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How to cite

ROSSI, Valentina A et al. Prognostic value of inflammatory biomarkers and GRACE score for cardiac death and acute kidney injury after acute coronary syndromes. In: European heart journal. Acute cardiovascular care, 2021, vol. 10, n° 4, p. 445–452. doi: 10.1093/ehjacc/zuab003

This publication URL: https://archive-ouverte.unige.ch/unige:161739

Publication DOI: 10.1093/ehjacc/zuab003

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ESC European Society of Cardiology

European Heart Journal: Acute Cardiovascular Care (2021) **10**, 445–452
doi:10.1093/ehjacc/zuab003

ORIGINAL SCIENTIFIC PAPER

Prognostic value of inflammatory biomarkers and GRACE score for cardiac death and acute kidney injury after acute coronary syndromes

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Received 28 May 2019; revised 29 July 2019; editorial decision 24 October 2019; accepted 12 January 2021; online publish-ahead-of-print 24 February 2021

Aims The aim of this study was to analyse the role of inflammation and established clinical scores in predicting acute kidney injury (AKI) after acute coronary syndromes (ACS).

Methods and results In a prospective multicentre cohort including 2034 patients with ACS undergoing percutaneous coronary intervention, high-sensitivity C-reactive protein (hsCRP), neutrophil count, neutrophil-to-lymphocyte ratio (NL-ratio), and creatinine were measured at the index procedure. AKI ($n = 39$, defined according to RIFLE criteria) and major cardiovascular and cerebrovascular events were adjudicated after 1 year. Associations between inflammation, AKI, and cardiac death (CD) were assessed by *C*-statistics and Cox proportional hazard models with log-rank test to compare survival. Patients with ACS with elevated neutrophil count >7.8 $\times$ 10^9/L, NL-ratio >5, combined neutrophil-count/creatinine, or NL-ratio/creatinine at baseline showed a higher incidence of AKI (all $P < 0.05$) and CD (all $P < 0.001$). The risk of AKI, CD, and their combination was increased in patients with higher neutrophil count/creatinine (heart rate (HR) = 3.7, 95% cardiac index (CI) 1.9–7.1; HR = 2.7, 95% CI 1.6–4.6; HR = 3.2, 95% CI 2.1–4.9); NL-ratio/creatinine (HR = 2.1, 95% CI 1.6–4.1; HR = 2.2, 95% CI 1.3–3.8; HR = 2.3, 95% CI 1.5–3.5); and hsCRP (HR = 1.8, 95% CI 0.9–3.5; HR = 2.2, 95% CI 1.3–3.6; HR = 1.9, 95% CI 1.2–2.8) after adjustment for age, diabetes, hypertension, previous heart failure, kidney function, haemodynamic instability at admission, statin, and renin–angiotensin–aldosterone antagonists use. Subjects with higher GRACE score 1.0/NL-ratio had higher rate of AKI, CD, and both (HR = 1.4, 95% CI 0.5–4.2; HR = 2.7, 95% CI 1.3–5.9; HR = 2.1, 95% CI 1–4.3).

Conclusions Inflammation markers may predict AKI after correction for renal function at the index procedure. hsCRP performed better than the NL-ratio. However, the integration of inflammation markers to traditional risk factors or scores does not add prognostic information.

Trial registration ClinicalTrials.gov, NCT01000701.

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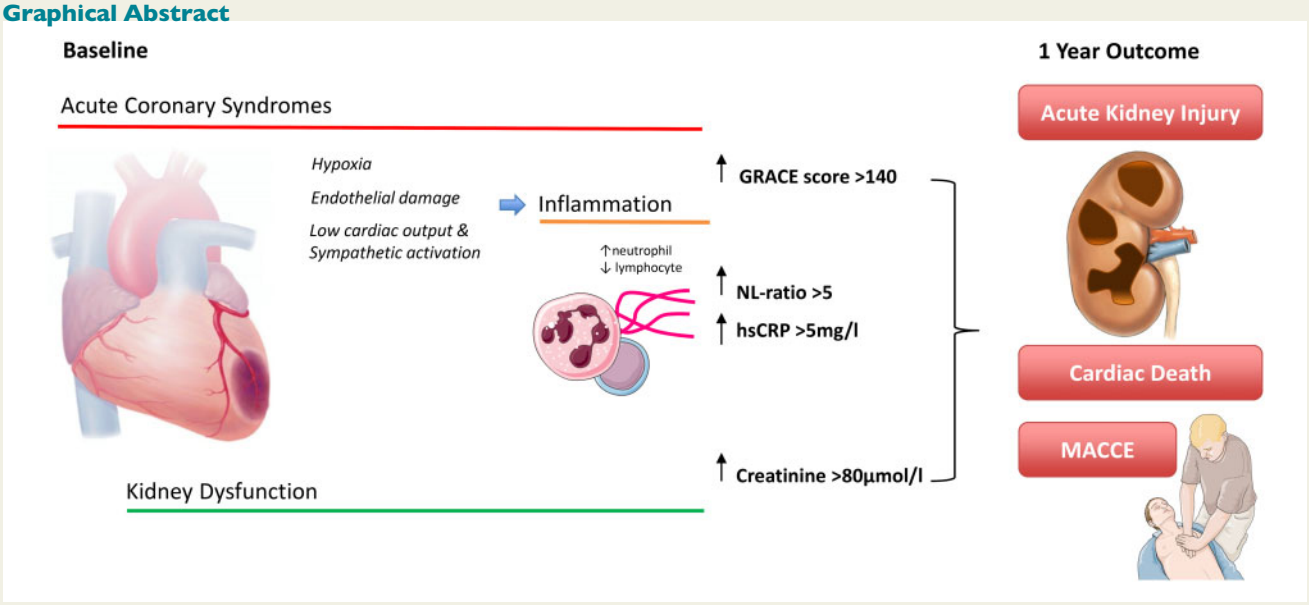
Graphical Abstract



Keywords Acute coronary syndromes • Inflammation • Acute kidney injury • hsCRP • Neutrophil-to-lymphocyte ratio • GRACE score

Introduction

Acute coronary syndromes (ACS) are the leading cause of morbidity and mortality worldwide.[1] Along with other traditional cardiovascular risk factors such as smoking, hypertension and dyslipidaemia, there is an increasing evidence suggesting that inflammation is a key player in atherogenesis and plaque destabilization, thereby acting as both a trigger and long-term risk factor.[2] Consequently, an improved understanding of mediators linking inflammation to coronary artery disease and ACS is warranted.

High-sensitivity C-reactive protein (hsCRP) is a well-established parameter of inflammation, which has been related to an increased cardiovascular risk.[3] Neutrophil activation following ACS promotes pro-inflammatory pathways and secrete pro-inflammatory mediators, thus favouring plaque development and instability.[4] Neutrophils release their nuclear content into the extracellular matrix, thereby activating NETosis, a specific type of programmed cell death due to inflammation, cytotoxicity and pro-thrombosis.[5] This mechanism likely contributes to the 'no-reflow' phenomenon due to vascular obstruction and, in turn, to the degree of myocardial injury.[5,6] Lymphocytes represent a regulatory pathway of the immune system and low lymphocyte counts are associated with adverse outcome in ACS patients.[7] Increasing data highlight the value of neutrophils and neutrophil-to-lymphocyte ratio (NL-ratio) as independent predictors of adverse outcomes both in short and long terms after cardiovascular events.[8] Particularly, an elevated NL-ratio has been related to adverse clinical outcomes after ACS and major vascular surgery such as coronary artery bypass grafting.[9,10] Similarly, absolute neutrophil count has been shown to be an independent predictor of mortality in haemodialysis patients (ref?).

Acute kidney injury (AKI) and cardiac death (CD) are common adverse events after ACS.[11] Patients with known chronic kidney disease, heart failure, haemodynamic instability at presentation, diabetes mellitus, hypertension, anaemia, and the elderly are at increased risk of developing AKI.[12,13]

However, few data are available about the relationship between AKI and inflammation following ACS. We hypothesized that inflammation processes are directly implicated in the development of AKI. Thus, the aim of this study was to evaluate neutrophil count, NL-ratio, and hsCRP as predictors for long-term AKI and CD in patients with ACS. Moreover, we aimed to evaluate the predictive value of GRACE score and a modified one with the addition of inflammatory markers in this setting.

Methods

Study population

A total of 2168 consecutive patients with ACS referred for coronary angiography to one of the four participating Swiss University Hospitals were enrolled in the prospective, multicentre Special Program University Medicine-ACS (SPUM-ACS) cohort between December 2009 and October 2013. The study was registered (NCT01000701) and approved by all local ethics committees in accordance to the Declaration of Helsinki. Informed consent was obtained from all patients.

Patients aged ≥18 years, presenting within 5 days after pain onset with a main diagnosis of ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction, or unstable angina, were included. To confirm the diagnosis, typical electrocardiographic changes, dynamic troponin changes and/or known coronary artery disease or newly

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documented ≥50% stenosis of an epicardial coronary artery during the initial catheterization had to be documented.

Blood tests

Blood samples for cardiac biomarkers, inflammation parameters, and kidney function were obtained from the arterial sheath before the index procedure and centrifuged at 2700 *g* for 10 min at room temperature to obtain serum and stored at -80°C until serial measurement (no prior freeze–thaw cycles) in the Zurich core laboratory, both at baseline and after 1-year follow-up. Haematology parameters were analysed upon arrival in the referral centre, before the index procedure.

Follow-up and study endpoints

A centralized electronic database was implemented providing comprehensive information on all patients. All adverse events occurring within 365 days after the index ACS event were followed up at 30 days by a telephone visit and at 1 year by a clinical visit and adjudicated by an independent clinical events committee consisting of three experienced senior cardiologists.

The primary endpoint was major adverse cardiovascular and cerebrovascular events (MACCE), stroke, myocardial reinfarction, cardiovascular, and non-cardiovascular mortality at 30-day and 1-year follow-up. AKI was registered as adverse event during follow-up as a secondary endpoint and was defined based on RIFLE classification (Risk, Injury, Failure, Loss of kidney function and End-stage renal disease based on either reduction in creatinine clearance compared to baseline or pathological reduction in urinary output or a combination of both).[14]

Statistical analyses

Continuous variables are presented as mean (± standard deviation (SD)), and categorical variables are expressed as percentage, unless otherwise stated. Differences in baseline characteristics between the groups were assessed by independent *t*-tests and Chi-square test as appropriate.

Receiver-operating characteristic (ROC) curves were calculated to assess the accuracy of inflammatory biomarkers and parameters of renal function for predicting AKI. The area under the curve (AUC) was calculated for each combination. *C*-statistics were performed with ROC curves. Cut-off values for leucocytes, CRP, and creatinine were derived based on their sensitivity and specificity and used to calculate their value in predicting events. The Kaplan–Meier estimator was used to calculate the survival function. The log-rank (Mantel–Cox) test was performed to compare survival distributions. Patients were censored at 30 or 365 days, or at last valid contact date, whichever came first. Cox regression was performed to investigate the association between AKI onset and inflammatory parameters after correction for confounding factors such as age, diabetes, hypertension, previous heart failure, kidney function at baseline, haemodynamic instability at presentation, statin, and renin–angiotensin–aldosterone antagonists. Haemodynamic instability at presentation was defined as a dichotomic variable after considering the need for inotropic drugs and/or intra-aortic balloon pump. Multivariate regressions were performed with a stepwise approach and the strength of relationships between events and predictors was tested with *F*-test ANOVA. Events were corrected for following confounding factors, unless otherwise stated: age, kidney function, renin–angiotensin–aldosterone antagonists, diuretics, statins, smoking, and glycaemia at the time of admission.

Because of relative exiguity of patients who developed AKI, a propensity matching score was performed to compare these patients with their paired controls according to confounding factors such as inflammation age, statin therapy, renin–angiotensin–aldosterone antagonists, diuretics, and smoking status. A two-sided *P*-value of 0.05 was considered to be statistically significant. All statistical analyses were performed with SPSS software (v25, SPSS Inc., USA).

Results

Baseline characteristics of patients with acute coronary syndromes

A total of 2168 patients with ACS were included. Among these, 2034 (93.8%) underwent percutaneous coronary intervention (PCI) and had available blood tests and follow-up data and were included in analyses. Eighty-two (3.8%) patients underwent coronary artery bypass surgery and were thus excluded from follow-up analyses. Baseline characteristics of the population are shown in *Table 1*. A total of 12.3% had an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 at baseline. Up to 1 year, 4.3% died from all causes, 3.3% died because of cardiovascular causes, 1.9% developed AKI, 3.4% had a myocardial reinfarction, and 1.1% suffered from stroke within 1 year. Among the patients who developed AKI, 5.1% needed replacement therapy and 20.5% died. A total of 28.2% of them developed AKI during the index hospitalization ($n = 11$). Among the patients who developed AKI, no relevant differences in the amount of administered contrast medium during PCI ($P = 0.958$) were found. However, a significant proportion of them needed IABP support (15.4% vs. 4.2%, $P = 0.006$), with no differences in vasopressor therapy administration (both 2.6%, $P = 0.980$).

Predictive accuracy of high-sensitivity C-reactive protein

After propensity score matching for age, smoking status, and medical therapy (renin–angiotensin–aldosterone antagonists, diuretic, and statins), no baseline differences were found between patients who developed AKI or CD and their paired controls ($P = 0.979$).

Results of ROC analysis for risk prediction are presented as Supplementary data. Increased values of hsCRP at the time of ACS were found to predict AKI, CD, stroke, myocardial reinfarction, and MACCE up to 1-year follow-up. An hsCRP with a cut-off value of >5 mg/L yielded a sensitivity of 54% and a specificity of 67% for AKI, while a creatinine cut-off of 80 µmol/L, as derived from ROC curves, had a sensitivity of 77% and a specificity of 52% for AKI.

Kaplan–Meier curves (*Figure 1*) and log-rank comparisons were calculated using the clinical cut-off value of 5 mg/L for hsCRP and 80 µmol/L for creatinine as mentioned above. Patients with higher values of both hsCRP and creatinine presented the highest cumulative AKI rate (14.2% vs. 3.4%, $P < 0.001$) as well as highest rate of CD and of the combined end-point of AKI and CD (11% vs. 2.1% and 15.6% vs. 3.3%, respectively; $P < 0.001$ for both), MACCE (22.3% vs. 9.2%, $P < 0.001$), stroke (3% vs. 0.8%, $P < 0.01$), and myocardial infarction (6.4% vs. 3%, $P = 0.01$). The combination of increased hsCRP and creatinine was a worse predictor for non-CD ($P = 0.317$).

In adjusted multivariable models, high values of hsCRP alone as well as combined with high creatinine at baseline were highly predictive of AKI, CD, the combined endpoint of AKI and CD, non-CD, and MACCE. Multivariate adjusted hazard ratio after correction for confounding factors is shown in *Table 2*. In multivariate linear regression analysis, a significant correlation was found for AKI and hsCRP

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Table 1 Baseline characteristics

Age (years)/m ale (%)	63.5 (12.4)/79
body mass index (BMI)(kg/m^2)	27.1 (4.3)
CAD history	25.2
Diabetes history	17.7
Hypertension	57.7
Dyslipidemia	61.8
Killip I/II/III/IV	86.4/8.4/1.7/2.7
NSTEMI/STEMI/UA	41.3/55.2/3.4
Onset <24 h/24–72 h/>72 h	66.3/24.4/8.7
GRACE score	95.3 (26.2)
Iodinated contrast (mL)	209.2 (81.3)
Aspirin	30.9
Statins	29.4
ACE-I/ARB	18.1/18.3
Neutrophils (10^9/L)	7.8 (3.5)
NL-ratio	8.4 (12.4)
Haemoglobin (g/L)	137 (17.5)
Glucose (mmol/L)	7.2 (2.9)
CRP baseline (mg/L)	8.8 (22)
eGFR (mL/min)	91 (27.5)
LDL-cholesterol (mmol/L)	3.2 (1.1)
CK (U/L)	458.2 (671.3)
LVEF (%)	51.2 (11.4)

Values are mean ± SD or % as appropriate. ACE-I, angiotensin-converting enzyme inhibitor; ARB, AT-1 receptor blocker; CAD, coronary artery disease; CK, creatine kinase; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; LDL-cholesterol, low-density lipoprotein cholesterol; ; LVEF, left ventricular ejection fraction; NL-ratio, neutrophil-to-lymphocyte ratio; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; UA, unstable angina.

($P < 0.001$, $R^2 = 0.071$), CD and hsCRP ($P < 0.001$, $R^2 = 0.039$), MACCE and hsCRP ($P < 0.001$, $R^2 = 0.035$), and stroke and hsCRP ($P = 0.001$, $R^2 = 0.032$) after correction for confounding factors.

Predictive accuracy of neutrophils, neutrophil-to-lymphocyte ratio, and creatinine

The results of ROC analysis for the prediction of considered outcomes are presented as Supplementary data. Cut-off values were defined based on ROC curves: A neutrophil cut-off value of 7.8 × 10^9/L yielded a sensitivity of 70–75% and a specificity of 55–60% for predicting both AKI and CD. NL-ratio with a cut-off value of 5 yielded a sensitivity of 70% and a specificity of 51% for AKI. No significant correlations were found between the amount of administered contrast medium and kidney function at follow-up or AKI ($P = 0.159$ and $P = 0.891$, respectively).

Kaplan–Meier curves (*Figure 1*) and log-rank comparisons were calculated using the above-mentioned cut-off values. The cumulative AKI rate was the highest in patients with ACS with higher neutrophils (8.1% vs. 3.7%, $P = 0.022$), higher NL-ratio (7.3% vs. 3.6%, $P = 0.05$), both higher values of neutrophils and creatinine (16.1% vs. 3.2%, $P < 0.001$), and NL-ratio and creatinine (12.3% vs. 3.6%, $P < 0.001$). Similarly, significant differences were found for CD and the combined endpoint of AKI and CD ($P < 0.001$ for all). For the outcome myocardial infarction, significant differences were found in survival analysis based on the combination of high NL-ratio and creatinine ($P < 0.05$), but not for neutrophil count and creatinine ($P = 0.742$). Conversely, no significant differences for the outcome non-CD were found ($P = 0.827$ and 0.469, respectively).

In adjusted multivariable models, ACS patients with both higher values of neutrophils and creatinine and NL-ratio and creatinine had the highest rate of AKI, CD, combined endpoint of AKI and CD, non-CD, and MACCE. Multivariate-adjusted hazard ratio after correction for confounding factors is shown in *Table 2*. A significant multivariate linear regression was found for the combined endpoint of AKI and CD and neutrophils, NL-ratio and eGFR ($R^2 = 0.064$, $R^2 = 0.011$ and $R^2 = 0.229$, $P \leq 0.001$ for all), MACCE and neutrophils, NL-ratio and eGFR ($R^2 = 0.051$, $P < 0.001$, $R^2 = 0.014$, $P = 0.003$ and $R^2 = 0.219$, $P < 0.001$, respectively), after correction for confounding factors.

Predictive accuracy of GRACE score 1.0

Results of ROC analysis for the prediction of events are presented as Supplementary data. Kaplan–Meier curves and log-rank comparisons were calculated using a cut-off of 140, as previously calculated for the same population (*Figure 1*).[15] The cumulative AKI rate was highest in patients with ACS with higher GRACE score (11.8% vs. 3.8%, $P = 0.031$) and both higher values of NL-ratio and GRACE score (19% vs. 5.1%, $P = 0.005$). As expected, the GRACE score predicted CD (20.8% vs. 2.3%, $P < 0.001$), with even better accuracy after its correction for NL-ratio values (32.3% vs. 2.8%, $P < 0.001$). The combined endpoints of AKI and CD yielded a similarly high statistical significance (22.6% vs. 3.3%, $P < 0.001$ for GRACE score >140 and 35.5% vs. 4.4%, $P < 0.001$ for modified GRACE score corrected for NL-ratio >5).

The combination of the GRACE score with parameters of inflammation did not improve its prognostic relevance for AKI alone in *C*-statistics; however, an improvement was found for the combined end-point of AKI and CD (Supplementary data). Similarly, patients with a GRACE score values (>140) had a significant higher risk of MACCE and stroke (35.8% vs. 8.9%, $P < 0.001$ and 5.7% vs. 1.1%, $P = 0.004$, respectively).

In adjusted multivariable models, higher GRACE score values at baseline corrected for higher NL-ratio were predictive of AKI, CD, combined endpoint of AKI and CD, non-CD, and MACCE. Multivariate adjusted hazard ratio after correction for confounding factors is shown in *Table 2*. A significant multivariate linear regression was found between GRACE score and AKI ($R^2 = 0.814$, $P < 0.001$), CD ($R^2 = 0.791$, $P < 0.001$), and MACCE ($R^2 = 0.790$, $P < 0.001$).

Discussion

This is the first prospective multicentre cohort addressing the role of inflammation as potential trigger for the development of AKI 1 year after ACS and, thus, beyond the assumed mechanisms underlying contrast-induced nephropathy among ACS patients. We found that neutrophils, NL-ratio, and hsCRP may be independent predictors of AKI even up to 1 year. Moreover, we found the GRACE score 1.0 to predict AKI in the long term. Thus, integration of inflammation markers in daily clinical practice may provide added value to identify

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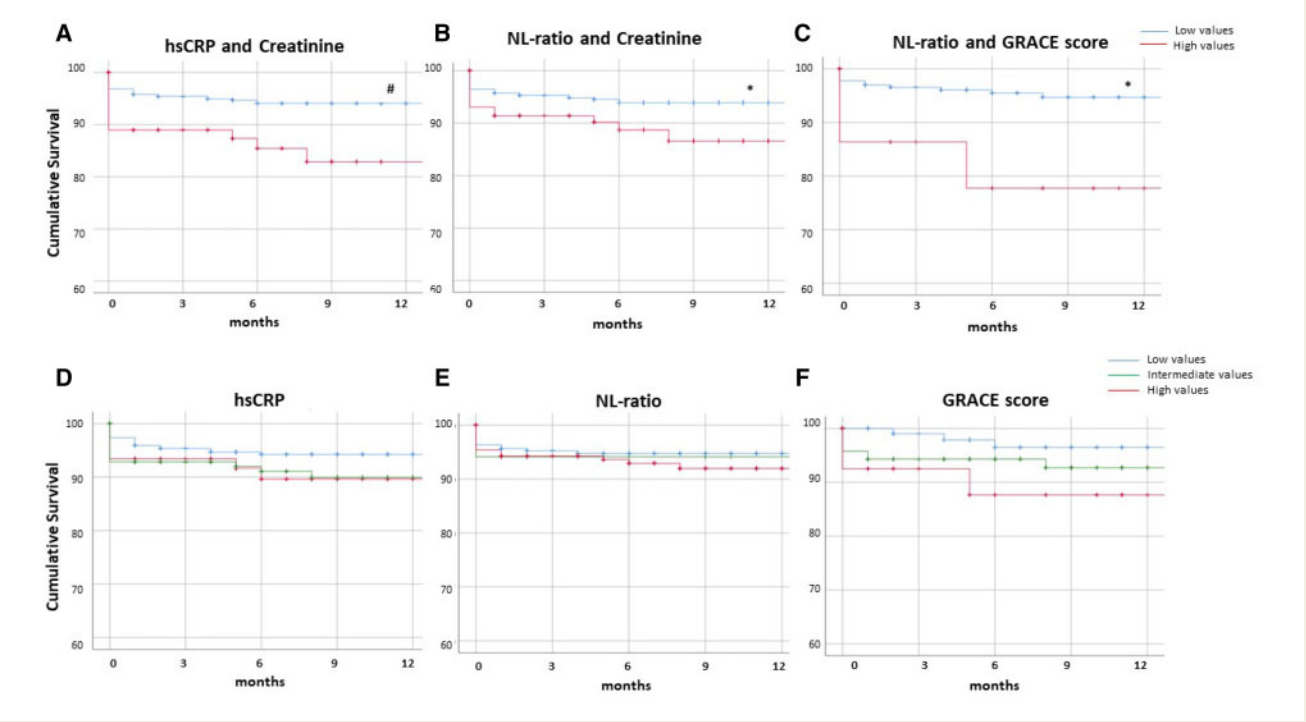

Figure 1 Survival curve for acute kidney injury in relation to neutrophil-to-lymphocyte ratio and creatinine values; neutrophil-to-lymphocyte ratio and GRACE score; high-sensitivity C-reactive protein and creatinine and high-sensitivity C-reactive protein, neutrophil-to-lymphocyte ratio and GRACE score alone. Freedom from acute kidney injury is represented on the *y*-axis. The following cut-offs were considered (*A*–*C*): neutrophil-to-lymphocyte ratio >5, creatinine >80 μmol/L, GRACE score >140, and high-sensitivity C-reactive protein >5 mg/L. Subjects with only one high parameter were left out from graphs (*A*)–(*C*). For (*D*), following cut-offs were considered: high-sensitivity C-reactive protein <2.2 mg/L (median, low values), high-sensitivity C-reactive protein 2.2–5 mg/L (intermediate values), and high-sensitivity C-reactive protein >5 mg/L (high values). Log-rank test was used for comparisons. For (*E*), following cut-offs were considered: neutrophil-to-lymphocyte ratio <4.8 (median, low values), neutrophil-to-lymphocyte ratio 4.8–5 (intermediate values), and neutrophil-to-lymphocyte ratio >5 (high values). For (*F*), following cut-offs were considered: GRACE score <94 (median, low values), GRACE score 94–140 (intermediate values), and GRACE score >140 (high values).

Table 2 Hazard ratio for acute kidney injury, cardiac death, combined endpoints of acute kidney injury and cardiac death, non-cardiac death, myocardial infarction, stroke, and major adverse cardiovascular and cerebrovascular events up to 1-year follow-up

	AKI, *N* = 39		CD, *N* = 67		CD–AKI, *N* = 99		Non-CD, *N* = 20		Myocardial infarction, *N* = 70		Stroke, *N* = 23		MACCE, *N* = 222	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Neutrophils	2.4*	1.1–5.1	3.6*	1.9–6.7	3.0*	1.9–5.9	2.4*	0.8–7.3	0.9	0.5–1.7	1.9	0.7–4.8	1.4*	1.0–1.9
NL-ratio	1.6*	0.7–3.4	3.8*	1.8–8.0	2.7*	1.6–4.6	1.1#	0.4–3.1	1.4	0.8–2.5	1.3	0.5–3.2	1.3*	0.9–1.8
Neutrophils + creatinine	3.7*	1.9–7.1	2.7*	1.6–4.6	3.2*	2.1–4.9	1.0*	0.3–3.1	1.1	0.6–2.1	1.8#	0.7–5.0	1.4*	1.0–2.0
NL-ratio + creatinine	2.1*	1.1–4.1	2.2*	1.3–3.8	2.3*	1.5–3.4	0.4*	0.1–1.6	1.5	0.8–2.6	1.5#	0.6–4.0	1.4*	1.0–1.9
hsCRP	1.8*	0.9–3.5	2.2*	1.3–3.6	1.9*	1.2–2.8	2.2*	0.9–5.6	1.9§	1.2–3.1	2.6#	1.1–5.9	1.5*	1.2–2.0
hsCRP + creatinine	2.7*	1.4–5.2	2.8*	1.7–4.7	2.5*	1.6–3.8	1.0*	0.3–3.0	1.8§	1–3.4	2.7#	1.1–7.0	1.8*	1.3–2.5
GRACE	1.3#	0.3–5.1	2.2*	0.9–5.4	1.6*	0.7–3.5	0.0§	0.0–0.0	1.8	0.5–6.8	2.7	0.6–12.1	2.2*	1.9–4.0
GRACE + NL-ratio	1.4*	0.5–4.2	2.7*	1.3–5.9	2.1*	1.0–4.3	0.0*	0.0–0.0	1.5	0.3–6.3	1.4§	0.2–11.3	1.7*	0.9–3.3

Adjustment for age, diabetes, hypertension, previous heart failure, kidney function at baseline, haemodynamic instability at presentation, statin, and renin–angiotensin–aldosterone antagonists. Considered cut-offs were: neutrophils >7.8 g/L, NL-ratio >5, creatinine >80 μmol/L, hsCRP >5 mg/L, GRACE score >140.
*$P < 0.001$; #$P < 0.01$; §$P < 0.05$.
AKI, acute kidney injury; CD, cardiac death; hsCRP, high-sensitivity C-reactive protein; MACCE, major adverse cardiovascular and cerebrovascular events; NL-ratio, neutrophil-to-lymphocyte ratio.

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patients with the highest risk for developing AKI who need to be closely followed up after an ACS.

Inflammation parameters as possible predictors of acute kidney injury

AKI is a relatively common event after ACS, occurring in 3–15% of patients the days following PCI.[11] AKI, immediately after PCI, has been widely analysed. However, no data are available regarding the onset of AKI in the long term. The underlying mechanisms of AKI in the setting of ACS are possibly related to ischaemia–reperfusion injury, transient or prolonged hypotension, contrast-induced renal injury, oxidative stress, and inflammation. These processes lead to the accumulation of neutrophils, macrophages, and lymphocytes in the perivascular regions of renal arteries and arterioles, most likely with mechanisms similar to those leading to microvascular myocardial occlusion.[16] These inflammatory pathways enhance the perivascular infiltration of macrophages, which promote both renal and vascular dysfunction and enhance renal fibrosis via cytokine-mediated pathways in the long term too.[16] The persistence of high levels of inflammation may lead short term to microvascular obstruction and, thus, long term to organ dysfunction as suggested by a higher incidence of AKI up to 1 year.

Both neutrophils and NL-ratio have been associated with contrast-induced nephropathy in patients undergoing routine or emergency PCI.[17] Patients with ACS with peri-procedural contrast-induced nephropathy have a higher risk of all-cause mortality at 24 months.[18] Only one study looked at the potential mechanisms underlying the development of renal dysfunction after ACS, concluding that this is not simply related to hypoperfusion and haemodynamic changes, but also to inflammatory mediators such as interleukin-10, interleukin-1β, interleukin-6, and endothelin-1, which are released after ACS and may represent the link between cardiac ischaemia and renal dysfunction.[19] However, there are no studies investigating the association between neutrophils and NL-ratio and AKI in a large prospective cohort of ACS patients.

hsCRP is a well-established marker of inflammation, which in the acute setting predicts no-reflow and in-hospital cardiovascular adverse events. Interestingly, hsCRP along with NT-proBNP and high-sensitivity troponin-T predicted the composite endpoint of all-cause mortality and reinfarction both at 30 days and 1 year after ACS.[15] We found that hsCRP performed particularly well in predicting AKI up to 12 months after the acute event, thus highlighting the strong association between inflammation and adverse events after ACS.

Neutrophils release cytotoxic substances which are mainly responsible for pathogen clearance during early infections. Endothelial damage and activation promotes neutrophil migration to the sites of inflammation, where reactive oxygen species are released and phagocytosis started. Such processes extend over the first 24 h to the entire blood vessel wall inducing local ischaemia, plaque destabilization, and thrombosis.[20] Relative lymphopenia is common and due to elevated endogenous cortisol levels in response to acute stress[7]; of note, in patients with myocardial infarction, lymphopenia leads to oxidation of low-density lipoprotein and has been associated with reinfarction and CD.[21] Elevated NL-ratio combines these inflammatory responses and is gaining value as a low cost and widely available parameter of inflammation. Here, we found that both neutrophils and the NL-ratio are good predictors of AKI up to 1 year, suggesting that atherosclerosis, ACS, and AKI share some cellular and molecular mechanisms.

Predictive value of kidney function parameters

Patients with ACS with peri-procedural contrast-induced nephropathy are at increased risk of all-cause mortality up to 24 months after the acute event.[18] In our population, a reduced kidney function predicted MACCE, CD, and AKI. Survival analysis with neutrophils and creatinine as variables demonstrated that patients with signs of active inflammation (i.e. higher neutrophils and NL-ratio) presented the worst outcome in terms of both AKI and CD.

Value of the GRACE risk score 1.0 to predict acute kidney injury

The GRACE score 1.0 proved to be a powerful prognostic tool in identifying patients who are more likely to develop AKI in the long term, both alone as well as in combination with neutrophil count. The predictive value of the GRACE score 1.0 for long-term major cardiovascular adverse events has already been shown to improve with the inclusion of neutrophil count, hsCRP, mean platelet volume, troponin-T, and natriuretic peptides.[15,22,23] However, so far, the GRACE score 1.0 has been only described to predict contrast-induced nephropathy after PCI in patients with ACS and normal renal function, thus comprising a short-term window. Yet, no data are available about its value to predict long-term AKI.[24] Both parameters defining the GRACE score and blood count are routinely drawn in patients presenting with ACS, their incremental value may be useful in the clinical practice to more accurately assess prognosis.

Inflammation parameters as predictors of cardiac death

We found a significant association between both neutrophils, with a cut-off value of 7.8 $\times$ 10^9/L, and NL-ratio, with a cut-off value of 5, and CD at 12 months, which is in line with previous studies[25,26] and meta-analyses.[10,27] Indeed, patients with STEMI and non-ST-elevation myocardial infarction and high NL-ratio had an increased risk for overall in-hospital and long-term mortality and major adverse cardiovascular events.[10,26]

However, results from the meta-analyses are to be evaluated with caution as they are often affected by substantial heterogeneity among the studies they regroup (I^2 64–80%).[10,26–28] When these meta-analyses were sub-grouped to reduce heterogeneity, an increased NL-ratio was associated with a 2.97- to 3.55-fold higher risk for cardiovascular events and CD up to 1 year after ACS.[27,28] An NL-ratio of >5 independently predicted CD even after correction for confounding factors such as previous therapy with statins and of renin–angiotensin–aldosterone antagonists, which all have moderate anti-inflammatory effects. Thus, inflammatory mechanisms other than the usual cardiovascular risk factors harbour a risk for mortality. The underlying mechanisms may be related to NETosis, an inflammation-induced type of cytotoxicity and programmed cell death with subsequent mechanical occlusion, which could negatively enhance the effect of pre-existent atherosclerotic plaques.[5]

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The use of anti-inflammatory drugs in this setting needs to be further investigated. The recent CANTOS trial investigated the effects of Canakinumab a monoclonal antibody targeting IL-1β in high-risk patients after ACS: Canakinumab reduced cardiovascular events in secondary prevention.[2] It is conceivable that reducing inflammation might also positively impact on renal function. It goes without saying that the putative beneficial effects on exaggerated inflammation have to be weighted against the potential risk of impaired host defence.

Limitations

Recruitment was based on written informed consent, impeding complete assessment of all patients with ACS. Only 39 patients developed AKI and 67 CD, thereby limiting the statistical power of multiple testing. Due to relative few AKI events, results might be underestimated. When using a combined end-point of CD (67 cases) and AKI, an improvement of prognostic relevance was found. This suggests that a larger sample size with more AKI outcome events could change the results of this study.

Data indicating how many ACS patients needed dialysis are missing. AKI was defined based on creatinine values and the CKD-EPI formula according to RIFLE criteria for all participants, with no differences based on BMI (although mean BMI was high normal) or age. Kidney Disease: Improving Global Outcomes (KDIGO) criteria would have likely been more sensitive, but not available for our population. Biomarker measurements in this study were performed before coronary angiography, i.e. *after* the decision for invasive management had already been made. This could represent another selection bias of this study.

Conclusions

AKI is a major complication following ACS both in the acute phase and in the long term. This is the first prospective multicentre cohort study analysing the role of inflammation in the development of AKI up to 1 year after ACS. Inflammation as assessed by neutrophil count, NL-ratio, and hsCRP levels at baseline was closely related to AKI up to 1 year, with hsCRP performing slightly better than the NL-ratio. However, the integration of inflammation markers as further predictor tool in addition to traditional risk factors or risk scores, such as the GRACE score, does not add meaningful prognostic information.

Nevertheless, we propose that patients presenting with high inflammation parameters and a high GRACE score should be followed more strictly for improved risk stratification. Along these lines, an individualized therapeutic approach, targeting the 'residual inflammatory risk', as recently reported, needs to be further investigated.[29,30]

Supplementary material

Supplementary material is available at *European Heart Journal: Acute Cardiovascular Care*.

Acknowledgements

The authors appreciate the work of the clinical event adjudication committee for SPUM-ACS: Matthias Pfisterer, University of Basel (chair); Tiziano Moccetti, CardioCentro Lugano; Lukas Kappenberger, University of Lausanne; the study nurses (Anika Adam, Maja Müller, Christa Schönenberger, Therese Fahrni, Saskia Bühlmann, Genevieve Legault, Véronique Berset, Nicole Bonvin, Anne Bevand, and Armelle Delort); the core laboratory technicians (Isabelle Peereboom, Monika Seiler, Anuschka Beccato); the central data monitors (Katja Heinimann, Daria Bochenek, Timon Spörri); the electronic data capturing system (2mt GmbH Ulm, Jürgen Nagler-Ihlein, Torsten Illmann), the research coordinator Lambertus J. van Tits, Sven Trelle, Marcel Zwahlen, ISPM Bern and CTU Bern; and the members of the catheter teams for their invaluable work.

Funding

The authors received support from the Swiss National Science Foundation (SPUM 33CM30-124112); the Swiss Heart Foundation; the Foundation Leducq; and the Foundation for Cardiovascular Research—Zurich Heart House, Zurich. The SPUM consortium was also supported by: Roche Diagnostics, Rotkreuz, Switzerland (kits for biomarkers); Eli Lilly, Indianapolis (USA); AstraZeneca, Zug; Medtronic, Münchenbuchsee; Merck Sharpe and Dome (MSD), Lucerne; Sanofi-Aventis, Vernier; and St Jude Medical, Zurich.

Conflict of interest: F.M. has received research grants to the institution from Amgen, AstraZeneca, Boston Scientific, Biotronik, Medtronic, MSD, Eli Lilly, and St. Jude Medical including speaker or consultant fees. S.W. has received research grants to the institution from Abbott, Boston Scientific, Biosensors, Biotronik, The Medicines Company, Medtronic, and St. Jude Medical and honoraria from Abbott, Astra Zeneca, Eli Lilly, Boston Scientific, Biosensors, Biotronik, Medtronic, and Edwards. T.F.L. received research and educational grants to the institution from Abbott-St. Jude, AstraZeneca, Bayer Healthcare, Biosensors, Biotronik, Boston Scientific, Eli Lilly, Medtronic, MSD, Merck, Roche, and Servier, including speaker fees by some of them. C.M.M. received research grants to the institution from Eli Lilly, AstraZeneca, Roche, and MSD including speaker or consultant fees. L.R. received speaker fees and research grants to the institution from St Jude Medical. All other authors have no conflict of interest to declare.

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