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Microalbuminuria as a Predictor of Outcome in Non-Diabetic Patients Undergo Percutaneous Coronary Intervention for Acute Coronary Syndrome

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ABSTRACT

Background: Acute coronary syndrome (ACS) is a medical emergency requiring prompt diagnosis and care. Percutaneous coronary intervention (PCI) has become integral part of management of coronary artery disease (CAD) and become lifesaving in acute STEMI patients. Microalbuminuria (MA) is a common phenomenon in patients with cardiovascular disease.

Objective: To assess importance of microalbuminuria as a predictor of outcome in non-diabetic patients undergoing PCI for ACS. **Subjects and methods:** This study was conducted on 123 patients admitted with ACS and were divided equally into three groups [unstable angina, non-ST-segment elevation myocardial infarction (NSTEMI) and STEMI). The patients were then divided into patients with negative and positive microalbuminuria (MA). Echocardiography, coronary angiography and estimation of microalbuminuria level were done to all patients.

Results: Mean age of patients 54.94 ± 9.86 years. There were 28 females (22.8%) and 95 males (77.2%). MA was more common in smokers than non-smokers were. There was statistically significant decrease in EF% and increase in WMSI in patients with positive MA than those with negative MA. There was statistically significant increase in the complications and mortality rate in patients with positive MA than those with negative MA. The univariate logistic regression analysis showed statistically significant association between presence of MA and wall motion score index (WMSI) >1.25, amount of dye > 160 ml, no reflow, occurrence of complications, EF pre ≤ 55%, and EF post ≤ 59%.

Conclusion: Albuminuria was a strong predictor of outcome in non-diabetic patients underwent PCI for ACS.

Keywords: Acute coronary syndrome, Percutaneous coronary intervention, Microalbuminuria.

INTRODUCTION

Acute coronary syndrome (ACS) is a term used to describe a range of conditions associated with sudden, reduced blood flow to the heart. It often causes severe chest pain or discomfort. A medical emergency requires prompt diagnosis and care. The goals of treatment include improving blood flow, treating complications and preventing future problems [(1)].

Percutaneous coronary intervention (PCI) is a nonsurgical technique for treating obstructive coronary artery disease, including unstable angina, acute myocardial infarction (MI), and multivessel coronary artery disease (CAD) [(2)].

Albuminuria is the most widely evaluated marker of renal damage. Microalbuminuria (MA) is a known marker of vascular permeability and endothelial dysfunction and has been found to be predictive of outcome in a wide variety of chronic and acute conditions, such as neoplastic disease, surgery, acute pancreatitis and trauma [(3)].

Microalbuminuria is a predictor of kidney dysfunction mainly in diabetic and hypertensive patients. In addition, there was a correlation between high levels of microalbuminuria and the poor outcomes seen in patients with ACS. MA can be estimated easily nowadays through the dosage of the albumin-to-creatinine ratio (ACR) through a simple urine sample instead of traditionally 24-hour collections [(4)].

Schrader *et al.* [(5)] showed that patients with higher proteinuria are at risk of developing higher degrees of ACS with adverse outcomes. **Deveci *et al.*** [(6)] found MA to be an independent predictor for the presence and severity of CAD. They concluded a strong relationship between MA and the severity of CAD. **Paudel *et al.*** [(7)] concluded that there is increased prevalence of microalbuminuria in ACS patents. MA was associated with statistically higher number of cases with history of smoking and hypertension and presence of increasing number of risk factors.

The aim of this work was to assess importance of microalbuminuria as a predictor of outcome in non-diabetic patients who underwent PCI for ACS**.**

PATIENTS AND METHODS

This prospective cohort study was conducted on 123 patients of acute coronary syndrome, at Cardiology Department, Faculty of Medicine, Zagazig University and in Cardiology Department, Air Force Military Hospitals through the period from March 2020 till April 2021 to measure levels of microalbuminuria in non-diabetic patients with ACS. The patients were divided into 3 groups (**41** patients in each group)**.**

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Group I: Patients presented with unstable angina, **group II:** Patients presented with NSTEMI, and **Group III**: Patients presented with STEMI. The patients were then divided into patients with negative MA and patients with positive MA.

Inclusion criteria: Age between 25 and 75 years, males or females, patients admitted to Coronary Care Unit suffering from chest pain typical for acute coronary syndrome, patients with unstable angina, NSTEMI and ST-segment elevation myocardial infarction (STEMI), candidate for successful PCI and ECG evidence of ACS with or without ST segment shift.

Exclusion criteria: Known patients with DM, cases showing random blood sugar ≥ 200 mg/dl and patients with chronic stable angina. In addition, patients with urinary tract infection showing pyuria with urine microscopy showing ≥ 8 WBC/hpf, patients with renal impairment (serum creatinine ≥ 1.5 mg/dl or with macroalbuminuria > 300 μg/mg creatinine by urinary dipstick, and patients with contraindication or refuse to do PCI.

All patients in the study were subjected to the following:

1. Careful history taking.
2. Complete clinical assessment.
3. Certain investigations including resting Electrocardiogram (ECG) and laboratory evaluation including complete blood count, cardiac enzymes, fasting blood glucose, HbA1c, kidney function tests and complete urine analysis.
4. Abdominal ultrasound.
5. Echocardiography with special care fpr assessment of left ventricular dimensions and ejection fraction, WMSI, LVMI before and six months after the procedure.
6. Estimation of microalbuminuria level.
7. Coronary angiography and percutaneous coronary intervention (PCI).

Follow up:

Clinical follow-up was done for all patients for 6-months after PCI. Post-PCI complications include cardiovascular death, ACS, cardiomyopathy cerebrovascular stroke and any revascularization including target vessel revascularization and new lesion revascularization.

Ethical consent:

An approval of the study was obtained from Zagazig University Academic and Ethical committee. Every patient signed an informed written consent for acceptance of the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis:

Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 23. The quantitative data were presented as mean, standard deviations and ranges when parametric and median, inter-quartile range (IQR) when data were non-parametric. In addition, qualitative variables were presented as number and percentages. Logistic regression analysis in the form of univariate and multivariate was done to assess the predictors of MA with their odds ratio (OR) and 95% confidence interval (CI). P-value ≤ 0.05 was considered statistically significant.

RESULTS

Table (1) showed that there was no statistically significant difference found between the three studied groups regarding age and sex with P-value = 0.073 and 0.415 respectively. In addition, there was no statistically significant difference found between the three studied groups regarding smoking and hypertension with P-value = 0.371 and 0.639 respectively.

Table (2) showed that there was no statistically significant difference found between the three studied groups regarding MA level or positivity with P-value = 0.056 and 0.306 respectively.

Table (3) showed that there was highly statistically significant decrease in EF% and increase in WMSI in patients with positive MA than in patients with negative MA with P-value < 0.001.

Table (4) showed that there was highly statistically significant increase for dye (ml) in patients with positive MA than in those with negative MA with P-value < 0.001. Besides, there was highly statistically significant increase in the percentage of patients with no reflow in positive MA group than in negative MA group with P-value < 0.001. TIMI2 was found with higher percentage in positive MA group than negative MA group with P-value = 0.001.

Table (5) showed that there was statistically significant increase in the complication rate and mortality rate in patients with positive MA than in those with negative MA with P-value < 0.001 and 0.019 respectively. In addition, the percentage of patients with revascularization and ICM was found higher in patients with positive MA than in those with negative MA with P-value < 0.001.

The univariate logistic regression analysis showed that there was highly statistically significant association found between presence of MA and WMSI >1.25, amount of dye > 160 ml, no reflow, occurrence of complications, EF pre ≤ 55%, and EF post ≤ 59%. In addition, the multivariate logistic regression analysis showed that the most important factors associated with presence of MA were amount of dye > 160 ml with P-value < 0.001 and OR (95% CI) of 14.620 (3.073 – 69.564) followed by no reflow with P-value = 0.017 and OR (95% CI) of 12.431 (1.568 – 98.530) and lastly occurrence of complications with P-value = 0.006 and OR (95% CI) of 11.381 (2.001 – 64.731) (Table 6).

Table (1): Comparison between unstable angina, NSTEMI and STEMI groups regarding demographic data and risk factors

		Group1 (Unstable angina)	Group 2 (NSTEMI)	Group 3 (STEMI)	Test value	P-value	Sig.
		No. = 41	No. = 41	No. = 41			
Age (years)	Mean ± SD Range	54.98 ± 10.35 35 – 73	57.41 ± 9.26 37 – 72	52.44 ± 9.54 35 – 71	2.682•	0.073	NS
Sex	Female Male	7 (17.1%) 34 (82.9%)	12 (29.3%) 29 (70.7%)	9 (22.0%) 32 (78.0%)	1.757*	0.415	NS
Smoking	Non-smoker Smoker	14 (34.1%) 27 (65.9%)	18 (43.9%) 23 (56.1%)	12 (29.3%) 29 (70.7%)	1.982*	0.371	NS
Hypertension	No Yes	14 (34.1%) 27 (65.9%)	15 (36.6%) 26 (63.4%)	18 (43.9%) 23 (56.1%)	0.895*	0.639	NS

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.001: highly significant (HS)
*:Chi-square test; •: One Way ANOVA test

Table (2): Comparison between the three groups regarding MA

		Group1 (Unstable angina)	Group 2 (NSTEMI)	Group 3 (STEMI)	Test value	P-value	Sig.
		No. = 41	No. = 41	No. = 41			
MA (mg\ day)	Median (IQR) Range	9.7 (7.1 - 18.3) 3.6 – 76.7	13.3 (7.3 - 20.5) 3.8 – 92.6	15.3 (10.21 - 27.8) 4.2 – 288.2	5.779‡	0.056	NS
MA	Negative Positive	37 (90.2%) 4 (9.8%)	35 (85.4%) 6 (14.6%)	32 (78.0%) 9 (22.0%)	2.365*	0.306	NS

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value < 0.001: highly significant (HS) *:Chi-square test; ‡: Kruskal Wallis test

Table (3): Comparison between negative and positive MA groups regarding Echocardiographic parameters

		Negative MA	Positive MA	Test value•	P-value	Sig.
		No. = 104	No. = 19			
EF (%)	Mean ± SD	57.50 ± 6.00	51.16 ± 7.95	4.020	<0.001	HS
LVID (mm)	Mean ± SD	49.19 ± 4.73	49.16 ± 5.28	0.029	0.977	NS
IVST (mm)	Mean ± SD	10.10 ± 1.12	10.32 ± 1.00	-0.798	0.426	NS
PWT (mm)	Mean ± SD	9.20 ± 1.19	9.74 ± 1.15	-1.817	0.072	NS
LVMI (g\m^2)	Mean ± SD	100.43 ± 21.66	102.37 ± 17.76	-0.368	0.713	NS
WMSI	Mean ± SD	1.21 ± 0.13	1.37 ± 0.21	-4.536	<0.001	HS

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value < 0.001: highly significant (HS), •: Independent t-test

Table (4): Comparison between negative and positive MA groups regarding amount of dye, no reflow and TIMI flow

		Negative MA	Positive MA	Test value	P-value	Sig.
		No. = 104	No. = 19			
Amount of Dye (ml)	Mean ± SD Range	125.87 ± 26.53 80 – 230	172.63 ± 46.89 80 – 250	-6.159•	<0.001	HS
No reflow	No Yes	101 (97.1%) 3 (2.9%)	14 (73.7%) 5 (26.3%)	14.504*	<0.001	HS
TIMI flow	TIMI 2 TIMI 3	0 (0.0%) 104 (100.0%)	2 (10.5%) 17 (89.5%)	11.128*	<0.001	HS

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value < 0.001: highly significant (HS)
*:Chi-square test; •: Independent t-test

Table (5): Comparison between negative and positive MA groups regarding complication rate and mortality rate

		Negative MA		Positive MA		Test value*	P-value	Sig.
		No.	%	No.	%			
Complications								
Non-complicated Complicated		97 7	93.3% 6.7%	11 8	57.9% 42.1%	18.774	<0.001	HS
Non-complicated ***ACS & Revas*** ***ICM***		97 6 1	93.3% 5.8% 1.0%	11 4 4	57.9% 21.1% 21.1%	22.857	<0.001	HS
Mortality	Alive Died	104 0	100.0% 0.0%	18 1	94.7% 5.3%	5.519	0.019	S

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value < 0.001: highly significant (HS), *: Chi-square test

Table (6): Univariate and multivariate logistic regression analysis for factors associated with presence of MA

	Uni-variety				Multi-variety			
	P-value	Odds ratio (OR)	95% C.I. for OR		P-value	Odds ratio (OR)	95% C.I. for OR	
			Lower	Upper			Lower	Upper
WMSI >1.25	<0.001	8.076	2.754	23.679	0.484	1.915	0.310	11.814
Amount of Dye (>160ml)	<0.001	16.500	5.164	52.725	<0.001	14.620	3.073	69.564
No reflow	0.002	12.024	2.586	55.897	0.017	12.431	1.568	98.530
Complications	<0.001	10.078	3.064	33.150	0.006	11.381	2.001	64.731
EF pre (≤55%)	<0.001	7.241	2.393	21.916	0.482	2.075	0.271	15.865
EF after 6month (≤59%)	0.007	5.986	1.645	21.787	0.526	0.539	0.080	3.633

DISCUSSION

In the present study, age ranged from 35 years to 73 years with a mean of 54.94 ± 9.86 years. There was no statistically significant difference between the three studied groups regarding age with P-value = 0.073. Our result is similar to a study conducted by **Al-Saffar *et al.*** [8] who assessed the prevalence of MA in seventy non-diabetic patients who presented with UA/NSTEMI and the relation of MA to the severity of coronary artery disease. They found that mean age was 56 ± 12 years (range 26–89 years). However, **Li *et al.*** [9] selected 309 patients with STEMI where the patients were aged 45-81 years with a median age of 63 years, and a mean age of 65.6 ± 12.8 years.

In the present study, there were 28 females (22.8%) and 95 males (77.2%). There was no statistically significant difference between the three studied groups regarding sex of the studied patients with P-value = 0.415. This is in agreement with **Hersi *et al.*** [10] who found in a study conducted in coronary syndrome patients that males were predominant (77%). **Mirghani *et al.*** [11] found that male dominance was evident (84.8%). **Li *et al.*** [9] found that 80.9% were men. **Paudel *et al.*** [7] investigated the prevalence of microalbuminuria among 100 non-diabetic acute coronary syndrome (ACS) patients and found that 68 were males while 32 were females with male: female = 2.12.

Our study showed that 27 patients (65.9%) in group I, 23 patients (56.1%) in group II and 29 patients (70.7%) in group III were current smokers and 27 patients (65.9%) in group I, 26 patients (63.4%) in group II and 23 patients (56.1%) in group III were hypertensive. There was no statistically significant difference between the three studied groups regarding smoking and hypertension with P-value = 0.371 and 0.639 respectively. In the study done by **Mirghani *et al.*** [11], STEMI, NSTEMI, and unstable angina were diagnosed in 73.3%, 21.6%, and 3.1% respectively. Hypertension was present in 33.3% (duration 1.4 ± 3.1 years) and smoking in 52% (no of cigarettes 14.4 ± 17.3, duration 9.9 ± 13.7 years). **Paudel *et al.*** [7] found that 98 out of 100 ACS patients were having one or more risk factors, 64 patients with history of smoking and 62 patients with hypertension.

Regarding MA, there was no statistically significant difference between the three studied groups. However, **Paudel *et al.*** [7] divided their patients into three groups; majority of patients had NSTEMI: 61% (no=61), 20% (no=20) had UA and 19% (no=19) had STEMI. Overall prevalence of MA was 73% (P-value=0.04). **Kumar *et al.*** [12] also showed similar prevalence for MA. **Al-Saffar *et al.*** [8] compared between 2 groups according to MA status and found it highly significant, P-value < 0.001. The study done by **Aziz** [13] found prevalence of MA to be 56.5% in angiographically proved severe CAD (luminal narrowing > 70%). The results of above studies cannot be matched with our study due to different inclusion criteria but they confirm the fact that MA is present in statistically significant number of cases in coronary artery disease.

In our study, MA test was positive in 19 (15.4%) patients from the studied sample. **Al-Saffar *et al.*** [8] showed that MA test was positive in 21 (30%) of patients from the studied sample.

In our study, the prevalence of MA was highest in STEMI group being 22%. The corresponding figures in NSTEMI and unstable angina were 14.7% and 9.8% respectively. The difference was statistically non-significant (P-value=0.306). **Memon and Kolachi** [14] in their study on relationship of MA in non-diabetic and non-hypertensive patients with acute myocardial infarction found MA in 53.17% STEMI and in 15.8% NSTEMI. In contraste, **Paudel *et al.*** [7] found that the prevalence of MA was highest in NSTEMI group being 81.96%. The corresponding figures in STEMI and unstable angina were 63.15% and 55% respectively. The difference was statistically significant (P-value = 0.035).

Among patients with a positive MA test (no= 19), the mean age was 55.15 years. In addition, **Al-Saffar *et al.*** [8] found that among patients with a positive MA test (no = 21), the mean age was 55 years. Out of 95 males and 28 females, MA was found positive in 12 (63.2%) males and 7 (36.8%) females respectively, with no statistically significant difference found between the two studied groups regarding sex (P-value = 0.111). Besides, **Bhalavi and Ghanekar** [15] showed similar results but a case control study done by **Basu and Jhala** [16] found a statistically significant higher numbers of males (83.33%) as compared to females (40%). In the study done by **Silva *et al.*** [17] on determination of MA in hypertensive patients and in patients with CAD found that MA was 23% in the age group 56 years and above and 5% in age group 55

years and below, which was statistically significant. **Paudel *et al.* [7]** found that out of 68 males and 32 females, MA was found positive in 47 (69.11%) males and 2 (81.25%) females respectively (P-value=0.202).

Our study shows that out of 79 patients with history of smoking, MA was present in 12 (63.2%) while out of 44 non-smokers, MA was found in 7 (36.8%) patients. The difference was statistically insignificant (P-value= 0.916). Additionally, **Bhalavi and Ghanekar [15]** in their study of correlation of MA and multiple risk factors in acute coronary syndrome found MA in 50% (6 out of 12) of patients with smoking, which was not statistically significant (P-value > 0.05). However, cases of diabetes mellitus were also included in their study. But, **Basu and Jhala [16]** in their study of 50 non-diabetic and non-hypertensive patients of ACS found that MA was present in 92% (23 out of 25) of patients with smoking while out of 25 non-smokers, MA was found in 10 (40%) of patients. The difference was statistically significant (P-value < 0.001). Moreover, **Paudel *et al.* [7]** found that out of 64 patients with smoking history, MA was present in 52 (81.25%) while out of 36 non-smokers, MA was found in 21 (58.33%) patients. The difference was statistically significant (P-value = 0.013). In the study done by **Bhalavi and Ghanekar [15]** on correlation of microalbuminuria and multiple risk factors in ACS, they found microalbuminuria in 86.66% with multiple risk factors compared to 44.44% with no risk factors and the difference was statistically significant.

Our study showed that out of 76 hypertensive patients, MA was present in 13 (68.5%) of the cases (no=19) while corresponding figures in 47 normotensive patients was 6 (31.6%). The difference was statistically insignificant (P-value = 0.518). In addition, **Al–Saffar *et al.* [8]** found microalbuminuria to be present in 8 (22%) of the 37 cases with hypertension while corresponding figures in 33 normotensive patients was 13 (39%). The results were statistically insignificant (P-value = 0.10), but STEMI cases were not included in their study. However, **Paudel *et al.* [7]** found that out of 62 hypertensive patients, MA was present in 51 (82.25%) of the cases while corresponding figures in 38 normotensive patients was 22 (57.89%). The difference was statistically significant (P-value = 0.013).

Our study showed that there was highly statistically significant decrease in EF% and increase in WMSI in patients with positive MA than in patients with negative MA with P-value < 0.001. Moreover, there was highly statistically significant increase for dye (ml) used in patients with positive MA than those with negative MA with P-value < 0.00. Moreover, there was highly statistically significant increase in the percentage of patients with no reflow in positive MA group than in negative MA group with P-value <0.001. TIMI2 was found with higher percentage in positive MA group than in negative MA group with P-value = 0.001. **Al-Saffar *et al.* [8]** found that patients with positive MA had either intermediate or high TIMI risk scores**.**

Our study showed that there was statistically significant increase in the complication rate and mortality rate in patients with positive MA than those with negative MA with P-value <0.001 and 0.019 respectively. In addition, the percentage of patients with revascularization and ICM was found higher in patients with positive MA than those with negative MA with P-value < 0.001. **Apostolovic *et al.* [18]** have concluded that MA is a significant predictor marker for long-term cardiovascular morbidity and mortality especially among patients with DM and hypertension.

The univariate logistic regression analysis showed that there was highly statistically significant association found between presence of MA and WMSI >1.25, amount of dye > 160 ml, no reflow, occurrence of complications, EF pre ≤ 55%, and EF post ≤ 59%. Moreover, the multivariate logistic regression analysis showed that the most important factors associated with presence of MA was found with amount of dye > 160 ml with P-value < 0.001 and OR (95% CI) of 14.620 (3.073 – 69.564), which was followed by no reflow with P-value = 0.017 and OR (95% CI) of 12.431 (1.568 – 98.530) and lastly occurrence of complications with P-value = 0.006 and OR (95% CI) of 11.381 (2.001 – 64.731). **Koulouris *et al.* [19]** evaluated the significance of microalbuminuria (MA) as a 3-year prognostic index in nondiabetic patients with acute myocardial infarction (MI). They found that MA is a strong and independent predictor of an adverse cardiac event. **Al-Saffar *et al.* [8]** found a strong correlation of microalbuminuria with echocardiographic changes and findings in coronary angiography in patients with UA/NSTEMI. **Kunimura *et al.* [20]** investigated whether the urinary albumin excretion rate could predict cardiovascular events in such a population. They enrolled 698 consecutive patients who underwent elective PCI. The patients were divided into those with normoalbuminuria, microalbuminuria, or macroalbuminuria. During follow-up (median: 1,564 days), 41 events occurred. After adjustment for conventional risk factors, Cox analysis revealed that hazard ratios for cardiac death and/or nonfatal myocardial infarction were 2.56 in those with microalbuminuria and 4.02 in those with macroalbuminuria compared to those with normoalbuminuria. In conclusion, an elevated urinary albumin excretion rate independently predicted adverse cardiovascular outcomes, with a gradual risk increase that progressed from microalbuminuria to macroalbuminuria in patients undergoing elective PCI. **Mok *et al.* [21]** concluded that albuminuria is an independent and a potent predictor of adverse outcomes among patients with MI.

Our study showed that by measuring MA in nondiabetic patients with UA/NSTEMI/STEMI, we could predict the severity of CAD and the risk of

adverse outcome. The mechanisms underlying the relation between microalbuminuria and cardiovascular disease are still unclear but are thought to reflect increased endothelial vascular damage, which cause atherosclerosis and lead to clinical cardiovascular disease. Furthermore, albuminuria has been associated with several other risk factors that might themselves be linked with atherosclerosis, including diabetes, hypertension, and obesity [(22)].

CONCLUSION

There was no difference in prevalence of microalbuminuria between males and females. In addition, highest prevalence of microalbuminuria was seen in patients with STEMI, which is a marker of high-risk CAD regardless of other traditional risk factors for CVD. Furthermore, microalbuminuria was associated with higher number of cases with history of smoking and hypertension and with increasing number of risk factors present. In addition, there was strong positive correlation between level of microalbuminuria and increased wall motion score index (WMSI) and increased amount of dye during PCI. Besides, there was strong negative correlation between level of MA and reduced EF. Lastly, patients underwent PCI for ACS with positive MA were associated with increased complications and mortality rate.

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