Original Paper

Estimated Glomerular Filtration Rate in Short-Risk Stratification in Acute Myocardial Infarction

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Key Words

Acute myocardial infarction • Glomerular filtration rate • Markers of inflammation • Renal dysfunction • Risk stratification

Abstract

Background/Aims: Renal dysfunction is associated with a higher risk of cardiovascular disease in patients with acute myocardial infarction (AMI). The aim of this study was to investigate the independent prognostic value of renal dysfunction and its incremental predictability risk after adjusting for well-known clinical factors in patients with AMI. **Methods:** 751 consecutive patients with AMI admitted to the Coronary Care Unit (CCU) were included. Patients were grouped into 2 categories according to the baseline estimated glomerular filtration rate (eGFR) on admission (eGFR <60 vs. eGFR ≥60 ml/min/1.73 m²). C-reactive protein and white blood cell count (WBC) as well as clinical prognostic variables were assessed. The endpoint was mortality during CCU stay. The discriminatory power was estimated by the C-index. **Results:** The patient group with an eGFR <60 ml/min/1.73 m² was older, had more cardiovascular risk factors, a lower left ventricular ejection fraction and higher cardiovascular mortality during CCU stay (13 vs. 3%). Logistic regression analysis revealed the following predictors of mortality: degree of renal impairment (eGFR <60 ml/min/1.73 m²), hazard ratio (HR) = 2.2 (95% CI 1.1–4.3; p = 0.028); WBC >11,000 × 10⁶/l, HR = 2.3 (95% CI 1.2–4.5; p = 0.017); Killip class on admission, HR = 3.8 (95% CI 1.7–8.5; p = 0.001), and New York Heart Association Functional Classification, HR = 3.6 (95% CI 1.7–7.4; p = 0.001). The adjusted C-index was 0.78 for baseline clinical variables and 0.84 for eGFR. **Conclusions:** In patients with AMI, decreased eGFR is an important prognostic factor for impaired cardiac function and mortality in the short-term follow-up. The eGFR may be reliably used in the risk stratification of patients with AMI.

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Introduction

Chronic kidney disease (CKD) increases cardiovascular risk and mortality in a broad spectrum of patients, including patients with cardiovascular disease, acute myocardial infarction (AMI), or chronic heart failure in population-based studies [1]. A low glomerular filtration rate (GFR) or high serum creatinine levels (SrCr) in patients with acute coronary syndrome on admission to the Coronary Care Unit (CCU) are important covariates for early prognostic stratification [2, 3]. On the other hand, several studies have addressed the role of inflammatory markers in patients with AMI as predictors of outcome [4–8]. However, it is still unclear whether adding renal dysfunction as a factor is truly useful in the clinical stratification of patients admitted with acute coronary disease [9]. We therefore undertook this prospective study to evaluate the prognostic value of the presence of moderate-severe kidney disease in the short-risk stratification of patients with AMI.

Patients and Methods

Patient Selection

This was a single-center prospective observational study. The study population was recruited from consecutive patients admitted with a diagnosis of AMI to the CCU from January 2006 to December 2009. AMI was defined based on the criteria established by the American College of Cardiology and the European Society of Cardiology [10]. Both ST elevation AMI (STEMI) and non-STEMI were included. Exclusion criteria were concomitant valvular disease, neoplastic or infectious connective tissue, or inflammatory diseases.

Demographic data were obtained from all patients. These included age, gender, body mass index, and classic cardiovascular risk factors. Additional clinical data included a detailed description of complications encountered during CCU stay. Cardiac failure was defined as progressive resting dyspnea associated with clinical signs of pulmonary or peripheral congestion based on Killip criteria. The endpoint was death during CCU stay.

All patients received recommended standard management for AMI with regard to thrombolytic therapy, aspirin, clopidogrel, low-molecular-weight heparin, glycoprotein IIb/IIIa inhibitors, β -blockers, statins, and angiotensin-converting enzyme (ACE) inhibitors, as appropriate.

Informed consent was obtained from all patients, and the protocol of the study was approved by the Institutional Ethical Committee of the hospital.

Categorization of Acute and Chronic Kidney Disease

Based on the recommendations of the National Kidney Foundation, CKD was defined by an estimated GFR (eGFR) <60 ml/min/1.73 m² [11]. eGFR was calculated using the modification of diet in renal disease (MDRD) equation, which includes SrCr, age, race, and sex. Patients were grouped into 2 categories according to the baseline eGFR on CCU admission, i.e. preserved renal function (GFR ≥ 60 ml/min/1.73 m²) and moderate-severe renal dysfunction (GFR <60 ml/min/1.73 m²).

Laboratory Analyses

Blood samples were collected from all patients on hospital admission for the following analyses: hemoglobin, white blood cell count (WBC), red blood cell count, platelets, hematocrit, urea and electrolytes, creatinine phosphokinase, creatinine kinase muscle brain isoenzyme (CK-MB), blood glucose, and biomarkers of renal function (SrCr and urea levels).

All analyses were measured by conventional laboratory methods in serum samples taken on arrival, during CCU stay and at CCU discharge. Troponin I level was measured by a third-generation immunoassay (IMMULITE assay; Diagnostic Products Corporation, Los Angeles, Calif., USA) with the clinical discriminator value 0.2 ng/ml for the diagnosis of AMI (detection range 0.010–25.00 ng/ml; sensitivity 100% and specificity 83.9% at 24 h). C-reactive protein (CRP) was determined using a high-sensitivity nephelometric assay (Behring Diagnostics GmbH, Marburg, Germany); reference values showed a coefficient of variation of $<10\%$.

Statistical Analysis

This prospective observational study was specifically designed to determine the prognostic risk of kidney disease defined according to an eGFR <60 ml/min/1.73 m² in patients with AMI, as well as to determine whether the prognostic value of impaired GFR remains after accounting for markers of inflammation. The continuous variables that displayed an abnormal distribution (Kolmogorov-Smirnov test) were transformed by neperian logarithm before the use of the data. The continuous variables were expressed as means $\pm$ SD or SEM, and the differences between the groups were analyzed by Student's *t* test. The categorical variables were compared using the χ^2 test.

The significant variables in the univariate analysis were introduced in a multivariate logistic regression model to obtain the predictive variables of adverse outcomes. Indicators were entered into the full multivariate model if the *p* value of the univariate association was <0.05 . The final multivariate model was constructed by a backward stepwise elimination of the least significant factors. Unadjusted and adjusted hazard ratios (HR) and their corresponding 95% CI were reported.

The discriminatory power was estimated by the C-index (i.e. probability of concordance between observed and predicted survival on the basis of pairs of individuals) and was calculated for baseline clinical variables, introducing acute-phase reactants, SrCr levels, and the eGFR afterwards into the model. Creatinine level ≥ 1.4 mg/dl, CRP ≥ 5 mg/dl, CK-MB ≥ 80 ng/ml and WBC $\geq 11,000 \times 10^6/l$ were also considered as dichotomous variables. Event rates for clinical outcomes were determined using the Kaplan-Meier method and compared using the log-rank test.

A value of *p* ≤ 0.05 was considered statistically significant. Data were analyzed using SPSS (version 9.0; SPSS Inc., Chicago, Ill., USA).

Results

Demographic Characteristics of the Patients

A total of 751 patients with AMI were available for analysis. Of these, 400 (58%) had diagnosed STEMI. The mean age of the cohort was 64 ± 12 years and 516 patients (75%) were males. The median time to admission from chest pain onset was 3 h (range 1–12 h), and the patients were discharged from the CCU within a median of 3 days (range 1–24 days). Upon admission, the mean eGFR was 74.2 ± 38 ml/min/1.73 m² (95% CI 10–110 ml/min/1.73 m²) and the SrCr level was 1.18 ± 0.03 mg/ml (95% CI 0.21–12.5 mg/ml). The all-cause mortality in the group was 5.46% (41/751 patients). In 103 patients (15%), a primary percutaneous coronary intervention (PCI) was performed. Table 1 shows the clinical characteristics of the population according to GFR. The proportion of patients with comorbid conditions at baseline increased with a decreasing eGFR. Patients with impaired renal function (GFR <60 ml/min/1.73 m²) were older, had hypertension more frequently, and had previous myocardial infarction and chronic renal failure. In addition, these patients were likely to have received more diuretics and inotropic agents during their stay at the CCU but less likely to have had a diagnostic angiography or PCI for the index event (65 vs. 76%; *p* = 0.003).

Univariate and Multivariate Analysis: C-Index

Univariate analysis showed a statistically significant association between endpoint and clinical and laboratory variables (table 2). No significant relationship was observed with respect to classic cardiovascular risk factors. Figure 1 shows the Kaplan-Meier estimates of the rate of mortality during CCU stay according to the eGFR at baseline (log-rank = 11.035; *p* = 0.001).

Table 3 lists the results of the logistic analysis. Killip class >1 , New York Heart Association (NYHA) Functional Classification >2 , GFR <60 ml/min/1.73 m², and WBC count were the independent predictors of mortality during CCU stay. Figure 2 illustrates the estimated contribution of each independent predictor in the model. As each of these novel risk factors was added to the model of traditional baseline characteristics, a noticeable increase in the

Table 1. Baseline characteristics of the study population (n = 751) stratified by eGFR

	eGFR <60 ml/min/ 1.73 m ² (n = 214)	GFR ≥60 ml/min/ 1.73 m ² (n = 463)	p value
Age, years	72 ± 10	61 ± 13	<0.0001
Females	33	22	0.002
BMI ≥30	26	27	NS
NYHA >2	12	7	0.039
Hypertension	74	55	<0.0001
Smoking	26	45	<0.0001
Diabetes mellitus	44	31	<0.0001
Dyslipidemia	51	50	NS
Peripheral vascular disease	14	3	<0.0001
Prior myocardial infarction	39	29	0.005
Previous PCI	22	16	0.042
Previous chronic renal failure	21	0	<0.0001
STEMI	53	61	0.036
Killip >I on admission	50	20	<0.0001
PCI	65	76	0.003
Primary PCI	10	17	0.018
LVEF, %	48 ± 15	52 ± 13	0.009
>1 vessel included	52	46	NS
CCU mortality	13	3	<0.0001
CCU stay, days	3.8 ± 3	3.17 ± 1.8	0.004
Pain (emergency department), h	9.29 ± 2	6.16 ± 1	NS
Admission serum biomarkers			
WBC, ×10 ⁶ /l	10,898 ± 3,863	10,849 ± 3,501	NS
Creatinine, mg/dl	1.8 ± 1.15	0.8 ± 0.18	<0.0001
BNP, pg/ml	777 ± 87	241 ± 22	<0.0001
CRP, mg/l	31 ± 4	16 ± 1.4	<0.0001
Maximum TnI, ng/ml	48 ± 5.6	48 ± 3.7	NS
Fibrinolysis	22	26	NS
Low-molecular-weight heparin	66	82	<0.0001
Aspirin	92	94	NS
Clopidogrel	69	71	NS
ACE inhibitor	52	59	NS
β-Blockers	31	47	<0.0001
Diuretics	49	21	<0.0001
Inotropic agents	23	4	<0.0001
Estatine	77	83	NS
Insulin	44	29	<0.0001

Data are expressed as means ± SD or SEM or percentage of patients. BMI = Body mass index; BNP = brain natriuretic peptide; LVEF = left ventricular ejection fraction; NS = not significant; TnI = troponin I; inotropic agents = dopamine, dobutamine, norepinephrine, and epinephrine.

Table 2. Univariate analysis: association of clinical and laboratory variables with mortality

	OR (95% CI)	p value
Age ≥ 65 years	2.9 (1.4–5)	0.001
Female	2.1 (1.1–3.8)	0.014
NYHA >2	3.6 (1.9–6.9)	<0.0001
Chronic renal failure	2.9 (1.3–6)	0.006
Killip >1 on admission	7 (3.5–14)	<0.0001
LVEF $<50\%$	3.4 (1.2–9)	0.012
GFR <60 ml/min/1.73 m ²	4.17 (2–7)	<0.0001
Creatinine ≥ 1.4 mg/dl	4.2 (2.3–7)	<0.0001
BNP >100 pg/ml	1.5 (1.2–1.8)	0.006
WBC $>11,000 \times 10^6/l$	2.4 (1.2–4.4)	0.004

BNP = Brain natriuretic peptide; LVEF = left ventricular ejection fraction.

Table 3. Multivariate analysis: independent predictors and adjusted HR for occurrence of endpoint

	HR (95% CI)	p value
Killip >1	3.8 (1.7–8.5)	0.001
NYHA >2	3.6 (1.7–7.4)	0.001
GFR <60 ml/min/1.73 m ²	2.2 (1.1–4.3)	0.028
WBC $>11,000 \times 10^6/l$	2.3 (1.2–4.5)	0.017

adjusted C-index was observed: the clinical variable was 0.78 (95% CI 0.72–0.85) for baseline, 0.81 (95% CI 0.74–0.87) for admission acute-phase reactants, 0.84 (95% CI 0.78–0.9) for admission creatinine, and 0.84 (95% CI 0.79–0.9) for eGFR.

Discussion

The most important finding of the present study is that the inclusion of impaired renal function in the short-risk model improves the risk stratification in patients with AMI. In recent years, a considerable number of studies have analyzed the prognostic role of different biochemical markers in patients with AMI with the objective of identifying patients at a high risk of death or myocardial infarction [12, 13]. Renal failure is known to be a sign of poor prognosis in both the short and long term for patients with ischemic heart disease [2, 3]. However, only a few studies include SrCr concentration along with other variables in the estimation of the risk of mortality associated with acute coronary syndrome [13]. Other types of initial stratification systems such as the well-known TIMI risk score for unstable angina and non-Q-wave myocardial infarction do not include kidney function data [14].

The SrCr concentration is the most common factor used, even though its value is influenced by patients' age, sex, muscular mass, and diet. In addition, its sensitivity is poor with respect to the detection of kidney failure, mainly in female and older patients [15]. Therefore, eGFR or creatinine clearance is preferred to quantitative renal function. The formulas most commonly used have been the Cockcroft-Gault (C-G) and the MDRD equations [11]. We used the MDRD because this equation can more accurately estimate the true GFR in patients with more severe renal disease and does not require weight measurements. In a review of 13 studies in which a direct comparison was performed, investigators concluded that both formulas perform better at a lower GFR, with the MDRD equation being less biased, more precise, and more accurate than the C-G equation, which tended to overestimate GFR [16]. Other authors [17] observed that the C-G equation is better than the MDRD equation at predicting mortality after a myocardial infarction. However, another group [18] compared the ability of both equations and observed that the use of the C-G and MDRD equation yielded similar results.

Since the association between renal dysfunction and adverse cardiovascular outcome persists after statistical adjustment for these covariates, we conclude that the increase of cardiovascular risk for people with renal disease is only partially explained by the presence of concomitant classic risk factors such as diabetes, hypertension, and dyslipidemia. It is possible that additional pathways, such as inflammatory or coagulation cascades, may mediate the association between renal dysfunction and cardiovascular risk [19]. In the CARE study, serum phosphate concentration was found to be inversely related to kidney function when the GFR was <60 ml/min/1.73 m² and directly correlated to kidney function when baseline GFR was ≥ 60 ml/min/1.73 m² [20]. Vascular calcification has been postulated as the link between hyperphosphatemia and adverse outcomes in the setting of kidney disease, perhaps accelerated by abnormal calcium levels and hyperparathyroidism [21].

It has been suggested that the relationship between GFR and cardiovascular outcome may be distorted due to inflammation and infarct burden. Moreover, the question has been asked whether the predictive ability of GFR following admission for acute coronary syndrome disappears after adjusting for common clinical variables [22, 23]. In previous studies, our group observed a significant association between a high CRP level and cardiac death, along with age and parameters of ventricular function (Killip class and ejection fraction) in survivors of AMI. However, the significance of the additive predictive influence of CRP was marginal, as suggested by the C-index of the model without and with CRP [6]. Our present

results confirm that the association between renal dysfunction and adverse cardiovascular outcomes is independent of and additive to baseline WBC levels. A similar conclusion was drawn by others [9] in a population excluding patients with a baseline creatinine level >2 mg/dl.

Study Limitations

This is a single-center study with a limited sample size. In our study cohort, 309 STEMI patients (77%) had a percutaneous intervention. It is probable that the contrast medium administered before the initial measurement of SrCr could have influenced baseline levels of creatinine; nevertheless, the extent of volume of contrast medium was inferior in patients with a GFR $<60\%$ [24]. Furthermore, we do not rule out that the underutilization of evidence-based therapies and procedures in the impaired renal function population could have influenced short-term mortality. Data from a recent cohort study suggest that patients with CKD who receive fewer evidence-based therapies have substantially higher mortality rates, a finding that was more pronounced among end-stage renal disease and non-STEMI patients [25]. Finally, we did not have information on albuminuria and proteinuria.

Conclusions

In patients with AMI, decreased eGFR is an important prognostic factor of impaired cardiac function and mortality in the short-term follow-up. Measurement of eGFR on admission could be reliably used in the risk stratification of patients with AMI.

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