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Microalbuminuria during acute myocardial infarction

A strong predictor for 1-year mortality

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Aims Urinary albumin excretion increases during acute myocardial infarction but little is known on the prognostic significance and the pathophysiological mechanisms of microalbuminuria in this clinical setting. The primary aim of the study was to examine whether urinary albumin excretion has predictive power for 1-year mortality after acute myocardial infarction. A secondary objective was to gain insight into the pathophysiological mechanisms of increased urinary albumin in myocardial infarction.

Methods and Results This is a prospective cohort study conducted in three coronary care units (Northeast Italy). Four hundred and thirty-two unselected, consecutively enrolled patients with acute myocardial infarction (66·3 ± 12·3 years of age) were studied. The incidence of mortality was related to the baseline urinary albumin:creatinine ratio. The best cut-off for total mortality approximated to 50 mg . g^{-1} on the first day after myocardial infarction, 30 mg . g^{-1} on the third day, and to 20 mg . g^{-1} on the seventh day. At multivariable Cox analysis, the albumin:creatinine ratio was the strongest among several independent predictors of mortality (adjusted relative risks: 3·6 (95% CI, 2·1–6·2) on the first day, 4·9 (95% CI, 2·9–8·2) on the third day and 4·0 (95% CI, 2·3–6·8) on the seventh day). Independent determinants of urinary albumin were plasma aldosterone on the first day, and inflammatory markers on the third and seventh days.

Conclusion Urinary albumin assessed in the first week after acute myocardial infarction is a strong prognostic marker for 1-year mortality.
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Key Words: acute myocardial infarction, microalbuminuria, albumin:creatinine ratio, aldosterone, inflammatory markers, prognosis.

Introduction

Several factors such as age, diabetes mellitus, prior angina, heart failure, depressed left ventricular function, etc. can adversely affect prognosis in subjects with acute myocardial infarction[1–4]. Microalbuminuria has been reported to occur in patients with acute myocardial infarction[5,6] and it has been associated with increased risk for in-hospital mortality[7]. Several studies have shown that microalbuminuria can predict all-cause (largely cardiovascular) mortality in the general population and in patients with diabetes mellitus[8–10]. However, it is not known whether microalbuminuria is an important indicator of long-term death in patients with acute myocardial infarction. Moreover, the mechanisms by which the albumin excretion rate increases in this clinical setting have not been elucidated.

The present report is a prospective analysis of an unselected sample of patients admitted to three coronary care units for acute myocardial infarction. The primary aim of the study was to examine whether urinary albumin excretion has predictive power for 1-year mortality after acute myocardial infarction. A secondary objective was to gain insight into the pathophysiological mechanisms of the increased urinary albumin in acute myocardial infarction.

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Methods

Patients

Four-hundred and seventy five consecutive and unselected patients admitted to the intensive care units

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Table 1 Baseline characteristics of the patients

Characteristic	Value
Age (years)	66·3 ± 12·3
Gender (females)	130 (30%)
Body mass index (kg . m^{-2})	25·5 ± 3·8
Current smoking	169 (39%)
Hypertension	198 (46%)
Diabetes	104 (24%)
History of angina	93 (21%)
Previous myocardial infarction	96 (22%)
Serum total cholesterol (mg . dl^{-1})	209 ± 52
Serum creatinine (mg . dl^{-1})	1·0 ± 0·3
CK peak (IU . l^{-1})	1498 ± 1331
CK-MB peak (IU . l^{-1})	173 ± 155
Anterior myocardial infarction	138 (32%)
Heart failure (1st week)	169 (39%)
LVEF% (n=316)	50·5 ± 12·8
Arrhythmias (1st week)*	125 (29%)
Thrombolysis	161 (37%)
Antiplatelets	357 (83%)
Anticoagulants	403 (93%)

Data are mean (± SD) or number of patients and %
CK=creatine kinase.
CK-MB=MB isoenzyme of creatine kinase.
LVEF=left ventricular ejection fraction.
*Tachy- and/or brady-arrhythmias during the first week of hospitalization.

at Bassano del Grappa (n=123), Adria (n=223) and Conegliano Veneto (n=129) Hospitals (Northeast Italy) for acute myocardial infarction were prospectively studied. Twenty-five patients with either urinary tract infections (n=12) or other concomitant clinical situations which could affect urinary albumin (n=13) [chronic renal failure (n=2), nephrotic proteinuria (n=2), dialytic treatment (n=1), myocardial reinfarction within 7 days following admission (n=2), traumatic diseases (n=2), bronchial infection (n=1), perioperative period of surgical patients (n=2) menstrual flow (n=1)] were excluded. Three additional patients were excluded because of the presence of neoplastic disease, five because of death within 3 days after admission and 10 for insufficient data collection. Thus, the final analysis was performed in 432 subjects. Their clinical characteristics are reported in Table 1. The presence and degree of heart failure was assessed on the first, third and seventh day after admission following the Killip classification[11]. Other details on patients' data collection were reported elsewhere[7]. All patients gave their informed consent and the study was approved by the Hospitals' Ethics Committees.

Measurements

All clinical and laboratory data were obtained during the first week of hospitalization. In 47 patients, seventh day data were not available because of early discharge or death. Acute myocardial infarction diagnosis was made according to previously described criteria[7]. Serum enzymes and electrocardiogram were performed every 4 h during the first 48 h after admission. Subsequently, the above tests were performed daily. The methods used for blood pressure and heart rate assessment, and for biochemical measurements were reported elsewhere[7].

Left ventricular ejection fraction was assessed in 352 consecutive subjects by two-dimensional echocardiography within 7 days after admission. Four- and two-chamber apical views were recorded in VHS cassettes and sent to the Conegliano Veneto Hospital where they were examined by two physicians who had no knowledge of patients' clinical data. Thirty-six subjects, in whom the echocardiographic images were technically unsatisfactory, were discarded from the analysis. Thus, left ventricular ejection fraction could be obtained for 316 patients.

Urinary albumin excretion was assessed in three 24-h urinary collections, performed on the first, third and seventh days after admission. Immediately after completion, volumes were measured and urine specimens frozen (− 20 °C) and sent to the University of Padova. Here, urinary albumin was measured by radioimmunoassay, using a Human ALB. KIT-double antibody, (Techno Genetics, Cassina De Pecchi, Milan, Italy)[12]. The detection limit of the method was 0·5 mg . l^{-1} and the between-batch coefficient of variation was =5%. For the same 24-h urine sample, creatininuria was also measured using the Jaffè method[13]. Urinary albumin excretion was expressed either as an albumin excretion rate in mg . 24 h^{-1}, or as the ratio of albumin (mg . l^{-1}) to creatinine (g . l^{-1}) in mg . g^{-1}.

In the last 150 consecutive patients, venous blood was drawn on the first, third and seventh days for measurement of hormones and inflammatory markers. The clinical characteristics of this subset of subjects were similar to those of the whole sample. Plasma renin was measured by immunoradiometric assay and aldosterone was measured by radioimmunoassay at the University of Padova, using kits from Nichols Institute, San Juan Capistrano, CA, U.S.A., and Radim, Angleur (Liège), Belgium, respectively. Venous blood samples were put in ice and centrifuged within 20 min at +4 °C, and the plasma was stored at − 20 °C until assayed. C-reactive protein was measured at the University of Padova by means of nephelometry with particle-bound goat anti-human C-reactive protein (Beckman Instruments, Inc. Fullerton, CA, U.S.A.). Blood neutrophil granulocyte count and erythrocyte sedimentation rate were also measured. These measurements were made soon after blood samples were drawn.

Follow-up

One year after recruitment, each patient was called for a clinical check-up. For those who died during a hospital stay, date and cause of death were obtained from hospital records (including postmortem report, where available). Mortality data for those who died outside

hospital were obtained through the private physician. No patients dropped out during follow-up. Endpoints considered for the study were all-cause mortality and total cardiovascular mortality. Sudden death was defined as either instantaneous unexpected death, or death occurring within 1 h of symptom onset.

Statistical analysis

Statistical analysis was completed using Systat 7·0 for Windows package (SPSS Inc. 1997, Evanston, IL, U.S.A.) and JMP 3.1.4 for Windows (SAS Institute Inc. 1995, Cary, NC, U.S.A.). Data accrued on each patient included both measured (continuous) variables, e.g. age, the albumin:creatinine ratio and other myocardial infarction correlates, and categorical predictors, e.g. survival status 1 year post acute myocardial infarction, gender, medical and risk indicators, such as diabetes and hypertension status, Killip class and smoking history. To correct for positive skewed distributions for the albumin:creatinine ratio and albumin excretion rate, log transforms were used. In statistical analysis presented in this paper, the albumin:creatinine ratio was used because it showed a slightly better predictive power than the albumin excretion rate. Dichotomous categorical indicator variables were classified such that being male, smoking, having diabetes, etc. scored 1 and the opposite scored 0. Killip class was considered as a 4-class variable. The albumin:creatinine ratio was utilized in some analyses as a continuous (logged) variable and in others as a dichotomous variable. When considered as a dichotomous predictor for relative risk assessment, the two classes were based on 'low' and 'high' albumin: creatinine ratio levels. Optimal cut-off values for each day separately for the albumin:creatinine ratio level were determined using a receiver operating characteristic curve analysis (MedCalc, Ver. 4.16H, Win 95, 1993-97, NL). A receiver operating characteristic operator curve analysis was also utilized to determine optimal cut points for other continuous variables used for relative risk analysis.

First, analyses were completed to discern if mean (logged) values of the albumin excretion rate and the albumin:creatinine ratio were statistically significantly different between patients alive 1 year post acute myocardial infarction vs those who had died within that year. These analyses utilized the unpaired Student's t-test separately for each day upon which the albumin: creatinine ratio was measured, i.e. the first, third, and seventh days after admission, followed by an overall between-group repeated measure ANCOVA with Tukey post-hoc tests, wherein data from all 3 days of observation were simultaneously assessed. The covariates used in each comparison are reported in the results section. Student's t-test and chi-square tests for other continuous and all categorical variables, respectively, were completed to discern additional significant correlates of 1 year survival status.

Next, three (one for each day of the albumin: creatinine ratio accrual) survival analyses using Cox proportional hazard regression models were completed to assess significant predictors of proportions of patients surviving during the first year post acute myocardial infarction. All risk factors considered significant based on the univariate analysis, were entered into initial Cox models. These models were reduced by removing the variable causing the least change in significance. This procedure was continued until no further variables could be removed without producing a significant change of the model[14]. These final models were determined to be the 'parsimonious' models. The heart rate and Killip class assessed on the same day as the urinary albumin measurement were used in these models. Separate models for each day were developed using the albumin: creatinine ratio as a continuous (logged) variable and as a categorical predictor based on the receiver operating characteristic curve analysis.

Relative risks of survival status were calculated for the albumin:creatinine ratio based on the two classes 'low' or 'high' albumin:creatinine ratio levels determined by receiver operating characteristic curve analysis. Survival curves, based on the dichotomized albumin:creatinine ratio levels were constructed by the Kaplan–Meier method and compared by log-rank test. Further, the relative odds of the categorized albumin:creatinine ratio levels, adjusted for other predictors in the models, and corresponding two-sided 95% confidence intervals were derived from the regression coefficients in the Cox models.

The positive predictive value was calculated as the proportion of patients with a positive test who died and the negative predictive value as the proportion of patients with a negative test who survived. The accuracy of the test was calculated as the proportion of patients correctly identified by the test.

Finally, analyses to discern the association between the albumin:creatinine ratio (logged) and other clinical variables were investigated. Variables found by preliminary bivariate correlation analysis to be associated with the albumin:creatinine ratio were entered as independent variables in forward stepwise multiple regression analysis, with the log-albumin:creatinine ratio as the dependent variable (minimum tolerance for entry into a model was set at 0·01; the α to enter or to remove was set at 0·15).

Data are presented as mean ± SD for continuous measures, unless otherwise specified and as a proportion for patients with a characteristic for categorical variables. All P are two-tailed and statistical significance was established as $P<0·05$.

Results

1-year mortality

During the year of follow-up, 77 (17·8%) patients (34 men and 43 women) died. Causes of death were reinfarction in seven subjects, stroke in six, heart failure or

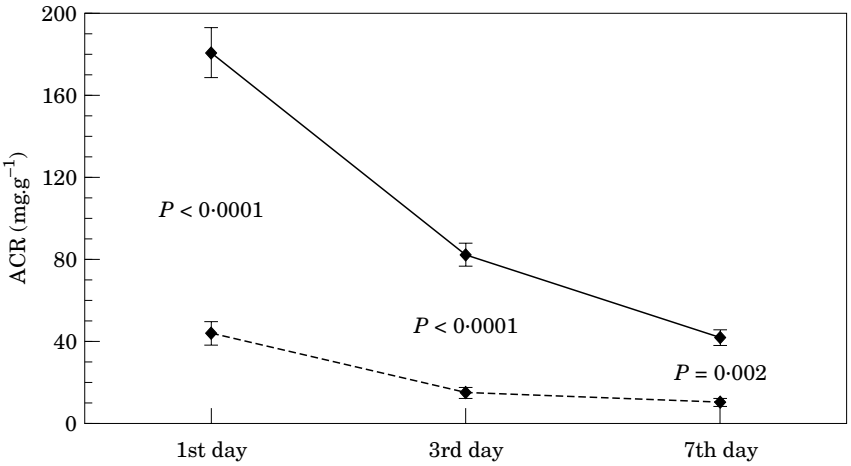

Figure 1 **Urinary albumin:creatinine ratios measured on the first, third, and seventh days after admission to hospital for myocardial infarction. Data of 77 patients who died (——) during the year of follow-up and 355 survivors (– – –) were compared by repeated-measure ANCOVA adjusting for age, gender, presence of diabetes, creatine-kinase-MB peak, heart failure, ACE-inhibitor and thrombolytic therapy (*P* for ANCOVA <0·0001). Values are means and error bars indicate SEM. ACR = albumin:creatinine ratio.**

cardiogenic shock in 25, sudden death in 18, other cardiovascular causes in 15, and non-cardiovascular causes in six.

The albumin:creatinine ratio throughout the first week after admission was much higher in the patients who died than in those who survived (Fig. 1). A similar difference was found for deaths from cardiovascular causes.

Since the albumin:creatinine ratio appeared to be a dynamic process with highest values on the first day and lowest ones on the seventh day, to identify subjects with a 'high' albumin:creatinine ratio, different cut-offs were chosen for the 3 days of the study. Using receiver operating characteristic curve analysis the albumin: creatinine ratio cut-off value that best discriminated between the patients prone to death and survivors approximated to 50 mg . g^{-1} on the first day, 30 mg . g^{-1} on the third day, and 20 mg . g^{-1} on the seventh day after admission.

By dividing the 77 patients who died according to whether they had an albumin:creatinine ratio above or below the specified cut-off points, the mortality rate turned out to be higher ($P<0·0001$ for all days) in the patients with a high albumin:creatinine ratio level throughout the first week after the acute myocardial infarction (Table 2). Similar results were obtained

Table 2 One year all-cause mortality rate and relative risks in the patients divided according to the albumin:creatinine ratio levels on the first, third and seventh days after admission to hospital

	Mortality rate		Relative risks		
1st day data	ACR<50 (n=295)	ACR≥0 (n=137)	Unadjusted RR (95%CI)	Adjusted (model 1) RR (95%CI)	Adjusted (model 2) RR (95%CI)
Alive, n (%)	271 (92)	84 (61)			
One-year mortality rate, n (%)	24 (8)	53 (39)	5·9 (3·7–9·7)	3·6 (2·1–6·2)	3·7 (2·0–7·0)
3rd day data	ACR<30 (n=333)	ACR≥30 (n=99)			
Alive, n (%)	307 (92)	48 (49)			
1-year mortality rate, n (%)	26 (8)	51 (51)	9·0 (5·7–14·7)	4·9 (2·9–8·2)	5·4 (2·9–10·3)
7th day data	ACR<20 (n=315)	ACR≥20 (n=70)			
Alive, n (%)	287 (91)	35 (50)			
One-year mortality rate, n (%)	28 (9)	35 (50)	7·6 (4·6–12·7)	4·0 (2·3–6·8)	4·1 (2·1–7·8)

Pearson chi-square=60·0, $P<0·0001$, chi-square=99·5, $P<0·0001$, chi-square=70·7, $P<0·0001$ for 1st, 3rd and 7th days, respectively.
ACR=albumin:creatinine ratio.
RR=relative risks and 95% confidence intervals. Model 1: adjusted for the same variables used in the Cox model (age, diabetes, history of angina, CK-MB peak, Killip class, heart rate, thrombolysis), n=432.
Model 2: adjusted for the same variables as in model 1 and for echocardiographic left ventricular ejection fraction (≥40% or <40%), n=316.

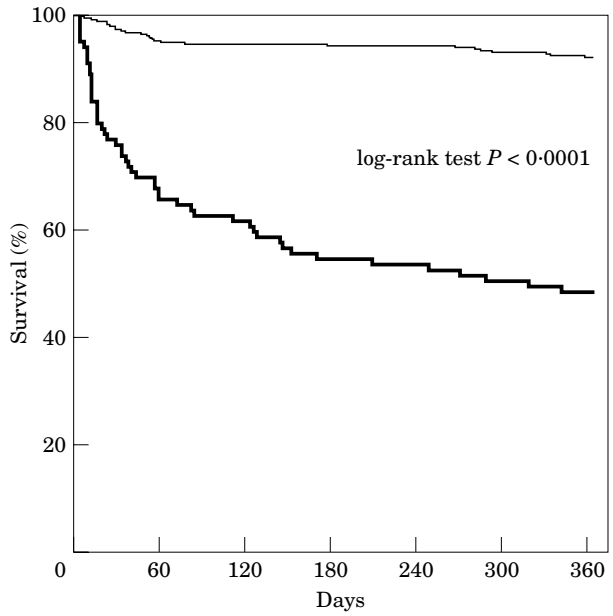

Figure 2 **Kaplan–Meier estimates of the probability of 1-year all-cause mortality in the patients stratified by urinary albumin:creatinine ratio ≥ 30 mg . g^{-1} or <30 mg . g^{-1} on the third day after admission (P for log-rank test <0·0001). ACR = albumin:creatinine ratio. ——= albumin:creatinine ratio <30 mg . g^{-1} (n=333); ——= albumin:creatinine ratio ≥ 30 mg . g^{-1} (n=99).**

using the albumin excretion rate instead of the albumin: creatinine ratio ($P<0·0001$ for all days).

Survival analysis

Kaplan–Meier curves relating to the third day of the albumin:creatinine ratio are shown in Fig. 2. The mortality rate was much higher in the subjects with an albumin:creatinine ratio ≥ 30 mg . g^{-1} than in those <30 mg . g^{-1} (log-rank test chi-square=121·3, $P<0·0001$). Similar patterns were observed for the first day and seventh days' data (chi-square=67·0, $P<0·0001$, and chi-square=87·7, $P<0·0001$, respectively).

Possible predictors of 1-year mortality were examined in a series of Cox proportional hazards univariate regression analyses (Table 3). Predictors found significant by these univariate analyses were entered into three separate multivariate Cox models for the three days of the albumin:creatinine ratio measurement. The albumin: creatinine ratio was closely associated to global mortality in all regressions, and in the third day's model it emerged as the strongest predictor of death (chi-square=27·5, $P<0·0001$). The predictive power of the albumin:creatinine ratio for mortality (chi-square=27·1, $P<0·0001$) was also greater than that of Killip class and creatine-kinase-MB in the first day's measurement, while it declined in the seventh day's measurement (chi-square=9·9, $P=0·001$). Similar associations were found for the albumin:creatinine ratio and mortality from cardiovascular causes. When the same analysis was repeated in the subset of 316 subjects with an echocardiographic left ventricular ejection fraction, the albumin:creatinine ratio remained the strongest correlate of mortality for the third day's measurement (Table 4). Virtually no change in the predictive power of the albumin:creatinine ratio was observed using actual blood pressure (as continuous variable) instead of history of hypertension in the Cox models.

The predictive power of the albumin:creatinine ratio for total mortality was significant both in men and women, and in subjects with or without diabetes, clinical or echocardiographic signs of heart failure, or thrombolytic treatment (Table 5).

Among the 150 patients in whom hormones and inflammatory markers were measured, renin and aldosterone on the first day ($P=0·005$ and $P<0·0001$, respectively) and third day ($P=0·01$ and $P<0·0001$, respectively) were significant predictos of mortality at univariate analysis. c-reactive protein and neutrophils were strong univariate predictors of mortality when measured on the third and seventh days ($P<0·0001$ for all). In the multivariate Cox model, the albumin: creatinine ratio also remained the strongest predictor of

Table 3 Univariate predictors of 1-year all-cause mortality at Cox analysis

Variables	Chi-square value	*P* value
ACR (mg . g^{-1})		
1st day	78·8	<0·0001
3rd day	104·5	<0·0001
7th day	51·3	<0·0001
Age (years)	82·3	<0·0001
Killip class		
1st day	68·2	<0·0001
3rd day	75·0	<0·0001
7th day	38·2	<0·0001
Heart rate		
1st day	32·9	<0·0001
3rd day	37·6	<0·0001
7th day	36·5	<0·0001
Gender (females)	26·9	<0·0001
Diabetes mellitus	23·1	<0·0001
Atrial fibrillation	21·8	<0·0001
Current smoking	14·2	<0·0001
CK-MB peak	10·3	0·001
AST peak	8·7	0·003
Pre-existing hypertension	8·5	0·003
Arrhythmias	7·2	0·007
History of angina	6·9	0·008
Anterior site of AMI	4·8	0·02
LVEF% (n=316)	51·7	<0·0001
Thrombolysis (negative fashon)	23·3	<0·0001
Beta-blockers (negative fashion)	25·0	<0·0001
ACE-inhibitors	8·3	0·003

ACR = albumin:creatinine ratio.
CK-MB = MB isoenzyme of creatine kinase.
AST = aspartate aminotransferase.
LVEF = left ventricular ejection fraction.
Blood pressure, body mass index, and history of myocardial infarction were unrelated to mortality.

Table 4 Cox proportional hazards models for all-cause 1-year mortality in the patients with left ventricular ejection fraction (n=316)

Independent variables	1st day ACR assessment			3rd day ACR assessment			7th day ACR assessment		
	Regression coefficient ± SE	Chi-square value	*P* value	Regression coefficient ± SE	Chi-square value	*P* value	Regression coefficient ± SE	Chi-square value	*P* value
ACR	0·56 ± 0·12	23·9	<0·0001	0·68 ± 0·13	30·4	<0·0001	0·25 ± 0·11	5·3	0·02
Age	0·08 ± 0·02	23·0	<0·0001	0·05 ± 0·02	8·2	0·004	0·07 ± 0·02	12·5	0·0004
LVEF (%)	− 0·04 ± 0·01	10·7	0·001	− 0·04 ± 0·01	12·1	0·0005	− 0·04 ± 0·01	11·0	0·0009
History of angina	0·78 ± 0·29	6·7	0·009	0·82 ± 0·29	7·2	0·007			
CK-MB peak	0·01 ± 0·01	6·2	0·01	0·01 ± 0·01	8·3	0·003	0·01 ± 0·01	8·9	0·002
Thrombolysis	− 1·07 ± 0·45	6·7	0·009	− 1·18 ± 0·48	7·1	0·007	− 1·05 ± 0·52	4·7	0·02
Diabetes							0·85 ± 0·33	6·4	0·01
Atrial fibrillation							0·89 ± 0·34	6·0	0·01

ACR=albumin:creatinine ratio; LVEF=left ventricular ejection fraction; CK-MB=creatine phosphokinase-MB isoenzyme.

Table 5 Mortality rate and age-adjusted prediction of all-cause mortality in the patients divided by gender, presence or absence of diabetes, presence or absence of heart failure, left ventricular ejection fraction, and thrombolytic treatment

Subgroups	Deaths/All	1st day ACR assessment			3rd day ACR assessment			7th day ACR assessment		
		Regression coefficient ± SE	Chi-square value	*P* value	Regression coefficient ± SE	Chi-square value	*P* value	Regression coefficient ± SE	Chi-square value	*P* value
Males	34/302	1·65 ± 0·38	21·2	<0·0001	2·21 ± 0·36	37·3	<0·0001	2·10 ± 0·38	27·8	<0·0001
Females	43/130	1·40 ± 0·33	19·7	<0·0001	1·25 ± 0·34	15·3	<0·0001	1·13 ± 0·35	10·4	0·002
Diabetes no	41/328	1·72 ± 0·34	28·3	<0·0001	2·39 ± 0·35	52·4	<0·0001	2·05 ± 0·35	32·3	<0·0001
Diabetes yes	36/104	0·87 ± 0·36	6·3	0·01	0·78 ± 0·36	5·0	0·02	0·94 ± 0·38	5·9	0·01
Heart failure no	18/263	1·26 ± 0·47	6·6	0·009	1·73 ± 0·48	11·1	0·0009	1·17 ± 0·60	3·1	0·07
Heart failure yes	59/169	1·24 ± 0·30	19·6	<0·0001	1·46 ± 0·30	27·6	<0·0001	1·41 ± 0·30	23·2	<0·0001
LVEF ≥40%	29/259	0·60 ± 0·14	20·5	<0·0001	0·58 ± 0·16	14·3	0·0002	0·31 ± 0·16	3·8	0·05
LVEF <40%	26/57	0·51 ± 0·20	7·3	0·007	0·74 ± 0·19	18·4	<0·0001	0·50 ± 0·16	11·0	0·0009
Thrombolysis no	66/271	1·33 ± 0·27	27·1	<0·0001	1·54 ± 0·27	36·0	<0·0001	1·45 ± 0·28	25·8	<0·0001
Thrombolysis yes	11/161	2·47 ± 0·78	13·9	0·0002	2·92 ± 0·68	20·8	<0·0001	2·48 ± 0·66	13·4	0·0003

ACR=albumin:creatinine ratio; LVEF=left ventricular ejection fraction.

Table 6 Results of simple and multivariable linear regressions for hormones and inflammatory markers as independent variables vs albumin:creatinine ratio as dependent variable during the first week of hospitaziation in 150 acute myocardial infarction patients. Other variables included in the multivariable models were age, gender, Killip class, blood pressure, presence of diabetes mellitus, thrombolytic therapy, and ACE inhibitor therapy

Variable	1st day		3rd day		7th day	
	Univariate	Multivariable	Univariate	Multivariable	Univariate	Multivariable
Renin (pg . ml^{-1})	r=0·16		r=0·11		r=0·01	
	P=0·04		ns		ns	
Aldosterone	r=0·30	T=3·2	r=0·29		r=0·01	
	P<0·0001	P=0·001	P<0·0001		ns	
Neutrophils	r=0·19		r=0·39	T=2·8	r=0·45	T=3·0
	P=0·02		P<0·0001	P=0·006	P<0·0001	P=0·003
C-reactive protein	r=0·07		r=0·27		r=0·36	T=2·2
	ns		P=0·001		P<0·0001	P=0·03
Erythrocyte sedimentation rate	r=0·01		r=0·19		r=0·23	
	ns		P=0·02		P=0·01	

Blank spaces mean that the variable was rejected by the regression model.

mortality in this subset of patients (P<0·001 for all days), and only aldosterone provided significant additional prognostic information for all days (P<0·01). Among the inflammatory markers, C-reactive protein measured on the third day (P=0·004) was the only independent predictor of outcome.

Relative risks

Unadjusted and adjusted relative risks for all-cause mortality are reported in Table 2. Relative risks were adjusted for the same variables used in the Cox analyses (model 1). In model 2, the echocardiographic left ventricular ejection fraction (≥40% or <40%) was also included (Table 2). In the multivariable analysis, the albumin:creatinine ratio showed the highest relative risk for global mortality in all three days of the study, as compared to the other dichotomized variables of the Cox models, regardless of whether Killip class or left ventricular ejection fraction was used in the models. Unadjusted relative risks for cardiovascular mortality (n=71) were 6·0 (95% CI, 3·7–10·1) for the first day's albumin:creatinine ratio, 9·7 (95% CI, 5·9–16·2) for the third day's albumin:creatinine ratio, and 8·2 (95% CI, 4·9–14·0) for the seventh day's albumin:creatinine ratio, and adjusted relative risks for model 1 were 3·4 (95% CI, 2·0–5·9), 5·0 (95% CI, 3·0–8·8) and 4·3 (95% CI, 2·4–7·5), respectively.

The predictive value of a positive test was 39% for the first day's albumin:creatinine ratio, 51% for the third day's albumin:creatinine ratio, and 50% for the seventh day's albumin:creatinine ratio, and the predictive value of a negative test was 92%, 92%, and 91%, respectively. The accuracy of the test was 75% for first day's albumin:creatinine ratio, 83% for third day's albumin: creatinine ratio, and 84% for seventh day's albumin: creatinine ratio. Taking into account subjects with the three albumin:creatinine ratio measurements above the respective cut-off, the positive predictive value rose to 65% while the negative predictive value virtually did not change (90%). The accuracy of the test increased to 87%. Since uncomplicated acute myocardial infarction patients are usually discharged before the seventh day after admission to hospital, the above values were calculated also for first and third day data. The predictive value of a positive test at both measurements was 59%, and the negative predictive value 91%. Accuracy was 85%. Left ventricular ejection fraction yielded lower positive and negative predictive values than the albumin: creatinine ratio (47·3% and 88·1%, respectively) with an accuracy of 81·0%.

Predictors of the albumin:creatinine ratio

Renin was $35{\cdot}6 \pm 5{\cdot}2$, $22{\cdot}0 \pm 2{\cdot}5$, and $29{\cdot}8 \pm 3{\cdot}5$ pg . ml^{-1} on the first, third and seventh days after admission, respectively. The corresponding values were $141{\cdot}6 \pm 13{\cdot}8$, $59{\cdot}8 \pm 5{\cdot}8$, and $73{\cdot}6 \pm 5{\cdot}7$ pg . ml^{-1} for aldosterone; 8169 ± 267, 5715 ± 203, and 4281 ± 170 per mm^3 for neuthophils; $1{\cdot}7 \pm 0{\cdot}2$, $4{\cdot}2 \pm 0{\cdot}3$, and $1{\cdot}9 \pm 0{\cdot}2$ mg . dl^{-1} for C-reactive protein; 23 ± 2, 39 ± 2, and 51 ± 3 mm . h^{-1} for erythrocyte sedimentation rate. On the first day, the albumin:creatinine ratio showed a weak correlation with renin in univariate analysis and a close correlation with aldosterone in both univariate and multivariate regressions (Table 6). On the third day, aldosterone was still correlated with the albumin: creatinine ratio in univariate but not multivariate analysis. No correlation between the albumin:creatinine ratio and hormones was found on the seventh day. The relationship between the albumin:creatinine ratio and inflammatory markers was weak on the first day, became stronger on the third day, and was maximal on the seventh day when all markers correlated with the albumin:creatinine ratio in univariate analyses. On

the seventh day, C-reactive protein and neutrophils correlated with the albumin:creatinine ratio also in the multivariate regression.

Discussion

Identification of patients at high risk of mortality represents one of the most challenging issues in acute myocardial infarction patients' care, and multiple clinical variables have been proposed to improve the assessment of the patient in this clinical setting[1–4,15,16]. However, due to poor sensitivity and specificity, many have not gained widespread clinical acceptance.

Urinary albumin excretion has not gained much attention in the setting of myocardial infarctional, though it has been shown to increase dramatically in the first days following acute myocardial infarction[5–7]. Our study is the first to examine the additional prognostic information provided by microalbuminuria for 1-year mortality over that already available from clinical and instrumental findings in patients with acute myocardial infarction and demonstrates that, in survivors of myocardial infarction, the albumin:creatinine ratio on repeat examinations after admission to hospital, is independently associated with increased long-term risk of cardiovascular and total mortality.

Albumin:creatinine ratio and mortality risk after acute myocardial infarction

Patients with a high albumin:creatinine ratio had a 3·6 to 4·9 increased risk of total mortality and a 3·4 to 5·0 increased risk of cardiovascular mortality for the three albumin:creatinine ratio measurements. Cox analysis showed a greater predictive power for the albumin: creatinine ratio measured on the first and the third day after admission than for an albumin:creatinine ratio measured on the seventh day, when the albumin: creatinine ratio tends to return to baseline level[7]. Some 40% of patients with an albumin:creatinine ratio $\geq$ 50 mg . g^{-1} on the first day and 50% with an albumin: creatinine ratio $\geq$ 30 mg . g^{-1} on the third day died during the year of follow-up. Conversely, only 8% of patients with an albumin:creatinine ratio below those values died during the year of observation.

The prognosis of patients with acute myocardial infarction is based on a synthesis of several indicators, such as clinical history, objective findings, laboratory data, and other investigations. In the present study, the albumin:creatinine ratio retained a statistically significant power for the prediction of death independent of other demographic, clinical, laboratory, and left ventricular scan variables. In particular, the albumin: creatinine ratio measured on the third day after admission emerged as the most powerful independent predictor of death. A shortcoming of most studies, including the present one, is the necessary limit to the number of potential prognostic variables assessed. Many circulating factors have shown prognostic utility in subjects with acute myocardial infarction but none was a stronger predictor of mortality than clinical signs of congestive heart failure and decreased left ventricular ejection fraction[17–19], and in some studies clinical and biochemical variables such as Killip class, cardiac arrhythmias and serum enzymes were not taken into account in the multiple regressions[20].

Markers of inflammation and heart failure

In a subset of subjects we also took into account some widely used markers of inflammation and heart failure. Univariate analyses showed the expected associations[21,22] of these circulating factors with 1-year mortality rate, which for renin and aldosterone peaked on the first day, and for the inflammatory markers peaked on the seventh day. However, in the multivariate Cox model the predictive power of most humoral indices was outweighed by the albumin:creatinine ratio, which remained the strongest predictor of mortality throughout the week of hospital stay. Only aldosterone provided additional prognostic information for outcome over all days. These results indicate that urinary albumin represents a comprehensive marker of the pathophysiological changes which occur during acute myocardial infarction, reflecting both severity of inflammation and degree of heart failure.

Clinical applications

The strong association of the albumin:creatinine ratio with mortality was observed despite the heterogeneity of the group under study, being present in both genders, and in subgroups of subjects with and without heart failure, or thrombolytic therapy. Diabetes is a clinical condition frequently associated with microalbuminuria and it is known that diabetic patients have poorer prognosis in acute myocardial infarction[8,23]. However, in the present study microalbuminuria also remained a strong independent predictor of mortality when diabetes was included in the multivariable regression. Moreover, the predictive power of the albumin:creatinine ratio was found both among the subjects with and those without diabetes. Thus, since low-level urinary albumin may be easily measured during the hospital stay, the albumin: creatinine ratio may constitute a suitable method for an adequate assessment of outcome in patients with acute myocardial infarction. The albumin:creatinine ratio in the present study showed a remarkably high negative predictive power for mortality indicating that subjects with a low albumin:creatinine ratio can be treated conservatively. Conversely, subjects with a high albumin:creatinine ratio were found to be at increased risk but the positive predictive power of the test was lower. However, the positive predictive power of the

albumin:creatinine ratio increased when the ratio was high in all urine samples and was greater than that of left ventricular ejection fraction. These data suggest that a patient with a low albumin:creatinine ratio can be considered at low risk and no other urinary measurements are needed. If a high albumin:creatinine ratio value is found this should be confirmed by other measurements.

Mechanism of increased urinary albumin in myocardial infarction

Different theories have been postulated to explain the increase in the albumin excretion rate during acute myocardial infarction. Heart failure, which frequently accompanies acute myocardial infarction, appears as one of the most important causative factors[7,24,25]. However, the normal levels of renin and aldosterone recently found by our group in acute myocardial infarction patients with no signs of heart failure suggest that increased excretion of urinary albumin in these patients is not due to subtle degrees of heart failure[7]. Inflammation is another important feature of acute myocardial infarction[26–28] which could involve the renal vascular system, thereby increasing glomerular permeability and the leak of urinary albumin. The results of the present study indicate that these factors can concur in determining the level of the albumin:creatinine ratio during acute myocardial infarction. During the first days after acute myocardial infarction, heart failure seems to be the main determinant of urinary albumin, as shown by the good correlation of the albumin:creatinine ratio with aldosterone; inflammation seems to play the key role from the third day. However, the loss of the relationship between hormones and albumin:creatinine ratio on the seventh day may be due to changes in renin and aldosterone induced by ACE-inhibitor or beta-blocker therapies.

Conclusions

The present results show that an early increase of urinary albumin is a strong independent predictor of adverse clinical outcome in both men and women with acute myocardial infarction. The albumin:creatinine ratio proved to be a better predictor for a poor long-term prognosis than established risk factors for mortality. It follows that stratification of patients into low- and high-risk groups can be facilitated by the albumin:creatinine ratio. On the basis of these results, we suggest that this measurement be included in the routine clinical work up of the patient with acute myocardial infarction.

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