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Long-term impact of acute kidney injury on prognosis in patients with acute myocardial infarction☆

Georgios Chalikias [a], Levent Serif [a], Petros Kikas [a], Adina Thomaidis [a], Dimitrios Stakos [a], Dimitrios Makrygiannis [b], Sofia Chatzikyriakou [c], Neofytos Papoulidis [b], Vassilis Voudris [c], Asimina Lantzouraki [a], Martin Müller [d], Spyridon Arampatzis [e], Stavros Konstantinides [a], Dimitrios Tziakas [a,]*

[a] *Cardiology Department, Medical School, Democritus University of Thrace, Alexandroupolis, Greece*
[b] *Cardiology Department, General Hospital of Kavala, Kavala, Greece*
[c] *Second Department of Interventional Cardiology, Onassis Cardiac Surgery Center, Athens, Greece*
[d] *Department of Emergency Medicine, Inselspital, Bern University Hospital, University of Bern, 3010 Bern, Switzerland*
[e] *Department of Nephrology and Hypertension, Inselspital, Bern University Hospital, University of Bern, 3010 Bern, Switzerland*

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ABSTRACT

Background: Little evidence exists regarding the long-term impact of acute kidney injury (AKI) during index hospitalisation for acute myocardial infarction (AMI). We prospectively assessed the long-term prognostic significance of the occurrence of in-hospital AKI in a multicentre cohort of patients admitted with AMI.
Methods: Data were obtained from 518 AMI patients with a median follow-up of 5.6 (IQR 4.6–6.5) years. Patients were followed up regarding the occurrence of death, major adverse cardiovascular events (MACE), and any deterioration in kidney function.
Results: From the study cohort, 84 patients (16%) had developed AKI at discharge during index hospitalisation. 96 patients died during follow-up, MACE occurred in 90 patients, and 30 patients showed evidence of deterioration in kidney function. Patients with AKI at hospital discharge had a three-fold increased mortality risk (HR 3.2, 95% CI 2.1–4.8; $P < 0.001$). This association was independent of possible confounding by variables that could influence prognosis (HR 1.9 95% CI 1.1–3.2; $P = 0.028$) evident only up to three years during follow-up. During long-term follow-up, patients with AKI during their index hospitalisation had a significantly ($P = 0.027$) higher incidence of MACE (26%) than those who did not develop AKI (15%). Patients with AKI had a higher incidence of deteriorating kidney function (10%) than those without AKI (5%) during follow-up, but this difference was not significant ($P = 0.124$).
Conclusions: Our findings emphasise in addition to the need for appropriate long term follow-up in such patients, an increased mortality and morbidity during the first three years after the index event.

1. Introduction

Acute kidney injury (AKI) is a common adverse event during hospitalisation for acute myocardial infarction (AMI) [1]. Several studies have shown that AKI occurrence during index hospitalisation has a detrimental impact on in hospital mortality, as well as on short- and long-term prognosis [1,2]. The bulk of evidence for short-term prognosis is based on in-hospital events up to one year, and studies exploring the long-term impact of AKI on AMI are up to three years since the index hospitalisation [1–3]. Long term survival analysis suggests that the prognostic impact of AKI is not only limited to the immediate period of the acute event, but has a longer effect, related to different factors, such as development of chronic kidney disease (CKD), less use of evidence-based medication, or the occurrence of rare complications, such as sepsis, lung injury, and heart failure [4].

Very little has been published about the long-term prognosis concerning the outcome for more than three years after the index event [5–12]. With the present study, we therefore investigated the prognosis up to seven years after the occurrence of AKI in patients hospitalised for AMI, and assessed whether the prognosis was associated with a transient or permanent decrease in renal function.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

* Corresponding author at: Cardiology Department, Medical School, Democritus University of Thrace, Dragana, 68100 Alexandroupolis, Greece.
E-mail address: dtziakas@med.duth.gr (D. Tziakas).

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2. Methods

2.1. Study design and patients

The present study was a prospective, observational, cohort study. A total of 805 acute ST-segment elevation myocardial infarction (STEMI) or non-ST elevation myocardial infarction (NSTEMI) patients admitted to the coronary care unit from three cardiology departments (Alexandroupolis, Kavala, Athens) in Greece were consecutively enrolled from July 2010 to May 2014, as previously described [13]. STEMI patients underwent either primary percutaneous coronary intervention (PCI), or fibrinolysis followed by rescue or elective PCI, as indicated [14,15]. NSTEMI patients underwent urgent intervention (<120 min), early invasive treatment (<24 h), invasive treatment (<72 h), or a primarily conservative strategy followed by elective PCI according to the current indication [15,16]. All patients received standard post-myocardial infarction (MI) medical therapy consisting of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, aldosterone antagonists, beta-blockers, anti-platelet agents, and statins [14,16]. We report here on following up these patients for 5.6 years (median follow up).

2.2. Definitions and study endpoints

Consecutive patients with acute STEMI or NSTEMI were recruited if they fulfilled the following inclusion criteria: 1) age ≥ 18 years; 2) ability to provide written, informed consent; and 3) acute, spontaneous (type 1) AMI. Main exclusion criteria were presence of pre-existing renal disease and AMI-related symptom onset ≤72 h from hospital admission. Patients with active malignancy, or infection, hepatic, thyroid, pulmonary or autoimmune disease at the time of inclusion or under treatment with anti-inflammatory drugs were excluded. Finally patients referred for urgent coronary artery bypass grafting and patients suffering a fatal event during the index hospitalisation were also excluded from the study.

Patients were assessed for the occurrence of AKI twice during hospitalisation: a) 48 h after admission using the Acute Kidney Injury Network (AKIN) and Risk, Injury and Failure (RIFLE) criteria, and b) at discharge using the RIFLE criteria and, slightly modified, the Kidney Disease: Improving Global Outcomes (KDIGO) criteria (changes in creatinine or glomerular filtration rate [GFR] were presumed to have occurred during hospitalisation) [17–20]. To enable a more practicable approach in survival analyses, patients were considered to have AKI during hospitalisation based on the modified KDIGO or RIFLE criteria. Serum creatinine on admission was considered as baseline for both assessments. Definitions of various clinical terms used throughout the present manuscript were previously described [13]. Of interest, pre-existing renal disease was defined as at least one of the following: history of or previous admission for renal artery stenosis; acute renal failure; acute or chronic glomerulonephritis; renal obstruction; overt hematuria, nephrotic syndrome; nephrectomy; reduced renal function at baseline (defined by serum creatinine levels ≥ 2.5 mg/dL or calculated GFR < 30 mL/min); permanent renal replacement therapy; history of kidney transplantation [13].

Patients were followed up for up to 7.7 years (5.6 years median follow up) after admission using a standardized protocol that included outpatient visits, telephone contacts, and the recording of recurrent cardiovascular or renal events. Information on kidney function was also documented at the follow-ups.

The primary endpoint of the study was death from any cause. Cardiovascular death was defined as death due to AMI, stroke, pulmonary embolus, aortic events, arrhythmias, heart failure, or cardiac surgery or interventions. All other deaths were considered non-cardiovascular. Secondary endpoints were i) new major adverse cardiovascular events (MACE) including any of the following: non-fatal recurrent AMI, hospitalisation for unstable or stable angina, any coronary revascularisation (PCI or coronary artery bypass grafting [CABG]) different from the index event, pulmonary embolism, or development of heart failure symptoms requiring hospitalisation, and ii) any deterioration in kidney function including any of the following: hospitalisation for acute renal failure, established at regular follow-up in outpatients renal department, transient or permanent renal replacement therapy, history of or planned kidney transplantation.

Peripheral blood samples for measurement of renal function were obtained from all patients on admission, 48 h after the index event, daily until discharge, and also during follow-up visits. The study protocol was approved by the institutional ethics committee (EC7/27/14.10.2010), and all patients gave written informed consent. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

2.3. Statistical analysis

Data are presented as percentages for categorical data, as means ± standard deviation (SD) for continuous variables that were normally distributed, and as medians with interquartile ranges (IQR) for non-normally distributed data. Normality was tested using the Kolmogorov-Smirnov test. Comparisons between categorical variables were performed using the chi-squared test or Fisher's exact test, when required. Differences in continuous variables between the two groups were assessed using Student's *t*-test or the Mann-Whitney *U* test, as appropriate.

Short- and long-term mortality rates between patients with or without AKI were analysed using a 2-sided chi-square test of proportions. In addition, time-to-event distributions were summarized with Kaplan-Meier curves and compared by log-rank test. For the combined study endpoint, subjects were censored after the first occurrence and no subjects contributed >1 endpoint to the analysis. For patients still alive on the date of the last contact with the study site, the date of this contact was the censoring date. Multivariate Cox proportional hazard analyses were performed to determine independent predictors of the study endpoint. Adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) were assessed in multivariate Cox models using as confounders variables that on univariate analysis were shown to statistically significantly affect the occurrence of the pre-specified study endpoint. Proportional hazard assumption was checked by plotting residuals against time. Variables which were not normally distributed were logarithmically transformed as required to approach normal distribution and to obtain equal variances to enable inclusion in all models. Variables retained in the final models were chosen with a backward stepwise selection method.

According to power analysis and a hypothesized 15% incidence of AKI, 800 patients would be needed for the present study to have an at least 80% statistical power to detect a two-tailed (superiority of either method) 100% increase in combined endpoint incidence, with a type I error of 5% and assumed incidence rate of 10% in the control group and 20% in the AKI group.

A P-value < 0.05 indicated statistical significance; all tests were two-sided. The IBM SPSS Statistics 20.0 statistical software package (SPSS Inc., Chicago, Illinois, USA) was used for all calculations.

3. Results

3.1. Baseline characteristics and AKI incidence

Follow-up information was available for 518 patients (64%) from the initial 805 patients (Suppl. Fig. 1). The median follow-up time was 5.6 years, with an (interquartile range of 4.6 to 6.5 years). Demographic data, clinical status at baseline, and medical history are shown in Table 1.

The incidence of AKI in our study population ranged from 6.6% to 16.2% (Suppl. Table 1) depending on timing (at 48 h vs. during hospitalisation), and on definition used (AKIN vs. RIFLE vs. KDIGO). Most patients had a stage 1 kidney injury and none required dialysis during hospitalisation.

The proportion of patients >70 years of age (36% vs. 26%; P = 0.004), prevalence of anaemia (20% vs. 11%; P = 0.001), previous history of PCI (13% vs. 8%; P = 0.019) and hospitalisation days [5 (2) vs. 6 (3); P = 0.009] differed significantly between the long-term follow-up patients and the subpopulation of patients not followed up. It is important to note that the incidence of AKI (16.2% vs. 11.8%; P = 0.097) did not differ between patients with and without follow-up.

3.2. Short- and long-term mortality rates

Table 2 displays the rates of overall and cause-specific early (death between admission and end of first year), late (death between the start of the second year and end of third year), and very late mortality (death after three years of follow-up). The corresponding Kaplan-Meier curves for the long-term survival estimates are shown in the Fig. 1. The overall mortality rate in the entire study population was 18.5%, with significantly higher mortality in patients who developed AKI during index hospitalisation (38.1% vs. 14.7%; chi-square test P < 0.001; log-rank test P < 0.001). Most deaths (42 out of 96) occurred during the first year of follow-up and most were due to cardiac causes (34 out of 42). After the first year, the incidence of non-cardiac mortality was at least equal to that of cardiac mortality. AKI contributed to an increased mortality up to the third year of follow-up (Table 2 & Suppl. Table 2).

3.3. Confounders

AKI incidence during index hospitalisation was associated with an approximately three-fold higher mortality during follow-up (hazard ratio [HR] 3.2, 95% confidence interval (CI) 2.1–4.8; P < 0.001). Of interest, the sub-group of patients with baseline eGFR < 60 mL/min had an increased incidence of AKI during index hospitalisation compared to patients with eGFR ≥ 90 mL/min [54 (25%) vs. 30 (12%); P < 0.001]. In survival analysis, among patients with eGFR < 90 mL/min presence of AKI during index hospitalisation had a poor prognosis (HR 2.3 95% CI 1.4–3.6; P = 0.001) whereas in patients with eGFR ≥ 90 mL/min presence of AKI was not associated with prognosis (HR 0.7 95% CI 0.4–

Table 1
Demographic, clinical and angiographic data at baseline and in-hospital characteristics of study cohort.

Variable	Study cohort (n = 518)
Age, years	63 (13)
Age > 70 years, n (%)	188 (36)
BMI, kg/m^2	28 (5)
BSA, m^2[a]	1.97 (0.19)
Male/Female, n (%)	406 (78)/112 (22)
Risk factors	
Hypertension, n (%)	296 (57)
Diabetes mellitus, n (%)	138 (27)
Dyslipidaemia, n (%)	208 (40)
Current smoker, n (%)	282 (54)
Co-morbidities	
Previous MI, n (%)	88 (17)
Chronic heart failure, n (%)	8 (2)
Peripheral arterial disease, n (%)	26 (5)
Previous stroke or TIA, n (%)	38 (7)
Atrial fibrillation, n (%)	
Paroxysmal	22 (4)
Chronic	8 (2)
Valve disease, n (%)	6 (1)
Previous PCI, n (%)	68 (13)
Previous CABG, n (%)	12 (2)
Anaemia, n (%)	102 (20)
Laboratory data	
Haemoglobin at admission, g/dL	14.1 (1.8)
Baseline creatinine, mg/dL	1 (0.3)
Creatinine at 48 h, mg/dL	1 (0.3)
Peak creatinine during hospitalisation, mg/dL	1.2 (0.6)
Baseline eGFR, mL/min[b]	93 (36)
eGFR at 48 h, mL/min[b]	90 (36)
Lowest eGFR during hospitalisation, mL/min[b]	84 (33)
Baseline eGFR classification, n (%)	
>90 mL/min	252 (48)
60–90 mL/min	190 (37)
30–60 mL/min	76 (15)
Ejection fraction during hospitalisation, n (%)	
Normal (>55%)	300 (58)
Mildly reduced (45–55%)	132 (26)
Moderately reduced (35–44%)	74 (14)
Severely reduced (<35%)	12 (2)
Total cholesterol, mg/dL	201 (50)
LDL cholesterol, mg/dL	128 (45)
HDL cholesterol, mg/dL	46 (21)
Triglycerides, mg/dL	152 (96)
Peak CPK during hospitalisation, IU/L	1114 (1581)
Peak CK-MB during hospitalisation, IU/L	89 (130)
Hospitalisation data	
Type of acute coronary syndrome	
STEMI, n (%)	362 (70)
NSTEMI, n (%)	156 (30)
Site of MI	
Inferior, n (%)	178 (34)
Anterior, n (%)	204 (39)
Lateral, n (%)	56 (11)
Infero-lateral, n (%)	60 (12)
Antero-lateral, n (%)	4 (1)
Posterior, n (%)	16 (3)
Heart rate at admission, bpm	79 (22)
Systolic BP at admission, mm Hg	130 (30)
Diastolic BP at admission, mm Hg	80 (5)
Low BP (<90 mm Hg) at admission, n (%)	30 (6)
TIMI risk score, n	3 (3)
Killip class, n (%)	
Class I	480 (92)
Class II	26 (5)
Class III	10 (2)
Class IV	2 (1)
Coronary artery disease, n (%)	
Non-significant disease	28 (6)
1-Vessel	280 (54)
2-Vessel	130 (25)
3-Vessel	80 (15)
Left main stem disease	38 (7)
ACS treatment strategy, n (%)	
Invasive during hospitalisation	304 (59)
Primarily conservative	214 (41)
In-hospital adverse events, n (%)	120 (23)
Contrast volume used, (mL)[c]	243 (122)
Contrast volume/eGFR (baseline) ratio,	2.6 (1.8)
Hospitalisation (days)	5 (2)
Medication use after admission	
ACE inhibitors, n (%)	41 (8)
Angiotensin receptor blockers, n (%)	399 (77)
Diuretics, n (%)	112 (22)
Aldosterone antagonists, n (%)	30 (6)
Nitrates, n (%)	63 (12)
Digitalis, n (%)	21 (4)
Beta-blockers, n (%)	447 (86)
Calcium channel blockers, n (%)	64 (12)
Amiodarone, n (%)	24 (5)
Statins, n (%)	429 (83)
Fibrates, n (%)	89 (17)
Aspirin, n (%)	496 (96)
P2Y12 antiplatelets, n (%)	510 (98)
Anticoagulants, n (%)	31 (6)
Antidiabetics, n (%)	72 (14)
Metformin, n (%)	36 (7)
Insulin, n (%)	24 (5)

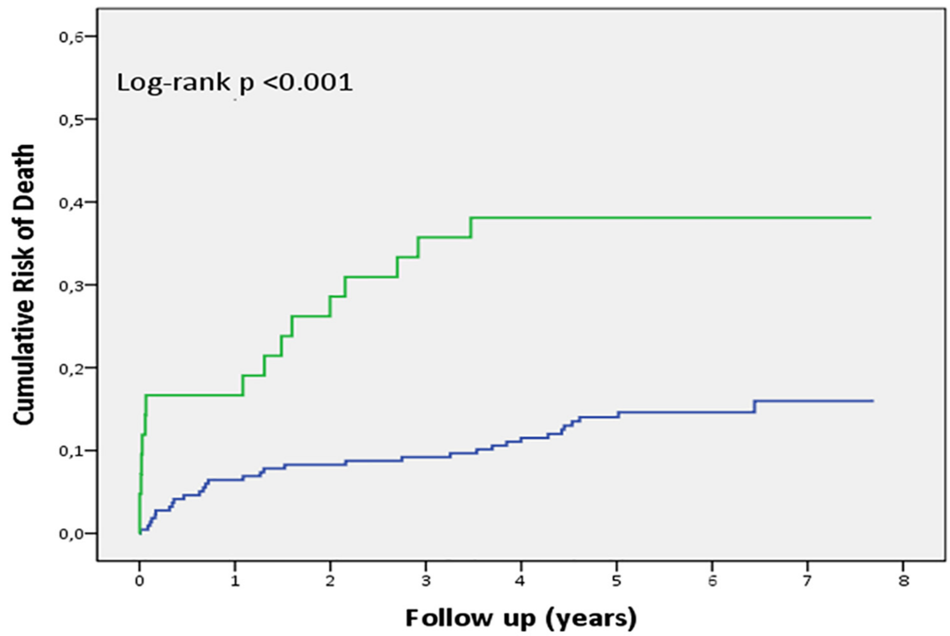
Values are expressed as means (with the corresponding standard deviation) for continuous variables, and as numbers of patients and percentages for categorical variables.
ACE, angiotensin-converting enzyme; BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass graft surgery; CK-MB, creatinine kinase myocardial fraction; CPK, creatine phosphokinase; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; GP, glycoprotein; HDL, high density lipoprotein; IV, intravenous; MI, myocardial infarction; NSTEMI, non-ST elevation myocardial infarction; LDL, low density lipoprotein; PCI, percutaneous coronary intervention; STEMI, ST elevation myocardial infarction; TIA, transient ischemic attack; TIMI, Thrombolysis in myocardial infarction.
[a] Calculated using the Mosteller formula.
[b] Calculated using the Cockcroft-Gault formula.
[c] In all patients a non-ionic, low-osmolarity contrast agent was used.

3.2; P = 0.691). However, AKI incidence continued to be associated with approximately two-fold higher mortality (HR 1.9 95% CI 1.1–3.2; P = 0.028) in a multivariable model including all variables that differed between patients with and without AKI (age > 70, gender, smoking status, haemoglobin levels, baseline GFR classification, ejection fraction classification, peak CPK levels during admission, site of myocardial

Table 2
Overall and cause-specific short, long and very long-term mortality.

	Study population (n = 518)	Patients without AKI[a] (n = 434)	Patients with AKI[a] (n = 84)	P-value
Death from any cause between admission and year 1	42 (8.1)	28 (6.5)	14 (16.7)	0.004
Cardiac	34 (6.6)	20 (4.6)	14 (16.7)	
Non-cardiac	8 (1.5)	8 (1.9)	0 (−)	
Death from any cause between year 1 and year 3	28 (5.9)	12 (3)	16 (22.9)	<0.001
Cardiac	8 (1.7)	4 (1)	4 (5.7)	
Non-cardiac	20 (4.2)	8 (2)	12 (17.2)	
Death from any cause from year 3 and beyond	26 (5.8)	24 (6.1)	2 (3.7)	0.756
Cardiac	14 (3.1)	12 (3.05)	2 (3.7)	
Non-cardiac	12 (2.7)	12 (3.05)	0 (−)	
Death from any cause between admission and end of follow-up	96 (18.5)	64 (14.7)	32 (38.1)	<0.001
Cardiac	56 (10.8)	36 (8.3)	20 (23.8)	
Non-cardiac	40 (7.7)	28 (6.4)	12 (14.3)	

Values are n (%).
AKI, acute kidney injury; KDIGO, Kidney Disease: Improving Global Outcomes and the Acute Dialysis Quality Initiative; RIFLE, Risk, Injury and Failure.
[a] AKI was defined using the modified KDIGO or RIFLE criteria during hospitalisation.



No at Risk	Admission	1 year	2 years	3 years	4 years	5 years	6 years	7 years
W/o AKIN	434	406	398	394	380	298	194	54
With AKIN	84	70	60	54	52	42	26	12

Fig. 1. Kaplan-Meier curves showing the cumulative risk of death in patients admitted with myocardial infarction who were dichotomized according to whether they developed acute kidney injury or not during their index hospitalisation. A total of 518 patients, about 65% of the initial study population, were followed-up long-term with a median of 5.6 years, and an interquartile range of 4.6 to 6.5 years. Overall, the long-term mortality rate differed significantly between the two study groups (38.1% vs. 14.7%; log-rank test P < 0.001). Blue line: patients without acute kidney injury; Green line: patients with acute kidney injury. AKI: acute kidney injury; w/o: without.

infarction, TIMI risk score, Killip class, presence of adverse event during index hospitalisation, and use of angiotensin receptor blockers during follow-up) (Suppl. Table 3).

3.4. AKI severity and associated prognosis

Stratification analysis using stages of AKI severity as the pre-specified strata showed that increasing AKI severity was associated with a worse prognosis (Suppl. Table 4). Cox regression analysis corroborated the aforementioned results of chi-square analysis (Fig. 2).

3.5. Secondary outcomes

Deterioration in kidney function was observed in 5.8% of the whole study population during follow-up. Patients with AKI during their index hospitalisation had a higher incidence of deteriorating kidney function (9.5%) than in patients without AKI (5.1%) during follow-up. The difference, however, was not significant (P = 0.124) (Suppl. Table 5). The incidence of MACE was 17.4% in the study population during follow-up. Patients with AKI during their index hospitalisation had a significantly (P = 0.027) higher incidence of MACE (26.2%) than in patients without AKI (15.7%) (Suppl. Table 5).

3.6. Impact of kidney dysfunction duration on prognosis

In a very small fraction of our study cohort patients who developed AKI at 48 h, kidney injury resolved upon hospital discharge [14 patients (3%)]. In this special study sub-group only 2 deaths were captured (mortality of 14%) during long term follow-up. Mortality rate in this subgroup was similar compared to patients who did not develop AKI during hospitalisation [2 deaths (14.3%) vs. 64 deaths (14.7%); P = 0.737].

We managed to obtain serum creatinine levels at the end of follow-up and also to capture the occurrence or not of additional factors detrimental to renal function in 344 patients (Suppl. Fig. 1, 66.4% of the followed-up cohort; 42.7% of the initial study cohort) who survived the 5.6-year follow-up. These factors were: additional use of contrast media for diagnostic or interventional purposes, hospitalisation due to sepsis, or hospitalisation in an intensive care unit. The mean creatinine level at the end of follow-up was 1.1 ± 0.8 mg/dL. The median (IQR) level for the absolute difference in creatinine levels between measurements at the end of follow-up and peak measurements during index hospitalisation was −0.02 mg/dL (−0.12 to 0.10 mg/dL). Conversely, the relative percent change observed was −2% (−13 to 11%). A second factor detrimental to renal function was reported during follow-up for 118 (34%) patients.

Among patients who developed AKI during index hospitalisation, creatinine measurements during long-term follow-up were available for 42 (50%) of the 84 patients followed up. In this sub-group of patients with increased creatinine levels (post-discharge), the absolute difference was −0.2 mg/dL (−0.5to 0.03 mg/dL), whereas the relative percent change was −15% (−30 to 3%). During follow-up, the creatinine levels decreased in two-thirds of the 42 patients (28/42; 67%) and increased in one-third in the remainder (14/42; 33%). The latter sub-group of patients with increasing creatinine levels had a higher incidence of MACE during follow-up than patients with declining creatinine levels (Suppl. Fig. 2, 28% vs. 0%, chi-square test; P = 0.016). Interestingly, patients with a permanent increase in creatinine levels showed a higher incidence of a second factor detrimental to kidney function than those in whom creatinine levels were declining (Suppl. Fig. 2, 57% vs. 7%; chi-square test; P = 0.001).

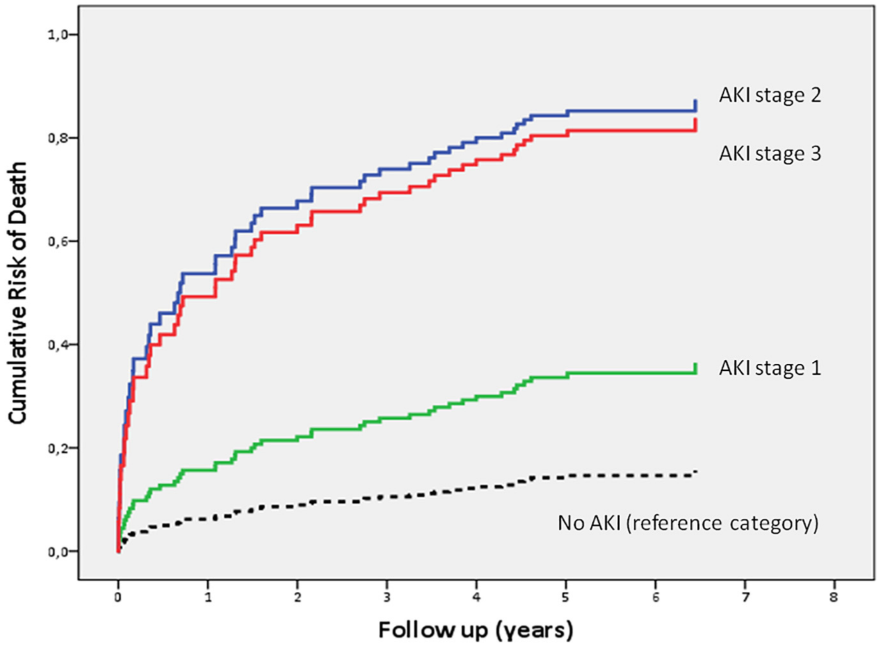


Fig. 2. Cox regression analysis curves showing cumulative risk of death in patients admitted with myocardial infarction who were stratified according to acute kidney injury during their index hospitalisation. Black dotted line: patients without acute kidney injury (reference line); Green line: AKI stage 1; Blue line: AKI stage 2; Red line: AKI stage 3. Modified KDIGO criteria were used for AKI staging (according to these, changes in creatinine and GFR were presumed to have occurred during hospitalisation). AKI: acute kidney injury; GFR: glomerular filtration rate; KDIGO: Kidney Disease: Improving Global Outcomes and the Acute Dialysis Quality Initiative.

Conversely, long-term creatinine level data were available from 302 (70%) of the patients who did not develop AKI during their index hospitalisation (302 out of 434 patients followed up). In this sub-group of patients, the absolute difference in creatinine levels was 0 mg/dL (−0.1 to 0.1 mg/dL) and the relative percent change was 0% (−11 to 11%). In the sub-group of patients with normal creatinine levels post-discharge, half (146; 48%) had declining creatinine levels and the other half (156; 52%) showed increasing creatinine levels during follow-up. No significant difference in incidence of MACE was observed between these two sub-group of patients during long-term follow-up (11% vs. 14%, chi-square test; $P = 0.488$). No differences with regard to the incidence of a second factor detrimental to kidney function were noted between patients with declining and patients with increasing creatinine levels (34% vs. 37%; $P = 0.632$).

4. Discussion

Recently, a large multicentre observational study from our group reported on the short-term prognosis (two-year follow-up) of the occurrence of AKI during hospitalisation in patients with AMI [13]. In our two-year follow-up, patients with AKI during index hospitalisation had higher total mortality than patients without AKI (22% vs. 6%; $P < 0.001$) [13]. Rehospitalisation and revascularisation rates were similar in the two groups, but patients who developed AKI during hospitalisation showed chronic kidney disease (CKD) more frequently during follow-up (12% vs. 2%; $P < 0.001$) [13]. Predictors of in-hospital AKI in our study population were age over 70 years of age, female gender, current smoking status, low haemoglobin levels, low baseline GFR classification, low ejection fraction classification, increased CPK levels during admission, anterior site of myocardial infarction, higher TIMI risk score and Killip class, presence of adverse event during index hospitalisation, and use of angiotensin receptor blockers. The present analysis of study patients showed over seven years of follow-up that the occurrence of AKI during index hospitalisation was associated with an increased in total cumulative mortality. Furthermore, this association was independent of the effect of possible confounders and was evident up to year three of follow-up. The severity of AKI had a statistically significant impact on the cumulative risk of death. MACE were more common during follow-up in patients with AKI during index hospitalisation. The association between the incidence of AKI and declining renal function was only marginal, defined with relevant endpoints such as hospitalisation for acute renal failure, regular follow-up at the renal outpatient clinic, transient or permanent renal replacement therapy, history of or planned kidney transplantation. This weak association may be partially explained by our finding that in two-thirds of our patients with AKI, kidney function returned to normal in the long-term in a sub-group of patients for whom creatinine levels were available at the end of follow-up. In contrast, one third of our AKI patients who developed permanent loss of kidney function had a very poor prognosis as suggested by the strong association with the incidence of MACE during long-term follow-up. This minority of AKI patients had an increased incidence of other factors detrimental to kidney function during follow-up.

Several mechanisms have been proposed to explain cardiac dysfunction and adverse outcomes after AKI, such as fluid overload contributing to pulmonary edema, endothelial dysfunction, hypercoagulation [21]. Several observational studies have contributed to a substantial improvement in our understanding of the impact of the occurrence of AKI during index hospitalisation on long-term prognosis [1,2,20]. Previous studies have mainly shown a robust and constant association between occurrence of AKI and prognosis, despite great heterogeneity of patients due to different definitions of AKI and different clinical settings [3,22,23]. Furthermore, several issues have been raised regarding quantification and interpretation of this association, especially the long-term prognosis, as it was evident that this association may be statistically significantly modified by pre-hospitalisation creatinine levels, the severity of AKI, recovery or not of kidney function after AKI, the timing of events, and presence or not of further factors detrimental to renal function during long-term follow-up [1,2,20]. Previous studies addressing these issues had a number of limitations such as restricted follow-up periods of only up to three years [6,8,9,12], retrospective design [6,8–11], and addressing only the effect of the severity of AKI on prognosis [5,7,9–11]. Only one study assessed the effect of recovery from kidney dysfunction (transient or permanent decline in renal function) [9], whilst a further study, in addition to cumulative events, assessed only the effect of timing of the outcomes observed [10].

Our finding of a two- to three-fold increase in cumulative mortality in AMI patients with AKI during follow-up is in-line with previous reports [5–12], and meta-analyses [2,22]. Similarly, our finding that a more severe AKI stage is associated with a more dismal prognosis has been also corroborated by previous studies [5,7,9–11]. In our study, MACE were more frequent in patients with a ‘permanent’ decline in kidney function, i.e. who did not recover fully from AKI. Goldberg et al. also found that patients with persistent moderate-to-severe AKI had the highest mortality, whereas patients with transient moderate-to-severe injury had an intermediate risk [9]. Similar findings were also reported by Latchamsetty et al. [24], and Wi et al. [25], although during shorter follow-up periods, and also by Maioli et al. [26] in patients with CKD (GFR < 60 mL/min) undergoing coronary angiography.

The weak long-term association between adverse outcome and AKI after the index AMI event in our study is in contrast to the findings of Parikh et al., who reported that during a ten-year follow-up period, the incidence of AKI continued to be associated with mortality even after excluding patients who died within three years of admission [10]. However, the gradient of risk across different severities of AKI was attenuated (HR 1.1 to 1.2). This discrepancy may have also occurred because of different patient cohorts since the retrospective analysed cohort consisted of patients who were hospitalised from 1994 through 1996 and probably reflect different and outdated in-hospital practices. In addition, our patient population had apparently a lower risk for renal complications given the relatively young age, and in particular concerning the basal renal function since only a small minority (15%) of patients had chronic kidney disease. Similarly, patients with severe LV dysfunction are unrepresented in this study and the global low risk profile may explain the lack of correlation between renal function and late mortality.

Findings of the current study are noteworthy from the perspective of a clinician caring for a patient with AMI after recovery from AKI. The occurrence of AKI during index hospitalisation for AMI should be documented in the patient's medical history since it is associated with a poor long-term prognosis (for at least three years after the initial event). After three years although the association with prognosis is attenuated a certain level of vigilance is required such as monitoring of renal function, adjustment of renally excreted medications, avoidance or withdrawal of nephrotoxic medications and consideration of interventions with renoprotective properties especially when procedures with use of contrast media are warranted. Currently only a minority of patients who develop AKI during hospitalisation and recover renal function receive long-term nephrology follow-up, demonstrating the necessity to establish targeted AKI follow-up programs in high-risk patients [27]. Our findings emphasise the need for appropriate involvement of renal services during index hospitalisation of such patients in order to allow appropriately targeted follow-up.

Marenzi et al. [2], were the first to suggest the concept of the ‘renal reserve’, claiming that the initial episode of AKI in patients with normal renal function is usually clinically uneventful and is associated with a poor prognosis only within the short-term. In the long-term, however, multiple episodes of AKI gradually deplete this ‘renal reserve’, resulting in the development of CKD and a poor survival prognosis. The hypothesis was adopted by the Acute Disease Quality Initiative (ADQI) in a recent consensus document in which five different hypothetical trajectories of acute kidney disease were proposed [20]. This sub-group of patients (patients who have suffered an AKI during their index hospitalisation but their creatinine returned to normal) represents a sub-clinical chronic kidney disease patients group (Stage 0B by ADQI) with no evidence of ongoing kidney damage who although are characterized with normal creatinine levels this occurs at the expense of their ‘renal reserve’. This ‘renal reserve’ may characterize the ability of a kidney to functionally overcome acute loss nephrons by adaptations in renal haemodynamics to maintain sufficient GFR, resulting in glomerular over-filtration in the residual nephrons and release of neurohormones that affect renal blood flow [2]. One more example of this scenario would be a patient who has undergone a nephrectomy, whereby the contralateral kidney might adapt to the loss of renal mass, but a significant portion of renal reserve has nonetheless been lost [20].

4.1. Study limitations and strengths

Our study has several limitations due to the incomplete information regarding some important variables. First, long-term follow-up was performed in about 2/3 of the initial study population and although selection bias cannot be ruled out, no statistically significant differences were found at baseline concerning AKI incidence between the patients who were followed up over the long term and analysed in the present study. Second, the residual LV function, severity of CAD and missing serum creatinine levels at the end of follow-up were not available from all survivors. Under the same notion, an increased representation of STEMI patients compared to NSTEMI patients (70:30 ratio) could have influenced our results since The pathophysiology of AKI in STEMI patients is somehow different in STEMI patients and is multifactorial compared to NSTEMI patients [28]. However, presence of AKI in both STEMI and NSTEMI patients was associated with increased mortality (STEMI patients, n = 362, HR 3.3 95% CI 1.9–5.5; P < 0.001 vs. NTEMI patients, n = 156, HR 3.3 95% CI 1.6–6.9; P = 0.002). Another limitation is that we have not captured the type of vascular access (femoral vs. radial) in our study population and its impact on AKI occurrence as there are contradictory data in current literature. Ando et al., showed that in acute coronary syndrome patients who underwent invasive management, radial access was associated with a reduced risk of AKI compared with femoral access [29] whereas Barbieri et al., showed absence of relationship between the angiographic access and the incidence of AKI in patients undergoing coronary angiography or/and PCI [30]. Furthermore, we have not used in our analysis the definition for contrast - induced nephropathy (increase in creatinine > 0.5 mg/dL) which has been characterized by a better prognostic ability for at least in-hospital mortality [31,32]. Finally, renal function was not determined at regular intervals during follow-up.

On the other hand, our study's strengths are its prospective and multicentre design, long-term follow-up, and assessment of factors that might modify the effect of AKI during index hospitalisation on the long-term prognosis such as the timing of the events, recovery or not of kidney function, and the severity of the AKI.

5. Conclusions

We analysed the association between the occurrence of AKI in AMI patients during index hospitalisation and long-term prognosis in a multicentre, prospective, observational, cohort study with long-term follow-up (median 5.6 years). The association weakened after three years, and cardiovascular morbidity (MACE) was statistically significantly affected by non-recovery of kidney function during follow-up. Presence of additional factors detrimental to renal function was more evident in patients whose kidney function did not recover. These results suggest that in addition to an expected increased mortality and morbidity during the first three years after the index event, patients should be regularly monitored concerning their renal function especially by means of avoiding a second renal ‘insult’.

Author contributions

Each one of the authors has contributed significantly to the submitted work. The original concept of the present study was developed by DT and GC. The study was designed and planned by DT, SK, GC, VV and NP. Acquisition of the data was done by LS, SC, PK, AT, DS, AL and DM. Statistical analysis was done by GC and MM. Data analysis and interpretation was done by DT, SK, GC, VV, NP, PK, AT, DS, AL and SA. The manuscript was drafted by GC, SC, DM, PK and AT. The manuscript was critically reviewed for intellectual content by DT,SK and SA. All authors approved the final draft for submission. All authors had full access to all data in the study and take responsibility for the integrity and accuracy of data analysis.

Conflict of interest statement

All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. No financial disclosures were reported.

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Appendix A. Supplementary data

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