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Microalbuminuria during acute coronary syndrome: Association with 22-year mortality and causes of death. The ABC-8* study on heart disease. (*ABC is an acronym for Adria, Bassano, Conegliano, and Padova Hospitals)

Heba T. Mahmoud [a,d,1], Giuseppe Berton [a,b,*,1], Rocco Cordiano [a,c,1], Rosa Palmieri [a,c,1], Stefania Petucco [a,e,1], Francnesco Bagato [a,b]

[a] The ABC Heart Disease Foundation-ONLUS, Conegliano, Italy
[b] Department of Cardiology, Conegliano General Hospital, Conegliano, Italy
[c] Department of Internal Medicine and Cardiology, Adria General Hospital, Adria, Italy
[d] Department of Cardiology, Minia University, Minia, Egypt
[e] Local Social Health Unit 7 (ULSS7), Vicenza, Italy

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ABSTRACT

Background: Microalbuminuria is associated with adverse outcomes in acute coronary syndrome (ACS) patients.
Methods: To evaluate the very long-term association between Microalbuminuria and the overall mortality and causes of death in this clinical setting, we prospectively studied 579 unselected ACS patients admitted to three hospitals. The baseline albumin-to-creatinine ratio (ACR) was measured on days 1, 3, and 7 in 24-h urine samples. Patients were followed for 22 years or until death.
Results: Virtually all patients completed follow-up; 449(78%) had died: 41% due to non-sudden cardiac death (non-SCD), 19% sudden cardiac death (SCD), 40% due to non-cardiac (non-CD) death.
Using unadjusted Cox regression analysis, ACR was a significant predictor of all-cause mortality (hazard ratio [HR] 1.26;95%confidence interval [CI] 1.22–1.31; p<0.0001) and the three causes of death (HR 1.40;95%CI 1.32–1.48; p<0.0001), (HR 1.22;95%CI 1.12–1.32; p<0.0001) and (HR 1.16;95%CI 1.09–1.23; p<0.0001) for non-SCD, SCD and non-CD respectively.
Using a fully adjusted model, ACR was a significant independent predictor of all-cause mortality (HR 1.12; 95% CI 1.08–1.16; p<0.0001) and only non-SCD (HR 1.21; 95%CI 1.14–1.29; p<0.0001).
There was a positive interaction between ACR level and history of AMI (HR 1.15; 95%CI 1.03–1.29; $p = 0.01$) and the presence of heart failure at admission (HR 1.11; 95%CI 1.01–1.24; $p = 0.04$), and negative interaction with higher than median LVEF (HR 0.89; 95%CI 0.80–0.99; $p = 0.03$) for all-cause mortality at the multivariable level.
Conclusion: Based on the present analysis, baseline urinary albumin excretion during ACS is a strong independent predictor of the very long-term mortality risk, chiefly due to non-sudden cardiac death.

1. Introduction

Urinary albumin excretion is one of the earliest biomarkers of kidney injury that reflects an endothelial dysfunction with increased glomerular permeability, and it has been independently associated with short- and long-term adverse outcomes in general populations, patients with and without diabetes or hypertension, and people at high risk for cardiovascular disease [1–4].

A sharp increase in albumin excretion rate during acute myocardial infarction (AMI) has been documented in several reports; results from our group and others showed that urinary albumin excretion is associated with increased risk for short and long-term mortality in patients with acute coronary syndrome (ACS) [5–11].

In the present prospective study, we examined the prognostic value of baseline urinary albumin excretion for mortality and causes of death in the ABC study patients discharged alive and followed for 22 years

* Corresponding author at: ABC Study on Heart Disease Foundation-ONLUS, Ospedale de Gironcoli, 4th floor, Via Daniele Manin, 110, 31015 Conegliano, TV, Italy.
E-mail address: giubeste@gmail.com (G. Berton).
[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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after index hospitalization with ACS. In addition, as virtually all previous studies examined the cardiovascular modes of death as a composite outcome, we also investigated whether albumin excretion has a different predictive value for sudden and non-sudden cardiac death.

2. Methods

2.1. Patients

The ABC Study on Heart Disease (http://www.abcheartdiseasestudy.org/en/) is an ongoing prospective study. It was designed to investigate an unbiased ACS patient population. Specifically, the study includes Caucasian patients admitted between June 1995 and January 1998 to intensive care units at three general hospitals in Italy's Veneto region for unstable angina, non-ST elevation myocardial infarction (NSTEMI), or ST-elevation myocardial infarction (STEMI). The aims of the ABC Study were (1) long-term follow-up regarding both fatal and non-fatal events and (2) evaluation of the prognostic value of several clinical variables at baseline. The criteria for a diagnosis of ACS are based on the clinical presentation and electrocardiography, as well as the presence of biochemical markers of necrosis in the patient's serum [5,6].

Of the 741consecutive unselected patients who were considered eligible at the time of admission, the study excluded 84 patients for having other diseases than ACS, 10 patients for having primary renal disease, urinary tract infections or other concomitant clinical situations that could affect urinary albumin excretion, and 23 due to missing baseline data. Forty-five of the remaining 624 patients died during the index hospitalization, leaving 579 patients in the post-discharge follow-up for whom the final analysis was performed (Supplementary Fig. 1). Data were anonymised through codes, and the study data did not include personal data or identifiers. Written informed consent was obtained from all enrolled patients. The protocols were approved by the ethics committees at the participating hospitals and were carried out following the Declaration of Helsinki.

2.2. Measurements

A thorough medical history was collected from the patient's medical records, as well as patient interviews, at the time of enrolment. Clinical and laboratory data to be analysed at baseline were obtained during the first week of the patient's hospitalization. The diagnosis of ACS was based on the presence of at least two of the following criteria: typical changes in serum enzymes (e.g., total creatine kinase (CK) and creatine kinase MB (CK-MB)), typical electrocardiogram changes (i.e., localized ST-T changes and/or pathological Q waves in at least two contiguous leads), and central chest pain lasting >30 min [12]. The details of the measured variables have been described in detail elsewhere [5,6,13]

2.3. Baseline albumin excretion rate measurement

Three 24-h urine collections, on the 1st, 3rd, and 7th days of admission, were performed under the supervision of trained nurses to minimize errors in diuresis measurement. After collection, the volumes were measured, and urine specimens were frozen (−20 °C) and sent to the University of Padova. Albumin was measured by radioimmunoassay, using a Human ALB. KIT-double antibody (Techno Genetics, Cassina De' Pecchi, Milan, Italy) [14,15]. For each 24-h urine sample, urinary creatinine was measured using the Jaffe method [16]. The albumin excretion rate was expressed as the ratio of urinary albumin (mg/dL) to creatinine (g/dL), (ACR (mg/g)). Standard urinalysis was performed at the time of urinary sample collection.

2.4. Follow-up and endpoints

Clinical check-ups were done for each patient 1, 3, 5, 7, 10, 12, 15, 17, 20, and 22 years after enrolment. Two cardiologists at each hospital monitored the patient cohort throughout the follow-up period. The sources of data were the public healthcare administration, family doctors, hospital records, scheduled examinations, medication records from the index hospitalization and follow-up visits, post-mortem examinations, and death certificates. All post-enrolment data were recorded prospectively according to the ABC Study on Heart Disease protocol [5]. Two different data sheets were used to record baseline and follow-up data, which were merged after the follow-up was completed.

The primary endpoint was all-cause mortality. Secondary endpoints were causes of death. They were classified as non-sudden cardiac death (non-SCD), sudden cardiac death (SCD), and non-cardiac death non-CD death. SCD was defined as out-of-hospital, witnessed cardiac arrest or death within 1 h of the onset of acute symptoms or unexpected, unwitnessed death (e.g. during sleep) in patients who were known to have been well in the previous 24 h [17]. All other cardiac deaths, including heart failure with the progression of congestive symptoms or pulmonary oedema or cardiogenic shock, were classified as non-SCD deaths. Causes of death were classified by 2 doctors blinded to baseline information.

2.5. Statistical analysis

Data were analysed as continuous variables or proportions. To correct for positively skewed distributions, log transforms were used as appropriate. The baseline ACR was analysed as a continuous variable, and as quartiles using the repeated measures data, the long format, of the three days measurements. For continuous variables, comparisons between groups were made using the unpaired Student's *t*-test and age-gender adjusted repeated measures ANCOVA. We analysed categorical variables using Pearson's chi-square test. The data of patients who dropped out before the end of the follow-up period were censored at that time.

We estimated the risk of death and cause-specific mortality using non-adjusted, age-gender adjusted and fully adjusted Cox regression. All variables considered significant based on univariable Cox analyses and/or believed to be of prognostic importance were entered into the initial (baseline) multivariable Cox model. This model was reduced by removing each variable that was non-significant and/or causing the least change in the significance. This procedure was continued until no further variables could be removed without producing a significant change in the model [18]. These final models were determined to be the "parsimonious" multivariable models. The following variables were included in the final fully adjusted models: age, gender, smoking, diabetes mellitus, hypertension, history of infarction, presence of heart failure at admission, and plasma total cholesterol level. We used Schoenfeld residuals with 95% confidence intervals (CIs) to test the proportionality assumption and quantified the risk estimates as hazard ratios (HRs). All cox survival regressions were performed on the reshaped (long) data considering the time-varying effects of independent variables on survival [19]. Survival curves were constructed using the cumulative hazard method. Relative risks were derived from Cox regression models. We also performed a Cox survival regression including a formal interaction term for death risk between ACR and several factors in fully adjusted models to study effect modification. To graphically show ACR quartiles HR ratios for all-cause mortality across the classes of different variables, marginal analysis was used. Categorical variables were summarized as numbers and percentages and continuous variables as the medians and interquartile ranges. Two-tailed $p < 0.05$ was considered significant. The software STATA 14 (College Station, Texas, USA) was used for all statistical analyses.

3. Results

3.1. Patients' characteristics and causes of death

All enrolled patients completed the follow-up unless pre-empted by

Table 1
Baseline characteristics according to patients' survival status at the end of 22 years of follow-up.

Variable	Overall Population	Surviving patients	Dead patients	*P* values
	(*n* = 579)	(*n* = 130)	(*n* = 449)	
Demographics and clinical data				
Age, yrs.	67 (58–74)	54 (48–60)	70 (63–76)	<0.0001
Females	29	15	33	<0.0001
Body mass index, kg/m^2*	26(24–28)	26(25–29)	25(24–28)	0.01
Current smokers	37	52	33	<0.0001
Education higher than primary school	26	42	21	<0.0001
Hypertension	47	35	50	0.002
Diabetes mellitus	22	8	26	<0.0001
History of angina	25	15	28	0.002
History of myocardial infarction	24	14	27	0.002
In-hospital characteristics				
Prehospital time delay, min* (*n* = 487)	185 (125–545)	145 (105–250)	245 (125–580)	0.0008
Systolic blood pressure, mmHg	122 (112−130)	119 (108–128)	125 (112–127)	0.06
Diastolic blood pressure, mmHg	80(70–80)	75(70–80)	80(70–80)	0.21
Heart rate, beats/min	70(60–82)	69(60–79)	72(62–83)	0.0002
Q wave myocardial infarction	61	65	60	0.3
Killip > 1†	33	10	40	<0.0001
Left ventricular ejection fraction, %	52(45–62)	59(51–66)	50(43–60)	<0.0001
Presence of arrhythmia†‡	25	23	25	0.59
Atrial fibrillation/ flutter†	10	2	13	0.001
Thrombolysis†	35	52	30	<0.0001
Laboratory data				
Creatine kinase peak, U/L*	826 (353–1619)	1058(325-1700)	766 (360–1596)	0.74
Creatine kinase-MB peak, U/L*	102(43–203)	117(42-231)	99(43–200)	0.82
LDH peak, U/L*	843 (512–1387)	778(473-1258)	861 (517–1404)	0.14
Haemoglobin, g/L	14(1315)	14(13–15)	14(12–15)	0.08
Blood glucose, mg/dL	119 (100–158)	117 (100–144)	121 (100–171)	0.004
Total cholesterol, mg/dL*	208 (179–243)	215(185-248)	206 (176–239)	0.03
Kidney and endothelial function				
Serum creatinine, mg/dL	1.0(0.8–1.1)	0.9 (0.8–1.0)	1.0(0.9–1.2)	<0.0001
eGFR (mL/min x 1.73 m^2) *	73(54–92)	90(70-116)	68(52–90)	<0.0001
ACR, (mg/g) *	18.1 (6.6–52.0)	10.3 (3.6–25.0)	20.6 (7.5–63.4)	<0.0001
Follow-up treatment§				
PTCA/CABG	36	68	26	<0.0001
Antiplatelet	88	98	85	<0.0001
Beta-blockers	53	83	44	<0.0001
ACEIs	68	72	67	0.31
Statin	47	90	35	<0.0001

Data are presented as median (interquartile range) or percentages.
ACR = Urinary albumin-to-creatinine excretion ratio**; ACEIs** = Angiotensin-converting enzyme inhibitors; **eGFR** = Estimated glomerular filtration rate calculated using the Modification of Diet in Renal Disease formula; **LDH** = lactate dehydrogenase-1 isoenzyme; **PTCA/CABG** = percutaneous transluminal coronary angioplasty/ Coronary artery bypass grafting.
* *P* values were calculated using Log-transformed data.
† During the first 7 days of hospital stay.
‡ Tachy- and bradyarrhythmias, excluding *peri* thrombolytic period.
§ At any time during follow-up.

death, except three patients for whom survival time was censored before 22 years; two withdrew consent and one moved overseas. At the end of the follow-up, 449(78%) of the patients discharged alive had died, and the entire sample represented 6756 person-years of follow-up. Among the deceased patients, 182 (41%) patients died from non-SCD, 88 (19%) patients died from SCD, and 179 (40%) patients died from non-CD causes (Supplementary Fig. 1).

The median (IQ) time to death was 7.7 (2.7–14.5) years for all-cause mortality, 5.8 (1.9–12.4) years for non-SCD, 3.7 (1.1–9.7) years for SCD, and 11.9 (6.0–17.2) years for non-CD. Table 1 shows the baseline features of the patients and the differences between the deceased and surviving patients at the end of the follow-up. Death was more frequently observed in older female patients. Most of the clinical characteristics were significantly different in dead patients compared with the survivors (Table 1).

3.2. The albumin/creatinine ratio

Throughout the first week after admission, ACR was consistently much higher in the patients who died during follow-up than in those who survived ($p = 0.008$, data were compared using an age-gender adjusted repeated-measure ANCOVA). A similar difference was found for deaths from non-SCD causes (Supplementary Fig. 2). As anticipated, the patients who died were also more likely to have lower eGFR (Table 1).

3.3. Survival and interaction analysis

Since the albumin excretion rate appeared to be a dynamic process with the highest values of ACR observed on the first day and the lowest ones on the seventh day, we used ACR quartiles (after longitudinal data rearrangement) to identify subjects with higher ACR values.

By stratifying the 449 patients who died according to the ACR quartiles, the cumulative hazard estimate curves shown in (Fig. 1) revealed that all-cause mortality non-SCD rates at the end of follow-up were significantly higher in patients with a baseline ACR > 75th percentile. The relative hazard post-estimate analysis also revealed the same significant positive trend between ACR levels and 22-year all-cause mortality and the non-SCD as well, and an insignificant positive trend for SCD and non-CD (Fig. 1).

The unadjusted and age-gender-adjusted Cox regression analysis revealed that ACR was a significant predictor of all-cause mortality and the three causes of death (Table 2). However, using a fully adjusted Cox regression model including baseline age, gender, smoking, diabetes mellitus, hypertension, history of infarction, presence of heart failure at admission, and plasma total cholesterol level as the potential confounding variables, ACR was a significant independent predictor of all-cause mortality and only non-SCD (Table 2). Similar results were obtained using a model where the variable presence of heart failure at admission was replaced by left ventricular ejection fraction (LVEF). Moreover, the results were the same even after adding the biochemical markers of necrosis (peak CK, CK-MB and LDH levels) to the previous model (HR = 1.11, 95%CI: 1.06–1.15; $p < 0.0001$), (HR = 1.19, 95%CI: 1.12–1.26; $p < 0.0001$), (HR = 1.04, 95%CI: 0.96–1.14; $p = 28$), and (HR = 1.06, 95%CI: 0.99–1.13; $p = 0.051$) for all-cause mortality, non-SCD, SCD and non-CD respectively. Nevertheless, expanding the first model to include eGFR and BMI, ACR remains a strong predictor of all-cause mortality (HR = 1.10, 95%CI: 1.06–1.14; $p < 0.0001$), and only non-SCD (HR = 1.17, 95%CI: 1.10–1.24; $p < 0.0001$) independently of kidney function.

Hence, a formal interaction term between ACR and several clinical variables was introduced into the survival models. This term revealed that ACR had a positive interaction with a history of AMI and the

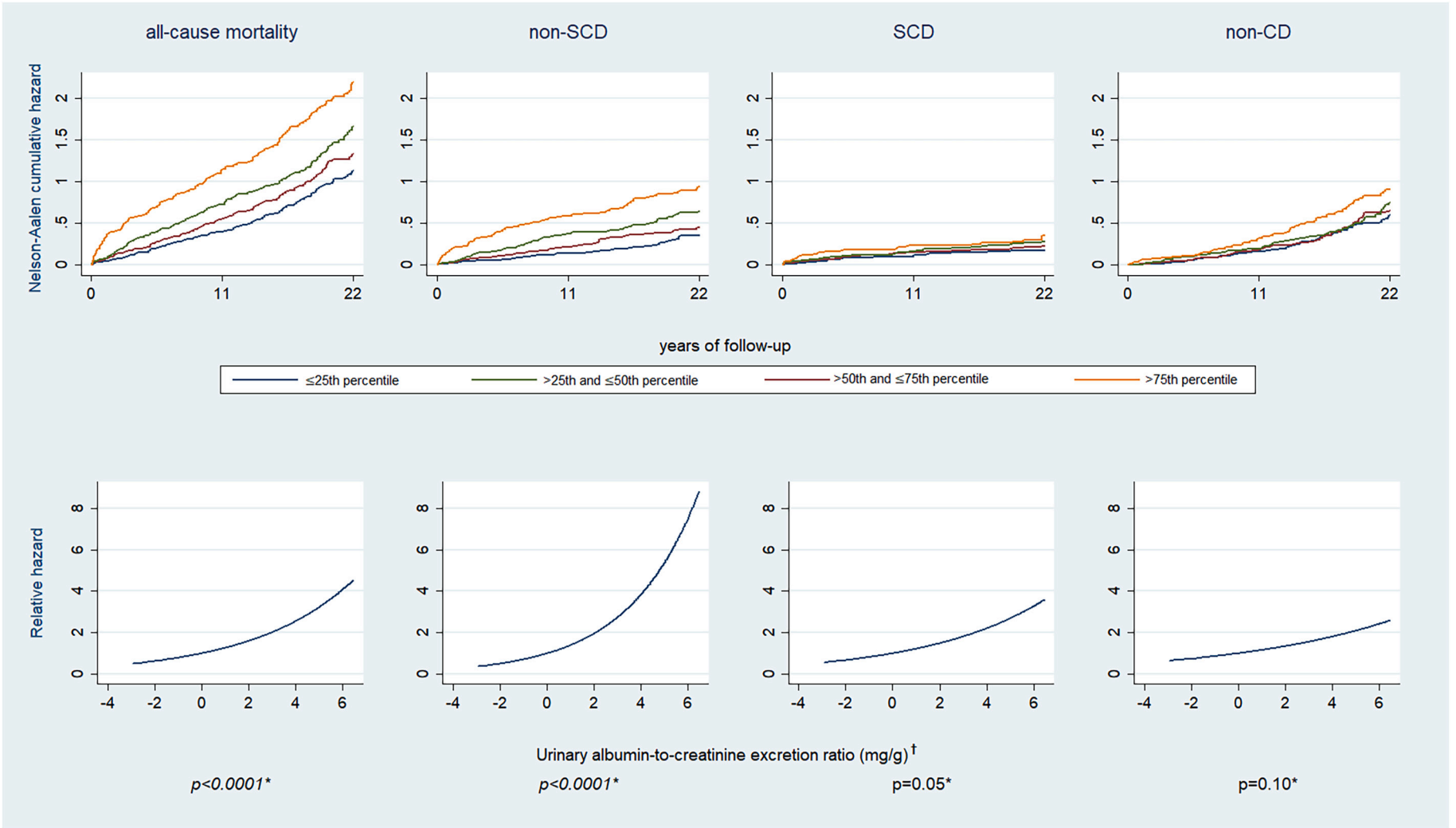

Fig. 1. Nelson-Aalen cumulative hazard and relative hazard estimates for all-cause and cause-specific mortality during 22 years of follow-up according to baseline ACR level.
ACR = Urinary albumin-to-creatinine excretion ratio (mg/g); **non-SCD** = non-sudden cardiac death; **non-CD** = non-cardiac death; **SCD** = sudden cardiac death.
† Analysis was done using log-transformed ACR.
* Values from the Cox regression analysis using a model adjusted for baseline age, gender, smoking, diabetes mellitus, hypertension, history of infarction, presence of heart failure at admission, and plasma total cholesterol level.

Table 2
Cox regression analysis for mortality risk by baseline ACR for all-cause mortality and main causes of death at the end of 22 years of follow-up.

	HR (95% CI)	z	*P* value
All-cause mortality			
Unadjusted ACR	1.26(1.22–1.31)	12.64	<0.0001†
Age-gender-adjusted ACR	1.16(1.12–1.20)	7.68	<0.0001†
fully adjusted ACR ‡	1.12(1.08–1.16)	5.91	<0.0001†
Interaction§,‡			
ACR*age	0.97(0.88–1.09)	−0.39	0.69
ACR*gender	0.91(0.82–1.02)	−1.65	0.1
ACR*smoking	1.04(0.94–1.16)	0.8	0.42
ACR*hypertension	0.99(0.90–1.09)	−0.23	0.82
ACR*total cholesterol	0.94(0.85–1.03)	−1.29	0.2
ACR*diabetes mellitus	1.03(0.92–1.16)	0.58	0.56
ACR*history of infarction	1.15(1.03–1.29)	2.53	0.01
ACR*heart failure at admission	1.11(1.01–1.24)	2.04	0.04
ACR*left ventricular ejection fraction	0.89(0.80–0.99)	−2.21	0.03
ACR*Antiplatelet	0.78(0.68–0.90)	−3.54	<0001
ACR*Beta-blockers	1.10(0.92–1.12)	0.24	0.67
ACR*ACEIs	1.05(0.95–1.17)	0.99	0.32
ACR*Statin	1.01(0.91–1.13)	0.30	0.76
Main causes of death			
non-SCD			
Unadjusted ACR	1.40(1.32–1.48)	11.54	<0.0001†
Age-gender-adjusted ACR	1.27(1.19–1.34)	7.88	<0.0001†
fully adjusted ACR ‡	1.21(1.14–1.29)	6.4	<0.0001†
SCD			
Unadjusted ACR	1.22(1.12–1.32)	4.81	<0.0001†
Age-gender-adjusted ACR	1.14(1.05–1.24)	3.22	0.001†
fully adjusted ACR ‡	1.09(1.00–1.18)	1.99	0.05†
non-CD			
Unadjusted ACR	1.16(1.09–1.23)	4.99	<0.0001†
Age-gender-adjusted ACR	1.07(1.00–1.13)	2.1	0.04†
fully adjusted ACR ‡	1.05(0.99–1.12)	1.63	0.10†

ACR = Urinary albumin-to-creatinine excretion ratio (mg/g); **CI** = confidence interval; **HR** = hazard ratio; **non-SCD** = non-sudden cardiac death; **non-CD** = non-cardiac death; **SCD** = sudden cardiac death.

† *P*-values were calculated using log-transformed data for ACR.

‡ The model is adjusted for baseline age, gender, smoking, diabetes mellitus, hypertension, history of infarction, presence of heart failure at admission, and plasma total cholesterol level.

§ For interaction analysis, quartiles of log-transformed ACR and 2 class variables for age, total cholesterol and left ventricular ejection fraction and the use of medications at any time during follow-up were used.

presence of heart failure at admission, and negative interaction with higher than median LVEF and the use of antiplatelets (aspirin and thienopyridine) at any time during follow-up for all-cause mortality at the univariate level. The interaction was tested in subsequent multivariable models after controlling for baseline age, gender, smoking, diabetes mellitus, hypertension, history of infarction, presence of heart failure at admission, and plasma total cholesterol level with almost the same results. (Table 2. Fig. 2).

4. Discussion

The present prospective study shows that baseline ACR is a strong independent predictor of 22-year adverse prognosis in patients who have sustained an ACS.

Urinary albumin excretion (albuminuria) is one of the earliest biomarkers of kidney injury that reflects an endothelial dysfunction with increased glomerular permeability, and it has been independently associated with short- and long-term adverse outcomes in general populations, patients with diabetes or hypertension, and people at high risk for cardiovascular disease [1–4,20].

Dynamic changes have been documented in urinary albumin excretion with peak albuminuria on the first day after ACS [21], and factors associated with albuminuria, such as obesity, diabetes and dyslipidaemia, co-vary with coronary artery disease [22,23]. Several studies have identified an association between microalbuminuria and mortality after ACS [7–11] even in the patients who were submitted to primary percutaneous coronary intervention [24]. Studies have also demonstrated that microalbuminuria significantly improved risk prediction beyond conventional predictors, including kidney function (e.g., estimated glomerular filtration rate (eGFR), and serum creatinine) [11,25,26]. Yet, albuminuria, a simple non-invasive bedside measurement, is seldom measured, especially not in emergency settings or unscheduled visits or hospitalizations [22].

This study represents an extension of our research that first demonstrated the association between baseline albumin excretion rate and early, intermediate, and long-term mortality after AMI [5,13,26,27], showing that baseline ACR kept its prognostic power up to 22 years after ACS independently of kidney function. Its predictive ability was chiefly related to non-SCD causes.

The pathophysiological linkage between microalbuminuria and poor outcome in patients after an ACS remains speculative, microalbuminuria may imply a vulnerability for atherosclerosis due to its correlation with inflammatory and prothrombotic changes involved in endothelial dysfunction [9,28].

Although, results from the current study partly contrast what was previously reported by Åkerblom et al. [29], where albuminuria in NSTE ACS patients was independently associated with 2-years overall mortality, but not with CV mortality. These differences could be attributed to the different methods used for albuminuria assessment. In the previously mentioned study, predefined measurement of albuminuria did not include a continuous measure or urinary creatinine; rather, albuminuria was captured by dipsticks, quantified, and reported as categorical values which may have decreased the power to detect an association of albuminuria. Nevertheless, dipstick albuminuria is known to be affected by urine concentration and pH and hence, ACR is considered an ideal measurement of kidney function (16) [23]. Furthermore, the timing of urine sampling, which was done on first-available urinary samples at the time of or after randomization, in relation to symptom onset may have affected albuminuria concentrations.

In contrast to our results also the results of Nazer et al. [30], where the independent predictive power of microalbuminuria for death 2 years after ACS patients was not significant. A potential explanation for these contras may be related to the study population characteristics since this upper mentioned post hoc study was based on data from a randomized clinical trial among selected patients for statin therapy versus placebo. Another explanation also includes the methodological differences as they measured urine albumin concentrations using a spot urine sample. Moreover, urine samples were obtained within 10 days after the onset of ACS and it could be hypothesized that albuminuria concentrations several days after the acute event may reflect the background or primary renal affection rather than the acute effects on endothelial or renal function. This hypothesis is supported by the non-significant changes in the patients' urine albumin concentration at the end of the study.

The examination of the causes of death could be useful for risk stratification and pathophysiological inferences. All the upper mentioned studies were concerned about overall and/or cardiovascular mortality [7–11,24,25]. They examined cardiovascular modes of death as a composite outcome. The present study showed that albumin excretion is strongly associated with all-cause mortality after ACS. Indeed, in the current results albumin excretion has been primarily associated with non-SCD, while no association with SCD and non-CD was observed which is consistent with our earlier results [31,32]. Albumin excretion is typically considered a marker of acute endothelial dysfunction during ACS, and it has been postulated that the degree of endothelial dysfunction might dictate different modes of death [33]. In fact, other studies documented that the extent and severity of coronary artery atherosclerosis, with the subsequent higher risk of adverse cardiac outcomes, were correlated with urinary albumin excretion [34,35]. Additionally, numerous previous studies have demonstrated associations of microalbuminuria with changes to cardiac structure and

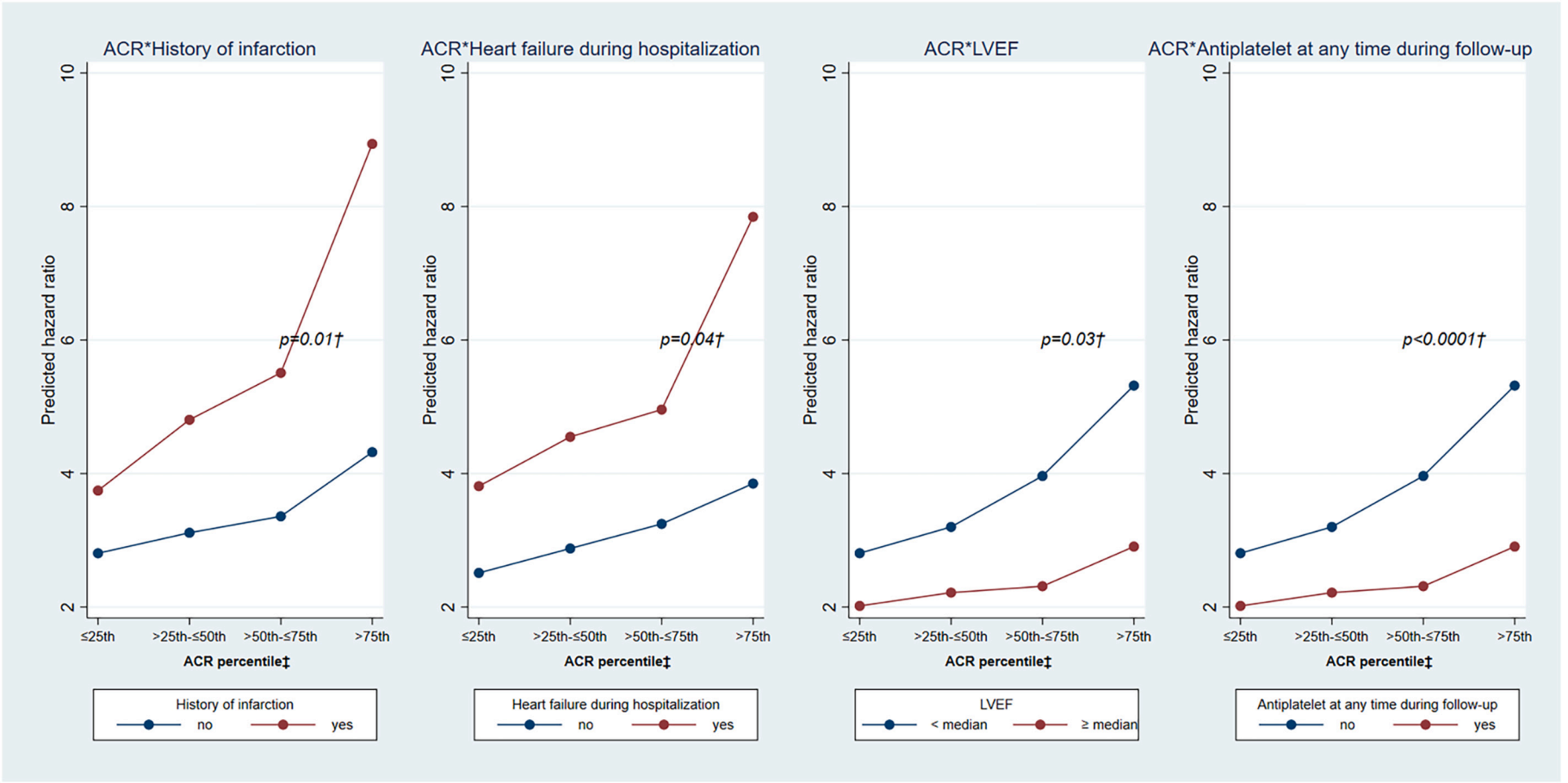

Fig. 2. Graphical representation of the interaction analysis showing the HRs for all-cause death of ACR quartiles across heart failure, history of infarction, 2 classes of LVEF and the use of antiplatelets at any time during follow-up in patients followed 22 years after ACS.

ACR = Urinary albumin-to-creatinine excretion ratio (mg/g); **HR** = hazard ratio; **LVEF** = left ventricular ejection fraction.

‡Log-transformed ACR values were used.

†Values from the fully adjusted Cox survival regressions, including a formal interaction term as in Table 2.

function including left ventricular (LV) systolic dysfunction, higher LV mass, and LV hypertrophy [36,37]. Studies have also documented that albuminuria is strongly linked to stroke risk [38]. Deo et al., reported that ACR predicts an increase in SCD risk in the general population, however in contrast to our analysis they did not account for left ventricular function as depressed LVEF is an established strong risk factor for SCD [2].

One of the main strengths of the present study likely lies in the very long duration of follow-up. To the best of our knowledge, our study is the first to examine the prognostic information provided by an increased urinary albumin excretion rate for as long as 22 years after acute coronary syndrome in an unselected heterogeneous sample of patients, almost with no dropouts, and demonstrates that, in ACS survivors, ACR on repeat examinations after hospital admission, is strongly associated with an increased very long-term risk of total and non-sudden cardiovascular mortality of independently of kidney function and other demographic, clinical, laboratory, and left ventricular scan parameters. Although, this study also has limitations.

A major limitation of the ABC Study was that, at the time of patient enrolment, percutaneous transluminal coronary angioplasty (PTCA) was not yet used to reopen coronary arteries in patients with STEMI. Thus, whether the results may have been altered by early mechanical reperfusion remains uncertain. Additionally, we have previously shown that thrombolytic therapy does not affect albumin excretion levels [5], but we do not know if PTCA does. However, several studies on ACS patients, where patients underwent percutaneous coronary intervention during hospitalization, showed similar associations between albumin excretion and up to 3-year mortality [9,24,29].

Another limitation of the study is that the diagnosis of myocardial infarction did not account for troponin measurement, as it was not in use at that time; therefore, we used the rise and gradual decline of creatine kinase and creatine kinase-MB as biochemical markers of necrosis. Nevertheless, these markers of necrosis are still recommended in the absence of troponin measurement [39].

Moreover, the imaging technologies allow for direct visualization of the injured myocardium and thus an accurate measurement of infarct size at the acute phase of ACS which affects renal function greatly was not available at the participating hospital at the time of enrolment. Alternatively, we accounted for that by measurement of biochemical markers of necrosis (CK, CK-MB and lactate dehydrogenase), as multicentre, randomized studies showed that peak enzymes release was correlated directly with the quantitative histologic measurements of infarct size in patients who died [40] and with single-photon emission computed tomographic infarct size [41].

Finally, as the patients in this study were all Caucasians, we cannot generalize the present findings to other populations and ethnic groups.

The present results show that an early increase of urinary albumin excretion in ACS is a strong independent predictor of the very long-term adverse clinical outcome. Based on these results, and since the level of urinary albumin is easily measured during the hospital stay, we suggest that this measurement be included in the routine clinical workup of the patient with ACS as it could be a suitable method for an adequate assessment of the outcome. Moreover, it could be included as a baseline variable in future intervention trials.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2022.12.025.

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Author statement

Dr. G. Berton and Dr. HT. Mahmoud designed the study. Dr. R. Cordiano, Dr. R. Palmieri, and Dr. F. Bagato contributed to the original data collection. Dr. S. Petucco and Dr. R. Cordiano contributed to data handling and patient follow-up. Dr. G. Berton and Dr. H.T. Mahmoud contributed to the data analysis and interpretation, tables, figures, and manuscript preparation. All authors contributed to ensuring the accuracy of the data analysis.

Declaration of Competing Interest

None.

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