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Prevalence, predictors and prognostic significance of microalbuminuria in acute cardiac patients: a single center experience

Serafina Valente · Chiara Lazzeri · Marco Chiostri · Bruno Alterini · Agostino Ognibene · Cristina Giglioli · Clara Pigozzi · Gian Franco Gensini

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Abstract The objective of this study was to prospectively assess the prevalence, predictors and prognostic significance of microalbuminuria in a large cohort of consecutive acute cardiac patients, admitted to an intensive cardiac care unit from 1 January 2008 to 30 June 2009. In 815 acute cardiac patients, microalbuminuria is detectable in 39.3%. Microalbuminuria shows a significant negative correlation with left ventricular ejection fraction (Spearman's $\rho = -0.228$; $p < 0.001$), while it is positively correlated with C-reactive protein (Spearman's $\rho = 0.239$; $p < 0.001$), NT-pro-BNP (Spearman's $\rho = 0.306$; $p < 0.001$) and glycemia (Spearman's $\rho = 0.191$; $p < 0.001$). Microalbuminuria is an independent predictor for in-hospital mortality (1 μg/min step) (OR 1.015; 95% CI 1.008–1.023; $p < 0.001$). In the acute phase of cardiac patients, microalbuminuria is a common finding, and it represents an independent predictor for early mortality. It is strictly linked to the inflammatory activation (as indicated by C-reactive protein) and to acute glucose values, thus suggesting that it may be part of the acute response to stress.

S. Valente (✉) · C. Lazzeri · M. Chiostri · C. Giglioli · C. Pigozzi · G. F. Gensini
Intensive Cardiac Care Unit, Heart and Vessel Department, Azienda Ospedaliero Universitaria Careggi, VialeMorgagni 85, 50134 Florence, Italy
e-mail: seravalente@hotmail.com

B. Alterini
Heart and Vessel Department, Azienda Ospedaliero Universitaria Careggi, Florence, Italy

A. Ognibene
Laboratorio Generale, Dipartimento di Diagnostica di Laboratorio, Azienda Ospedaliero Universitaria Careggi, Florence, Italy

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Introduction

Microalbuminuria 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 [1, 2], surgery [3], acute pancreatitis [4] and trauma [5].

In acute setting, microalbuminuria has been shown to be a useful tool to predict illness severity and outcome in critically ill adult patients admitted to an intensive care unit (ICU) [6–8], but in these studies acute cardiac patients are scarcely or not represented. Gopal et al. [6] report that microalbuminuria predicts ICU mortality and inotrope requirement, as well as or better than APACHE II and SOFA scores in a mixed population (including about 10% cardiac surgery patients). Similar results are reported by Abid et al. [7] in a small subset of 40 medical patients (three patients with cardiorespiratory arrest), and by Thorevska et al. [9] in 104 critically ill patients (sepsis was present in the 43.3% of all population).

The aim of the present investigation was therefore to prospectively assess the prevalence, predictors and prognostic significance of microalbuminuria in a large cohort of consecutive acute cardiac patients, admitted to our intensive cardiac care unit (ICCU).

Methods

We prospectively enrolled all 888 patients admitted to our ICCU from 1 January 2008 to 30 June 2009. Exclusion

criteria were as follows: pre-existing chronic renal failure (60 patients), no urine output on the first day of admission, on renal replacement therapy, or overtly bloody urine (13 patients) [9]. Our study population was 815 patients.

Microalbuminuria was measured on the first day of admission (in the overnight urine collection), and was defined as ranging from 20 to 200 μg/min [10]. On ICCU admission, after PCI, in a fasting blood sample the following parameters were measured: glucose (g/l), troponin I (Tn I, ng/ml), uric acid (mg/dl) [11], NT-pro brain natriuretic peptide (NT-BNP) (pg/ml) [12], leukocytes count ($\times 10^3$/μl), fibrinogen (mg/dl), erythrocyte sedimentation rate (ESR), lactate, C-reactive protein (C-RP, mg/dl). Creatinine (mg/dl) was also measured in order to calculate glomerular filtration rate (ml/min/1.73 m^2) [13]. Glucose values were measured three times a day and peak glucose was considered. In patients with STEMI and UA/NSTEMI Tn I was measured three times a day and peak Tn I was reported [11, 12].

Transthoracic 2-dimensional echocardiography was performed on ICCU admission in order to measure left ventricular ejection fraction (LVEF).

In-ICCU mortality was the end point of outcome in our study.

Statistical analysis

Data were processed by means of SPSS 13.0 statistical package (SPSS Inc., Chicago, IL, USA). A two-tailed p value <0.05 was considered statistically significant. Data are reported as frequencies (percentages) and medians [95% Confidence Interval (CI)] and analyzed by means of χ^2 (or Fisher's exact text, when appropriate) and Mann–Whitney U test. By means of Spearman's rho the correlations between the presence of microalbuminuria, LVEF, C-reactive protein, admission glycemia and NT-pro BNP were assessed. A backward stepwise logistic regression analysis was conducted in order to identify the variables correlated to microalbuminuria and in-ICCU death. In the logistic models, candidate variables were chosen as those that were significantly different at univariable analysis, or were clinically relevant. Backward procedure (probability for entry 0.05; probability for removal 0.10) was repeated until all variables in the model reached statistical significance. For each model, calibration was assessed by means of a Hosmer–Lemeshow goodness of fit test; pseudo R^2 were also assessed. Receiver operating characteristic (ROC) curves were constructed for microalbuminuria and in-ICCU death.

Results

Our series comprises the following subgroups according to admission diagnosis, as follows:

1. ST elevation myocardial infarction [14]: in our hospital, in Florence, the reperfusion strategy of STEMI patients is represented by primary PCI [12]. The patients are first evaluated by the Medical Emergency System in the pre-hospital setting, and then directly admitted to the catheterization laboratory or transferred to it after a rapid stabilization in the emergency department (ED). After primary PCI, they are admitted to our ICCU.

Table 1 Clinical Characteristics of the 815 patients included into the study

	Median (IR) or frequency (%)
Age [median (IR), years]	72 (62–79)
Gender [Males/Females, frequency (%)]	549/266 (67.4/32.6)
Comorbidities	
Diabetes mellitus [frequency (%)]	200 (24.5)
Hypertension [frequency (%)]	524 (64.3)
Diagnoses	
STEMI [frequency (%)]	252 (30.9)
UA/NSTEMI [frequency (%)]	330 (40.5)
Acute heart failure [frequency (%)]	81 (9.9)
Arrhythmias [frequency (%)]	36 (4.4)
Other [frequency (%)]	116 (14.2)
LOS [median (IR), h]	72 (48–96)
In-ICCU mortality [frequency (%)]	33 (4.0)

IR interquartile range, *STEMI* ST elevation myocardial infarction, *UA/NSTEMI* unstable angina/Non ST elevation myocardial infarction, *LOS* length of stay, *ICCU* intensive cardiac care unit

Table 2 Comparison between patients with and without microalbuminuria

	No microalbuminuria 469 (57.5%)	Microalbuminuria 346 (42.5%)	*p* value
Age (years)	70 (59–78)	74 (64–82)	<0.001
Gender [males/females, frequency (%)]	322/147 (68.7/31.3)	227/119 (65.6/34.4)	0.365
BMI [median (IR), kg/m^2]	26.0 (24.0–28.0)	25.8 (23.1–28.0)	0.150
Hypertension [frequency (%)]	277 (59.1)	247 (71.4)	<0.001
Diabetes [frequency (%)]	101 (21.5)	99 (28.6)	0.021
EF [median (IR), %]	50.0 (42.0–55.0)	45.0 (35.0–55.0)	<0.001
NT-pro BNP [median (IR), pg/ml]	879 (257–2469)	2767 (832–8302)	<0.001
Tn I [median (IR), ng/ml]	4.25 (0.21–44.85)	7.81 (0.46–63.45)	0.005
C-Reactive protein [median (IR), mg/dl]	9.0 (8.0–21.5)	17.0 (9.0–57.8)	<0.001
Leukocytes [median (IR), ×1000/μl]	8.1 (6.5–10.3)	9.7 (7.3–12.9)	<0.001
Uric Acid [median (IR), mg/dl]	5.6 (4.7–6.7)	6.0 (5.0–7.4)	<0.001
Glycemia [median (IR), g/l]	1.08 (0.91–1.38)	1.24 (0.98–1.69)	<0.001
Fibrinogen [median (IR), mg/dl]	426 (357–505)	466 (400–563)	<0.001
Lactate [median (IR), mmol/l]	0.90 (0.70–1.50)	1.50 (0.90–2.70)	<0.001
eGFR [median (IR), ml/min/1.73 m^2]	90.2 (74.8–106.8)	72.5 (47.2–102.7)	<0.001
LOS [median (IR), %] (h)	61 (44–96)	72 (48–120)	<0.001
Dead patients [frequency (%)]	3 (0.6%)	30 (8.7%)	<0.001

BMI body mass index, *IR* interquartile range, *EF* left ventricular ejection fraction, *NT-pro BNP* N terminal pro Brain Natriuretic Peptide, *Tn I* troponin I, *eGFR* estimated Glomuerular Filtration Rate, *LOS* length of stay

2. Unstable angina/non-ST elevation myocardial infarction [15]
3. Acute heart failure (AHF) [16]
4. Dyarhythmias
5. Other (i.e. stable angina, pulmonary embolism)

Table 1 depicts the clinical characteristics of the 815 patients included in the study. Men are more prevalent (67.4%), and hypertension is present in more than half of the patients (64.3%). Acute coronary syndrome (that is STEMI and UA/NSTEMI) is the most frequent admission diagnosis accounting for 71.4%. In-ICCU mortality rate was 4% (33/815).

Among patients with estimated glomuerular filtration rate (eGFR) ≥60 ml/min/1.73 m^2 (who accounted for 84.4%), microalbuminuria is detectable in the 35%, while in patients with eGFR <60 ml/min/1.73 m^2 it is found in 62.4%.

Table 2 depicts the comparison between the patients with microalbuminuria and those without. In our series, microalbuminuria is detectable in 39.3% (294/815 patients). Patients with microalbuminuria are older ($p < 0.001$), more hypertensive ($p < 0.001$) and diabetic (0.02). They show lower values of LVEF ($p < 0.001$) and eGFR ($p < 0.001$) and higher values of NT-pro BNP ($p < 0.001$), Tn I ($p = 0.005$), uric acid ($p < 0.001$), glycemia ($p < 0.001$) and lactate ($p < 0.001$). A higher inflammatory activation is observed in patients with microalbuminuria, as inferred by the higher values of C-reactive protein ($p < 0.001$), leukocytes ($p < 0.001$), fibrinogen ($p < 0.001$). Length of stay is higher in patients with microalbuminuria ($p < 0.001$), as well as in-ICCU mortality rate ($p < 0.001$).

Microalbuminuria shows a significant negative correlation with LVEF (Spearman's $\rho = -0.228$; $p < 0.001$), while it is positively correlated with C-reactive protein (Spearman's $\rho = 0.239$; $p < 0.001$), NT-pro-BNP (Spearman's $\rho = 0.306$; $p < 0.001$) and glycemia (Spearman's $\rho = 0.191$; $p < 0.001$).

The following variables are independently associated with the development of microalbuminuria (when adjusted for age, hypertension, diabetes, eGFR, C-RP and EF): NT-pro BNP (100 pg/ml step: OR 1.004; 95% CI 1.002–1.007; $p = 0.002$); glycemia (1 g/dl step: OR 1.686; 95% CI 1.201 to 2.366; $p = 0.003$). Nagelkerke R^2 0.16; Hosmer–Lemeshow goodness of fit 6.329, $p = 0.610$.

At backward regression analysis, the following variables are independent predictors for in-ICCU mortality: Admission eGFR (1 ml/min/1.73m2 step) (OR 0.973; 95% CI 0.959–0.988; $p < 0.001$); LVEF (1% step) (OR 0.944; 95% CI 0.914–0.975; $p < 0.001$); Microalbuminuria (1 μg/min step) (OR 1.017; 95% CI 1.010–1.024; $p < 0.001$). Nagelkerke R^2 0.34; Hosmer–Lemeshow goodness of fit 11.626, $p = 0.169$.

Based on the ROC curve for the entire population, the optimum microalbuminuria threshold for in-ICCU death

should be 20 μg/min. This threshold would have yielded a sensitivity of 91% (95% CI 76–98%) and a specificity of 60% (05% CI 56–63%). The positive predictive value is 8.7%, while the negative predictive value is 99.4%. The corresponding RR for microalbuminuria >20 mg/dl is 13.6 (95% CI 4.5–41.7; $p < 0.001$).

Discussion

The main finding of the present investigation is that in a large cohort of consecutive acute cardiac patients, microalbuminuria on admission shows a high prevalence (being detectable in the 39.3%), and it is an independent predictor of in-ICCU mortality.

Microalbuminuria is recognized as a strong and independent indicator of increased cardiovascular risk among subjects with and without diabetes [17], its presence substantially increases the cardiovascular risk, and it is an independent predictor of ischemic heart disease in a population-based cohort [18]. In chronic heart failure, elevated albumin excretion is a powerful prognostic marker for all-cause mortality, independent of diabetes, hypertension, or renal function [19].

Our series includes mainly patients with acute coronary syndromes who undergo mechanical revascularization (accounting for 71.4% of the entire population), but available evidence of the prognostic significance of microalbuminuria in these patients is so far controversial. In patients with acute myocardial infarction (AMI) [20–22] microalbuminuria has been reported to occur early, yielding prognostic information about in-hospital mortality additional to that provided by clinical or echocardiographic evaluation of left ventricular function. In non-diabetic patients with AMI [23], microalbuminuria has been shown to be a predictor not only for mortality but even for morbidity. In hypertensive patients with AMI [24], the combination between microalbuminuria and hypertension is associated with a higher risk of in-hospital mortality, independent of other possible confounders (such as heart failure). Previous investigations have been performed in heterogeneous populations of patients with hypertension and myocardial infarction, diabetic and non-diabetic, submitted either to thrombolysis or to mechanical revascularization or not revascularized. Conversely, in our paper [25], in the early phase of 257 STEMI hypertensive patients without previously known diabetes all submitted to mechanical revascularization, microalbuminuria, though a common finding, did not yield prognostic information about in-hospital mortality or complications.

In the present investigation, microalbuminuria shows a strong independent prognostic role for early mortality, independent of the admission diagnosis. This can be probably related to the fact that microalbuminuria is strictly linked to the inflammatory activation (as inferred by C-RP) and glucose values, as a part of the acute stress response. C-RP is a well known prognostic marker in cardiovascular diseases, both in chronic and acute cardiac conditions [26–29]. In a previous paper [25] performed in hypertensive non-diabetic STEMI patients, microalbuminuria was associated with acute glucose dysmetabolism (as inferred by hyperglycemia and the prevalence of insulin-resistance), thus suggesting that it can be considered as the part of the acute metabolic response to stress.

In our series, microalbuminuria correlates with NT-pro BNP values, which is known as a strong predictor for cardiovascular mortality [30]. Our findings are in agreement with recent investigations performed in humans [31] and in animal models [32]. In Japanese hypertensive patients, a concomitant reduction in BNP and microalbuminuria is observed after therapy [33], while in hypertensive rats, microalbuminuria is significantly correlated with reductions in cardiac mass and hypertrophy markers (such as BNP), thus suggesting a potential link between microalbuminuria and BNP. In the acute phase of STEMI [10], NT-pro BNP is related to the extension of myocardial injury (as inferred by peak Tn I), and to inflammatory activation (as indicated by C-RP). It is an independent predictor for early mortality.

The main limitation of the present study is that it comprises unselected patients admitted to our ICCU because of varying diagnoses (from acute coronary syndrome to acute pulmonary embolism). On the other hand, our population including consecutive acute cardiac patients, reflects the "contemporary clinical practice" in an ICCU of a tertiary center.

In conclusion, in the acute phase of cardiac patients, microalbuminuria is a common finding and it represents an independent predictor for early mortality. It is strictly linked to the inflammatory activation (as indicated be C-RP) and to acute glucose values, thus suggesting that it is the part of the acute response to stress.

Conflict of interest None.

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