictors of CI-AKI among diabetic patients with normal Scr underwent cardiac catheterization in a total of 250 patients, he reported that patients who were receiving ACEI either as a treatment of heart failure or as a treatment for HTN were higher among those who developed CI-AKI with highly significant correlation (p < 0.001). This could be explained by the effect of chronic use of ACEI in decreasing the renal perfusion by vasoconstriction of the afferent renal arteriole. On the other hand, in the study conducted by Uzunhasan et al. [10], ACEI/ARBs use did not show statistical significance between the two studied groups. This contradiction could be explained by a small percentage of ACEI/ARBs users included in Uzunhasan et al. [10] study (10%) in comparison to the present study (55%) and Zaki et al. [12] study (35%).

In the current study, there was statistical significance between the two studied groups according to low LVEF (EF <45%) on admission (p = 0.001). We can contribute this to LV dysfunction results in low effective intravascular volume leading to renal hypoperfusion, in addition to concomitant use of ACEI and diuretics among this population. The same was reported by Uzunhasan et al. [10] (p < 0.001). This agreement could be explained by the similarity of inclusion and exclusion criteria between our study and that reported by Uzunhasan et al. [10].

In the current study, there was statistical significance between the two studied groups regarding estimated CrCl by Cockcroft-Gault formula (p = 0.013). On the other hand, there was no significance regarding eGFR by MDRD and CKD-EPI equations. This was in agreement with the study by Narula et al. [13] who studied the short- and long-term outcomes of patients who developed CI-AKI from the large-scale HORIZONS-AMI trial. The study included 2968 STEMI patients who underwent primary PCI from a total of 3602 patients enrolled in the HORIZONS-AMI trial. He reported that baseline estimated CrCl by Cockcroft-Gault formula before PCI was statistically significant between the two studied groups (p = 0.04) and concluded that CI-AKI was associated with poor short- and long-term outcomes after primary PCI in STEMI patients. On the contrary, Centola [14] who studied the incidence, risk factors, and long-term prognosis of CI-AKI according to two different definitions (traditional CI-AKI definition vs. AKI Network definition) in a total of 402 STEMI patients underwent primary PCI, reported that eGFR by CKD-EPI equation before PCI was statistically significant between the two studied groups (CI-AKI and non-CI-AKI) according to the traditional CI-AKI definition (p = 0.001). Furthermore, the study by Uzunhasan et al. [10] who reported that baseline eGFR <60 mL/min/1.73 m² by MDRD equation before PCI was statistically significant between the two studied groups (p = 0.026). This contradiction could be explained by all the patients selected in our study being with baseline eGFR <60 mL/min/1.73 m².

We found that there was a statistical significance between the two studied groups regarding the contrast volume (p < 0.001). The mean contrast volume used among patients who developed CI-AKI was 224.1 ± 52.57 mL while it was 178.8 ± 39.01 mL among patients who did not develop CI-AKI. This was in agreement with the study by Celik et al. [11] who reported that the CI-AKI group received more contrast volume (153 mL) versus 135 mL in the non-CI-AKI group (p = 0.003). On the contrary, the study by Kim et al. [15] who studied predictors and clinical outcomes of CI-AKI in patients with CKD after PCI for a total of 297 patients reported that there was no statistical difference between the two studied groups (CI-AKI and non-CI-AKI) regarding contrast volume. This contradiction could be explained by almost the same contrast volume which was given to the studied groups (197 ± 64 mL vs. 194 ± 80 mL).

We found that there was statistical significance between the two studied groups regarding the number of DES (p = 0.001). We can contribute this to a larger volume of contrast used in the deployment of more than 1 stent. On the contrary, the study by Kim et al. [15] reported that there was no statistical significance between the two studied groups regarding the number of stents used. This contradiction could be explained by almost the same contrast volume which was given to the studied groups (197 ± 64 mL vs. 194 ± 80 mL).

In our study, there was statistically significant between the two studied groups regarding lesion(s) anatomy (LAD, LCX, and LAD + LCX) (p = 0.008, 0.004, and 0.004, respectively). This was in agreement with the study by Yuan et al. [9] who reported that LAD lesions...
were significantly associated with the CI-AKI group (p = 0.003). On the contrary, Celik et al. [11] reported that there was no statistical significance between the two studied groups regarding the infarct-related artery. This contradiction could be explained by the distribution of the same percentage of lesion(s) anatomy between the two studied groups (almost half of patients with LAD lesions developed CI-AKI while the other half did not).

In the current study, the comparison between the two studied groups regarding the number of lesions showed that there was no statistical significance. The same was reached by Watabe et al. [7]. On the contrary, the study by Uzunhasan et al. [10] reported that multivessel disease ratio was higher in patients with CI-AKI (p = 0.002). This contradiction could be explained by limited study population and a small percentage of multivessel disease patients in our study (24%) in comparison to 52% which was included in the study of Uzunhasan et al. [10].

In the current study, serum MK 2 h and 24 h post-PCI showed statistical significance between the two studied groups (p < 0.001). This was in agreement with the study by Malyszko et al. [5] who tested the hypothesis whether serum MK could represent an early biomarker of CI-AKI in 89 patients with normal SCr undergoing PCI due to stable angina using an iso-osmolar contrast agent. In this study, serum MK, serum and urinary NGAL, and cystatin C were evaluated before and 2, 4, 8, 24, and 48 h after PCI. Furthermore, SCr and blood urea were assessed before and 24 and 48 h after PCI. Malyszko et al. [5] found a significant rise in serum MK as early as 2 h after PCI (p < 0.001) when compared to the baseline values (2.46 vs. 0.50 ng/mL). Serum MK was also significantly higher 4 h after PCI (p < 0.05) then returned to the baseline values after 24 h.

Limitations

- A limited number of patients
- A single-center study
- A limited serial measurement of serum MK
- Inability to use other novel biomarkers for CI-AKI in comparison with serum MK.

Conclusion

- Serum MK can detect CI-AKI as early as 2 h after PCI in ACS patients with eGFR <60 mL/min/1.73 m²
- The best cutoff value of serum MK to predict CI-AKI is >0.59 ng/mL with a sensitivity of 70.37% and specificity of 61.64%.

Statement of Ethics

The included patients gave informed consents before participation in the study after explanation of the study protocol and the aim of the work. Furthermore, medical research and ethics committee in Kasr AlAiny Teaching Hospitals approved the study.

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