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TITOLO TESI

THE CARDIO-RENAL AXIS. NON ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION RISK STRATIFICATION ACCORDING TO RENAL DYSFUNCTION

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ABSTRACT

Background: Chronic kidney disease (CKD) is one of the strongest risk factor for myocardial infarction (MI) and mortality. The aim of this study was to assess the association between renal dysfunction severity, short-term outcomes and the use of in-hospital evidence-based therapies among patients with non–ST-segment elevation myocardial infarction (NSTEMI).

Methods: We examined data on 320 patients presenting with NSTEMI to Maggiore's Emergency Department from 1st Jan 2010 to 31st December 2011. The study patients were classified into two groups according to their baseline glomerular filtration rate (GFR): renal dysfunction (RD) (GFR<60) and non-RD (GFR≥60 ml/min). Patients were then classified into four groups according to their CKD stage (GFR≥60, GFR 59-30, GFR 29-15, GFR <15).

Results: Of the 320 patients, 155 (48,4%) had a GFR<60 ml/min at baseline. Compared with patients with a GFR≥60 ml/min, this group was, more likely to be female, to have hypertension, a previous myocardial infarction, stroke or TIA, had higher levels of uric acid and C-reactive protein. They were less likely to receive immediate (first 24 hours) evidence-based therapies. The GFR of RD patients treated appropriately increases on average by 5.5 ml/min/1.73 m^2. The length of stay (mean, SD) increased with increasing CKD stage, respectively 5,3 (4,1), 7.0 (6.1), 7.8 (7.0), 9.2 (5.8) (global p <.0001). Females had on average a longer hospitalization than males, regardless of RD. In hospital mortality was higher in RD group (3,25%).

Conclusions: The in-hospital mortality not was statically difference among the patients with a GFR value ≥60 ml/min, and patients with a GFR value <60 ml/min. The length of stay increased with increasing CKD stages. Despite patients with RD have more comorbidities then without RD less frequently receive guideline –recommended therapy. The GFR of RD patients treated appropriately improves during hospitalization, but not a level as we expected.

ABBREVIATIONS

RD	Renal Dysfunction
CKD	Chronic Kidney Disease
RRT	Renal Replacement Therapy
ESRD	End Stage Renal Disease
NKF-K/DOQI	The National Kidney Foundation – Kidney Disease Outcomes Quality Initiative
CVD	Cardiovascular Disease
LVH	Left Ventricular Hypertrophy
STEMI	ST-Segment Elevation Myocardial Infarction
NSTEMI	Non-ST-Segment Elevation Myocardial Infarction
CHD	Coronary Heart Disease
CAD	Coronary Artery Disease
ACS	Acute Coronary Syndromes
PCI	Percutaneous Coronary Intervention
GFR	Glomerular Filtration Rate
CHF	Congestive Heart Failure
LV	Left Ventricle
CRS	Cardio-Renal Syndromes
AKI	Acute Kidney Injury
TIA	Transient Ischemic Attack
PAD	Peripheral Artery Disease
CRP	C-Reactive Protein
UA	Uric Acid
LMWH	Low Molecular Weight Heparin

1. INTRODUCTION

1.1 Definition of CKD

Chronic kidney disease (CKD) is a worldwide public health problem, becoming more and more relevant with the increased life expectancy of the population.

The overall prevalence of Chronic Kidney Disease (CKD) defined as MDRD-estimated glomerular filtration rate (GFR) <60 ml/min per 1.73 m2 and/or the presence of albuminuria, for three months or more, appears to have increased significantly in the period from 1999 to 2004 compared with 1988 to 1994. [Jones CA,1998][Nissenson AR,2001]. Reduced renal function has been estimated to affect almost 1 in 5 people in North America [Class CM GA, 2002][Go AS, 2004]. Furthermore renal dysfunction is associated with significant comorbidity that increases with progressive renal decline.

All individuals with a glomerular filtration rate (GFR) <60 ml/min/1.73 m^2 for at least 3 months are classified as having chronic kidney disease, independently from the presence or absence of kidney damage. The rationale is that reduction in kidney function to this level or lower represents the loss of half or more of the adult level of normal kidney function, which may be associated with a number of complications. On the other hand, all people with renal damage are classified as having chronic kidney disease, including persons with a GFR > 60 ml/min/1.73 m^2; as a matter of fact GFR may be sustained at normal or increased levels despite substantial kidney damage and patients with kidney damage are at increased risk of the two major outcomes of chronic kidney disease: loss of renal function and development of cardiovascular disease.

The loss of protein in the urine is regarded as an independent marker for worsening of renal function and cardiovascular disease.

1.2 Stages of CKD (NKF-K/DOQI Classification)

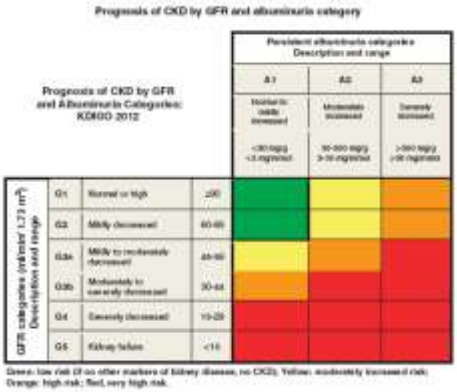
The National Kidney Foundation – Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) workgroup has classified CKD in five stages (Figure 1):

- Stage 1: Slightly diminished function; kidney damage with normal or relatively high GFR (≥90 mL/min/1.73 m^2). Kidney damage is defined as pathological abnormalities or markers of damage, including abnormalities in blood or urine test or imaging studies.

- Stage 2: Mild reduction in GFR (60–89 ml/min/1.73 m^2) with kidney damage. Kidney damage is defined as pathological abnormalities or markers of damage, including abnormalities in blood or urine test or imaging studies.
- Stage 3: Moderate reduction in GFR (30–59 ml/min/1.73 m^2), further divided in stage 3A (GFR 45–59) and stage 3B (GFR 30–44).
- Stage 4: Severe reduction in GFR (15–29 ml/min/1.73 m^2) with the need to prepare the patient for renal replacement therapy.
- Stage 5: Established kidney failure with a GFR <15 ml/min/1.73 m^2, permanent renal replacement therapy (RRT), or end stage renal disease (ESRD).

Both early stages CKD and End Stage Renal Disease (ESRD) are associated with high morbidity and increased health care utilization. In early stage CKD (stages 1-2) we notice an independent association between microalbuminuria and CVD; as a matter of fact microalbuminuria may represent kidney dysfunction itself or be a manifestation of systemic endothelial disease burden, with an higher prevalence of surrogate of CVD (LVH, carotid arterial intima-media thickening, etc.) in patients with microalbuminuria. The elevated prevalence of CVD we found in incident dialysis patients (CKD stages 3-4) suggests that CVD develops before the onset of kidney failure; there is an higher prevalence of coronary artery disease, heart failure and CVD risk factors in CKD stage 3-4 compared to the general population. In particular, there is a graded and independent correlation between estimated GFR and CVD outcomes, especially in patients with estimated GFR<45 ml/min/1.73 m^2 [Shani Shastri, 2010]. Last but not least, roughly fifty percent of dialysis patients have three or more comorbid conditions, the number of hospitalizations and hospital days are 1.9 and 12.8 per patient-year, respectively, and self-reported quality of life is far lower in dialysis patients than in the general population. [United States Renal Data System, USRDS 2010][United States Renal Data System, 2009; McClellan WM, 1991] Once an individual reaches ESRD, cardiovascular disease is responsible for approximately half of deaths. These individuals are 20 times more likely to have a CV-related death than for their kidneys to progressively fail to require dialysis or transplantation.

[Figure 1 NKF-K/DOQI guidelines on CKD]



1.3 CKD as risk factor, for CVD, and predictor of outcomes

It is widely known that Chronic Kidney Disease (CKD) is associated with an increased risk of cardiovascular disease, stroke, peripheral arterial disease and high mortality.

Cardiovascular disease is the principal cause of morbidity and mortality in patients with CKD and ESRD. Patients with CKD not only have a high prevalence of traditional CVD (cardiovascular disease) risk factors, but also are exposed to other non-traditional uremia-related CVD risk factors. A lot of Clinical trials demonstrated a correlation between worse CV outcomes and more severe CKD, with progressively higher incidence in stages 3, 4 and 5; patients undergoing dialysis have the highest CV risk and mortality in the renal population.

Many studies evaluated the risk of acute coronary artery disease in CKD patients; an higher incidence of ST-Segment Elevation Myocardial Infarction (STEMI) and Non-ST-Segment Elevation Myocardial Infarction (NSTEMI), compared to population without CKD, was noted. The risk of MI is related to CKD stage, being progressively elevated in stage 3, 4 and 5. In addition same studies have shown that the patients with CKD have in higher proportion NSTEMI than STEMI [Fox C, 2010].

CKD represents a risk factor for poor outcomes once CVD has developed. Furthermore CKD patients presenting with NSTEMI have more comorbidities and receive guideline-recommended therapies less frequently than do patients without CKD [Caroline S. Fox, 2010].

Patients with renal dysfunction are known to have poor outcomes after the occurrence of MI; among patients presenting with MI the presence of CKD is associated with an increased risk of death and major bleeding.

CKD is an independent risk factor for the development of coronary artery disease, and for more severe coronary heart disease (CHD) [Sarnak MJ, 2003; Chen J, 2004; Kaysen GA, 2004; Ix JH, 2003]. CKD is also associated with adverse outcomes in those with existing cardiovascular disease [Muntner P, 2002; Drey N, 2003; Shlipak MG, 2004]. This includes increased mortality after an acute coronary syndrome, after percutaneous coronary intervention (PCI) with or without stenting [Shlipak MG, 2002; Al Suwaidi J, 2002; Gibson CM, 2003; Best PJ, 2002; Reincke H, 2003], and after coronary artery bypass.

There are a lot of observational studies demonstrating that a reduced GFR and proteinuria are both independently associated with an increased risk of cardiovascular events in populations of patients who were not selected based upon the presence of known kidney or cardiovascular disease [Muntner P, 2002; Foley RN, 2005; Hallan S, 2007; Pinkau T, 2004; Hillege HL, 2002; Weiner DE, 2004; Tonelli M, 2006].

1.4 Pathophysiology of CVD in CKD

The pathophysiologic forms of CVD in patients with CKD include 3 main alteration: atherosclerosis, arteriosclerosis and cardiomyopathy. Atherosclerosis consists of an occlusive disease of the vasculature, with focal plaque formation resulting in luminal narrowing; it's the manifestation of risk factors that are prevalent as kidney dysfunction progresses, including an highly atherogenic lipid profile. Concerning arteriosclerosis, this represents a nonocclusive remodelling of the vasculature, characterized by diffuse dilatation and hypertrophy of large arteries with loss of arterial elasticity and reduced arterial compliance. Manifestations of arteriosclerosis include LVH, decreased coronary perfusion and increased systolic blood pressure and pulse pressure. LVH resulting from either pressure or volume overload reflects appropriate adaptation by the heart to these forces. As a matter of fact, as workload increases over time, increased oxygen demands by the hypertrophied left ventricle ultimately may exceed its perfusion, resulting in ischemia and eventual myocyte death. The end stage of this process is cardiomyopathy.

1.5 Cardiovascular risk factors in patients with CKD

Hypertension, diabetes, smoking, dyslipidemia and older age are highly prevalent in CKD populations, and the number of this kind of cardiovascular risk appears to correlate with the severity of kidney dysfunction, defined as "traditional" atherosclerotic risk factors in the Framingham Heart

Study [Foley RN, 2005]. There are a number of uremia-related risk factors, such as anemia, retention of uremic toxins, chronic inflammation, alteration in calcium/phosphorus metabolism and a hypercoagulable milieu that also play a role in promoting CVD. Recent epidemiologic data suggest that many conditions related to the uremic state may be associated with cardiac disease. For example, anaemia is clearly associated with LVH, congestive heart failure, hospitalization and mortality. Other variables include dialysis dose and abnormalities of calcium-phosphorus metabolism. Chronically uremic patients also have an increased prevalence of hyperhomocystinemia, inflammation, oxidative stress and endothelial dysfunction, compared with patients who have normal kidney function.

[Figure 2 – From Ronco et al., 2010]

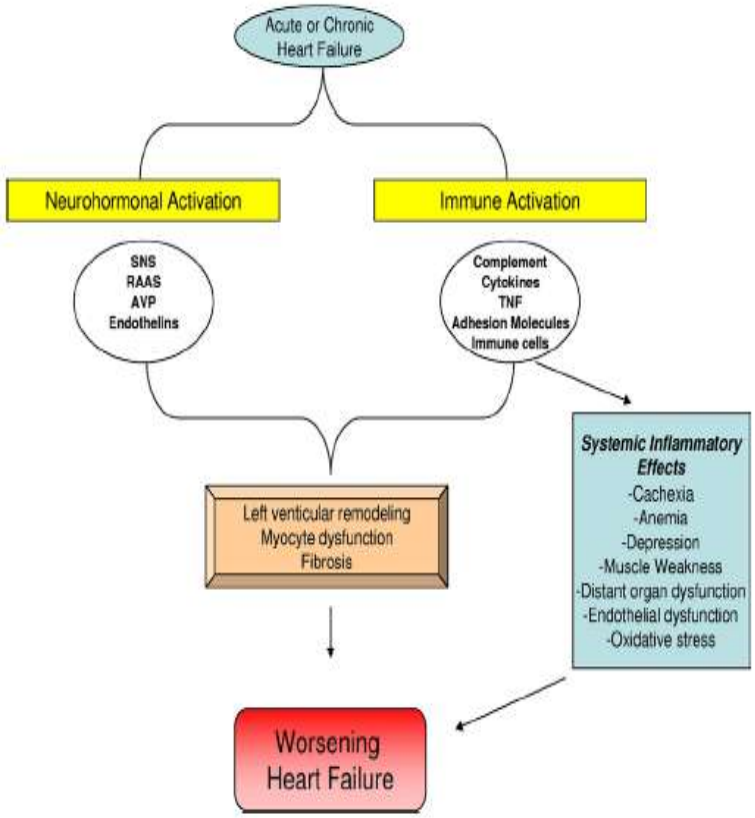


Figure 1. The role of inflammation in HF. Acute or chronic HF leads to concomitant activation of both neurohormonal and inflammatory pathways that result in deleterious effects on left ventricular function and structure. Inflammatory pathway activation also leads to important systemic effects that increase the morbidity and mortality associated with HF. AVP, arginine vasopressin; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system.

The incidence and severity of coronary artery disease increases as GFR declines. [Nakano T, 2010; Chonchol M, 2008]. CAD shows a pattern of diffuse multi-vessel involvement with coronary calcification. CV morbidity and mortality are inversely and independently associated with kidney function, particularly at estimated GFR < 15 ml/min per 1.73 m^2. Although the absolute incidence and mortality rate of MI is clearly elevated in advanced CKD [US renal data system. USRDS 2008], standard cardiovascular risk factors are common in the setting of CKD, but do not fully explain the high incidence of CV events or increased mortality rates.

CKD is also associated with increased prevalence of concomitant Congestive Heart Failure (CHF), ischemic heart disease, cardiac arrhythmias and valvular calcification [Ronco C, 2010; Schrier RW, 2007]. In observational studies, CHF prevalence increases with declining kidney function, representing the leading cardiovascular condition in CKD patients.

1.6 Pathophisiology of CHD in CKD

CKD determines three major mechanisms that facilitate the development of cardiomiopathy and induce LV failure:

1. pressure overload
2. volume overload
3. CKD-associated non-hemodynamic factors (Figure 1)

The first one is the result of long-standing hypertension and vascular stiffness; increased LV wall stress determines changes in the composition and function of the myocardium, and this process is amplified by CKD-associated abnormalities. CKD progression is accompanied by progressive LVH and diastolic dysfunction. Arterial stiffening could be an important etiological aspect in CKD leading to CVD.

Beyond hemodynamic factors, inappropriate activation of the renin-angiotensin system, catalytic iron-dependent oxidative stress, inflammation and stimulation of prohypertrophic and profibrogenic factors (cardiotrophin-1, galectin-3, TGF-β, FGF-23) may be relevant.

LV diastolic dysfunction is frequent among CKD patients and is associated with the risk of CHF and increased mortality; impaired diastolic function may occur early in CKD, even without LVH [Cerasola G, 2011]. The imbalance we found in CKD patients between exaggerated collagen synthesis and unchanged or depressed collagen degradation lead to myocardial fibrosis; this is a

major determinant of LV stiffness, increased LV filling pressure and diastolic filling disturbances, resulting in a predisposition to the development of diastolic dysfunction/failure [Lopez B, 2008].

Usually in patients with renal dysfunction the resting LV systolic function is normal or even hyperdynamic, at least in the absence of ischemic heart disease or severe hemodynamic stress. [Curtis BM, 2005].

1.7 Role of renal dysfunction: cause or consequence of cardiovascular disease?

The term Cardio-Renal Syndromes (CRS) is used to describe the wide array of interrelated derangements between heart and kidney, and to underline the bidirectional nature of their interactions. CRS are defined as pathophysiologic disorders of both organ system, in which acute or chronic dysfunction of one may induce acute or chronic dysfunction of the other [Ronco C, 2010].

CRS are divided into 5 subtypes that reflect pathophysiology, time frame and nature of concomitant cardiac and renal dysfunction (Figure 3).

[Figure 3 – From Ronco et al., 2010]

Table 1. CRS

General definition
Pathophysiologic disorder of the heart and kidneys whereby acute or chronic dysfunction in one organ induces acute or chronic dysfunction in the other
CRS type I (acute CRS)
Abrupt worsening of cardiac function leading to AKI
CRS type II (chronic CRS)
Chronic abnormalities in cardiac function causing progressive and permanent chronic kidney disease
CRS type III (acute renocardiac syndrome)
Abrupt worsening of renal function causing acute cardiac disorders
CRS type IV (chronic renocardiac syndrome)
Chronic kidney disease contributing to decreased cardiac function, cardiac hypertrophy, and/or increased risk of adverse cardiovascular events
CRS type V (secondary CRS)
Systemic condition (eg, diabetes mellitus, sepsis) causing both cardiac and renal dysfunction

CRS type 1 and 2 are conditions we typically found in the field of cardiology, especially in the area of heart failure. Both acute heart failure leading to acute kidney injury (AKI), and chronic heart failure leading to progressive renal insufficiency and CKD represent conditions that easily may become interchangeable. Sometimes it can be hard to distinguish the two entities, which often differ only in the timeframe of the clinical history of the patient (Figure 4).

Reduced cardiac output, passive congestion of the kidneys, and increased intra-abdominal pressure may contribute to the disorder. Heart, kidneys, renin-angiotensin system, sympathetic nervous system, immune system, and vasculature interact through intricate feedback loops.

[Figure 4 – From Ronco et al., 2010]

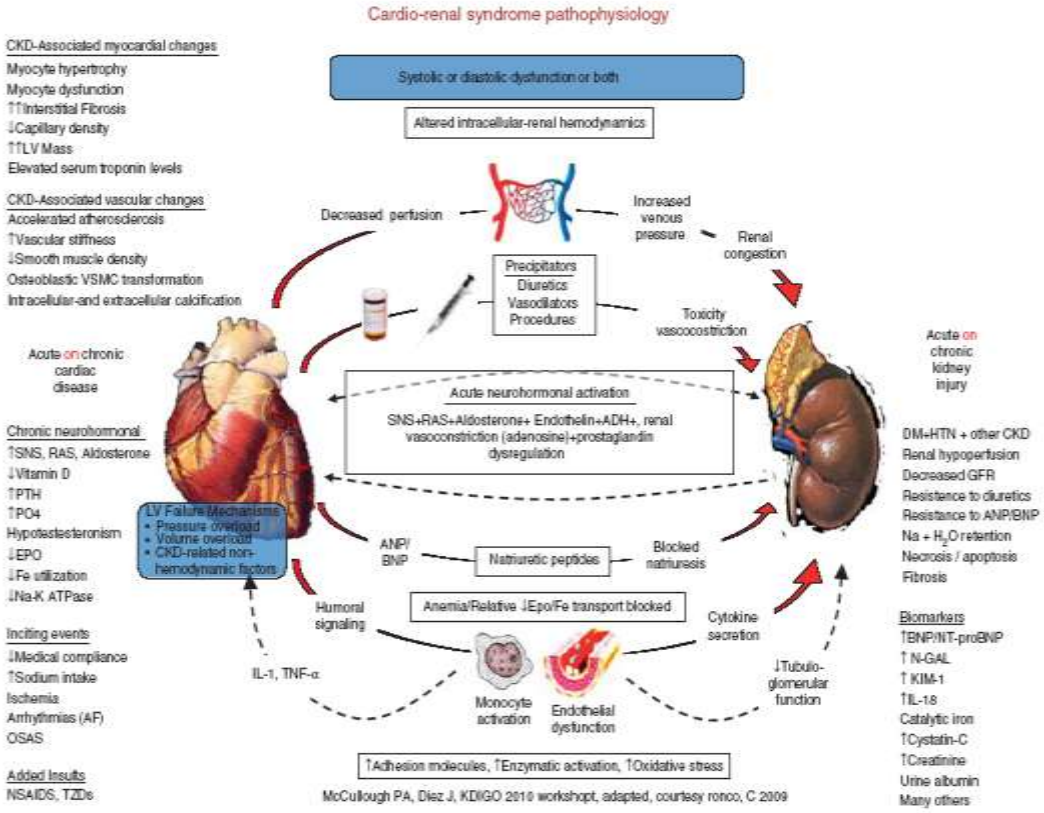


Figure 1 | Cardio-renal syndrome pathophysiology. ADH, antidiuretic hormone; ANP, atrial natriuretic peptide; BNP, B-type natriuretic peptide; CKD, chronic kidney disease; DM, diabetes mellitus; EPO, erythropoietin; HTN, hypertension; IL-1, interleukin-1; KIM-1, kidney injury molecule-1; LV, left ventricular; N-GAL, neutrophil gelatinase-associated lipocalin; NSAID, non-steroidal anti-inflammatory drug; OSAS, obstructive sleep apnea syndrome; PTH, parathyroid hormone; SNS, sympathetic nervous system; TNF-α, tumor necrosis factor-α; TZD, thiazolidinediones; VSMC, vascular smooth muscle cell.

CRS type 3 represents a different entity, because we usually see this condition in critically ill patients admitted to intensive care unit where AKI may induce defective myocardial contractility and secondary heart failure.

As regarding CRS type 4, this has been defined for many years as increased cardiovascular risk in patients with CKD; nowadays we know that, even in the very early stages of CKD, altered metabolism and gene expression may induce a complex derangement mediated by aldosterone receptors, oxidant stress and other factors. The unfriendly milieu related to uremia and the effects of iron deficiency and anaemia are analyzed in light of significant combined damage (Figure 5).

Recently the role of inflammation has been underlined as an important mechanism for kidney damage in heart failure, in addition to the classic hemodynamic and neurohormonal damage.

[Figure 5 – From Ronco et al. Factors involved in cardio-renal physiology]

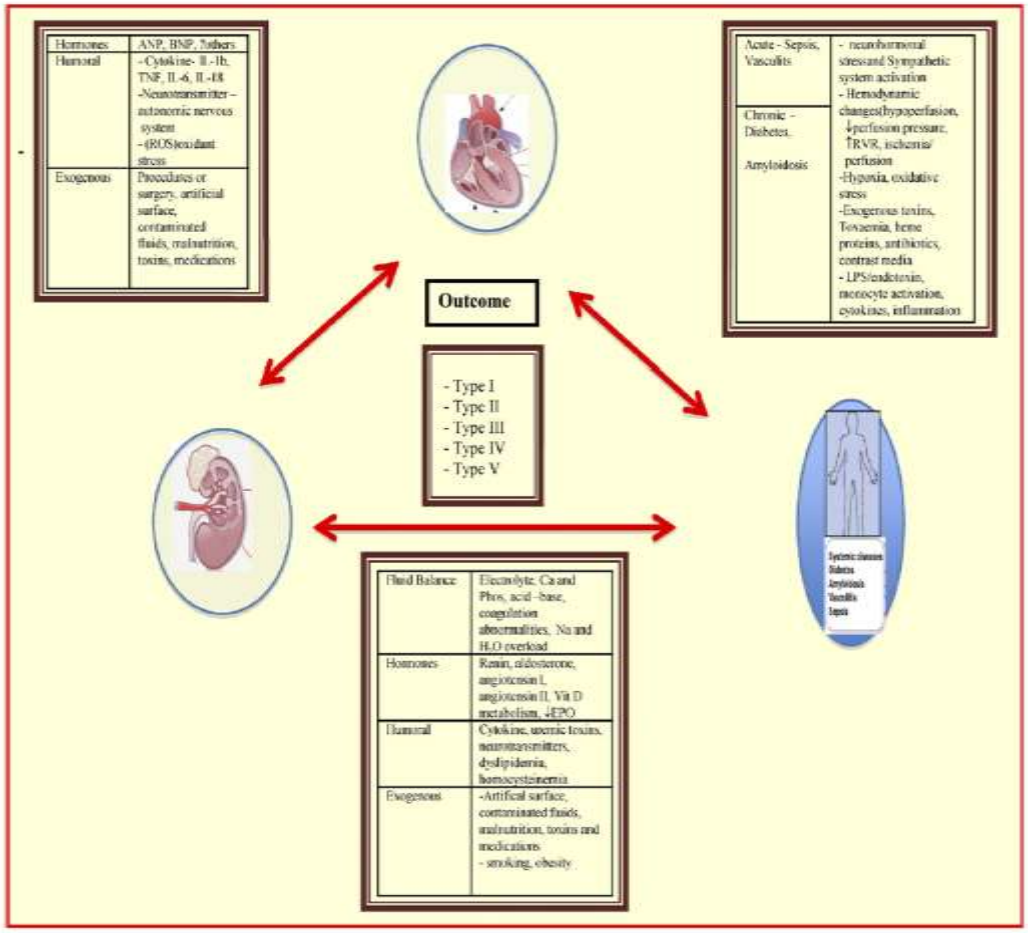


Figure 2. Factors involved in cardio-renal physiology. The diagram highlights the complex interaction of CRS. After a primary insult to heart, kidney, or secondary organ there is production of active factors with local and systemic effects. The primary insult may in itself cause organ dysfunction or stimulate the organ to produce counter-regulatory factors. These secondary factors may be directly toxic or secondarily toxic by altering systemic physiology. The outcome based on predominant pathophysiology can be classified as CRS types 1 to 5. The net result of any of these types of CRS will lead to the following: (1) development of acute and chronic organ dysfunction; (2) acceleration of underlying renal and cardiac disease—apoptosis, fibrosis, blood vessel endothelial dysfunction, smooth muscle proliferation, low-density lipoprotein (LDL) oxidation, accelerated atherosclerosis, myocardial damage (cardiac remodeling, increased ischemic risk, left ventricular hypertrophy, left diastolic dysfunction, decreased coronary perfusion, inflammation, and coronary and tissue calcification), neurohormonal abnormalities (eg, renin angiotensin system [RAS] activation); (3) Others—anemia of chronic disease (AOCD) (erythropoietin resistance, inflammation), bone remodeling, muscle metabolism, reduced appetite, acute phase reactants, adipocytokine production, insulin resistance, body mass index, and propagation of systemic inflammation. The severity of organ damage is related to the size of primary or secondary insult, time to diagnosis and implementing required therapies and resolution of the initiating cause. Modified from Ronco et al.[1]

2. Aim of the study

The purpose of this analysis was to characterize the short-term outcomes (in hospital mortality, the length of hospitalization) related to CKD in a NSTEMI population. In addition we evaluated use of evidence –based (guideline-recommend) therapy, particularly the immediate therapy (first 24 hours) in this population.

3. Material and methods

3.1 Study simple

We examined data on 320 patients presenting with non ST-segment elevation myocardial infarction (NSTEMI) to Maggiore's Emergency Department from 1st Jan 2010 to 31st December 2011. The study population was analyzed retrospectively, extracting information from the electronic medical records of the patients with respect to ethical conditions. We excluded 168 patients from a number of 488 patients for insufficient electronic documentation.

3.2 Patients selection

The study patients were classified into two groups according to their baseline glomerular filtration rate, estimated using Cockcroft-Gault formula: renal dysfunction (RD) (GFR <60 ml/min/1.73 $m^{2)}$ and non-RD (GFR ≥ 60 ml/min/1.73 $m^{2)}$.

Patients were then classified into four groups according to their KDOQI chronic kidney disease (CKD) stages (GFR≥60 ml/min/1.73 $m^{2,}$ GFR 59-30 ml/min/1.73 $m^{2,}$ GFR 29-15 ml/min/1.73 m^2, GFR <15 ml/min/1.73 m^2). On the basis of prior studies and the purpose of our study we are included patients with CKD stages 1 and 2 in non renal dysfunction group. Since we could not acquire information on admission microalbuminuria or hematuria, our data only allowed correct classification of patients in CKD stages 3-5.

3.3 GFR estimation and KDOQI classification

Cockcroft -Gault formula

Women: GFR (ml/min) = 0,85 x (140-age [years]) x weight [Kg] / 72 x serum creatinine [mg/dl]

Man: GFR (ml/min) = (140-age) [years] x weight [Kg] / 72 x serum creatinine [mg/dl]

KDOQI classification

Stage1 – kidney damage with normal or ↑ GFR, (GFR ≥ 90 ml/min/1.73 $m^{2)}$

Stage 2 – kidney damage with mild ↓GFR, (GFR 60-89 ml/min/1.73 $m^{2)}$

Stage 3 – moderate ↓ GFR, (GFR 30-59 ml/min/1.73 $m^{2)}$

Stage 4 – severe ↓ GFR, (GFR 15-29 ml/min/1.73 $m^{2)}$

Stage 5 – kidney failure, (GFR <15 ml/min/1.73 $m^{2)}$

Chronic kidney disease is defined as either kidney damage or GFR < 60 ml/min/1.73 m^2 for ≥ 3 month. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.

3.4 Statistical analysis

The risk factors which we included in analyses were defined like in the CHADSVASC Score:

- Age
- Gender
- Diabetes mellitus
- Hypertension
- Congestive heart failure/left ventricular dysfunction,
- Prior myocardial infarction,
- Peripheral artery disease,
- Prior stroke/TIA

In addition we included as the variable in the statistical models in hospital markers (Troponin I, C-reactive protein and uric acid), and in hospital medication (aspirin, clopidogrel, low weight molecular heparin, betablockers, statins, ACE-inhibitors).

We created a variable definite as immediate therapy related to association the aspirin, clopidogrel, low weight molecular heparin (LWMH), betablockers in the first 24 hour from hospital admission.

The first two groups: RD patients and non RD patients were compared on continuous variables using the t-test or the Mann-Whitney test and on categorical variables using the chi-square or Fisher exact test when appropriate.

The four group ((GFR≥60, GFR 59-30, GFR 29-15, GFR <15) were compared on continuous variables using ANOVA F or Kruskal-Wallis test, followed by post-hoc pairwise tests, and on

categorical variables using the chi-square test. Immediate treatment was defined as the association of Aspirin, Clopidogrel, LWMH, Betablockers, and it was coded as 1 if present or 0 if absent.

The change in GFR from baseline to discharge was estimated for patients with and without RD and as a function of treatment appropriateness using a general linear model. In this model, the estimates were adjusted for gender, age and days of admission. Patients undergoing dialysis were excluded from this analysis.

All analyses were carried out using Stata, version 12, or SPSS, version 20.0.

4. Results

4.1 Baseline characteristics of the patients

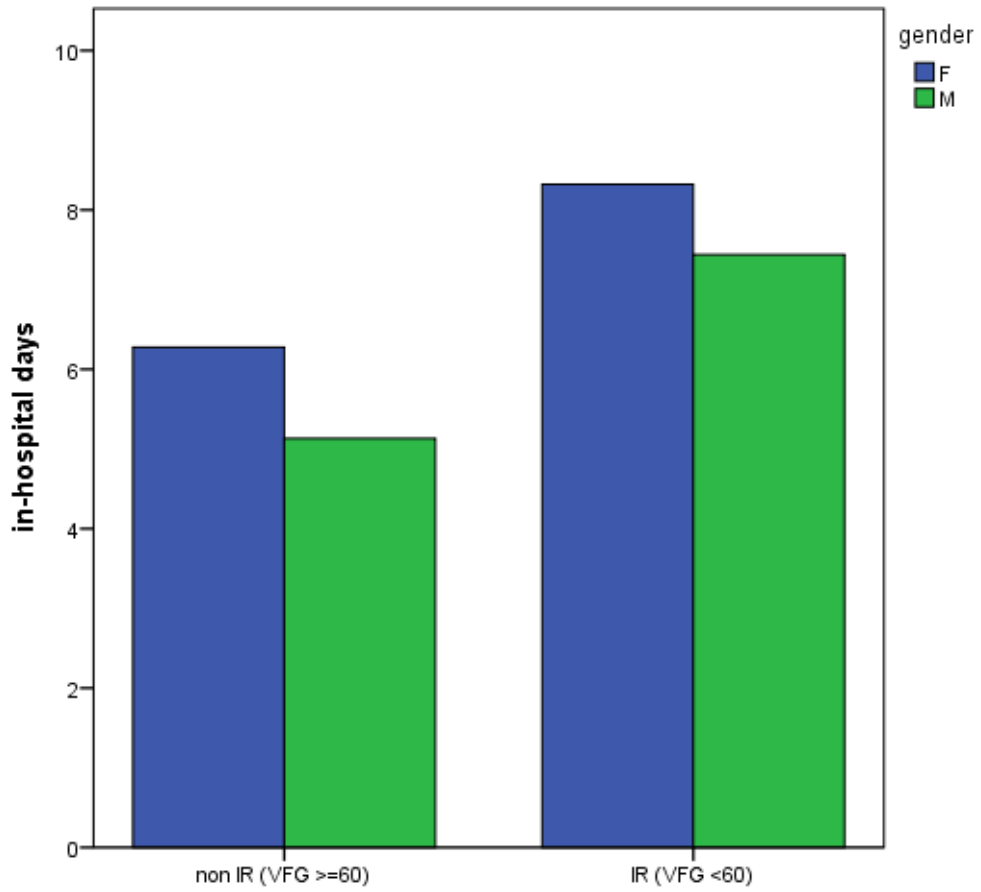
Of the 320 patients, 155 (48%) had a GFR<60 ml/min/1.73 m^2 at baseline. Compared with patients with a GFR ≥ 60 ml/min/1.73 m^2 , this group was on average 14 years older, was more likely to be female, to have hypertension, a previous MI, stroke or TIA, had higher levels of uric acid (an average by 1.1 mg/dl), and C-reactive protein (an average by 1.95 mg/dl) (Table 1).

Table 1. *Baseline characteristics in non RD patients and RD patients*

	Non-RD (GFR≥60) (n=165)	RD (GFR<60) (n=155)	p-value
Age (mean, SD) – y	66.3±11.3	82.0±8.44	<.0001
In hospital days (mean, SD)	5.33±4.12	7.95±6.4	<.0001
Male, n (%)	129 (78.1)	73 (47.1)	<.0001
History of lipid disorders, n (%)	99 (60.0)	81 (52.3)	.29
History of diabetes, n (%)	45 (27.3)	55 (35.7)	.36
History of hypertension, n (%)	120 (73.2)	126 (81.3)	.12
History of PAD, n (%)	8 (4.85)	24 (15.6)	.05
Prior myocardial infarction, n (%)	54 (32.9)	87 (87.9)	.005
Prior stroke/TIA, n (%)	12 (7.27)	28 (18.1)	.0009
Presentation characteristics, n (%)			
Heart failure	24 (14.55)	52 (33.55)	.08
Left ventricular dysfunction (EF<=40)	24 (14.55)	40 (25.81)	.28
In hospital markers, n (%)			
Troponin I	7.02±15.1	7.08±15.4	.97
C-reactive protein (CRP)	1.31±2.64 (n=159)	3.26±5.19 (n=147)	<.0001
Uric acid	6.28±1.99 (n=147)	7.36±2.31 (n=136)	<.0001
Angiographic findings, n (%)			
Coronarography	155 (94.5) (n=164)	87 (58.8) (n=148)	<.0001
1-vessel CAD	50 (32.9) (n=153)	14 (15.6) (n=92)	.003
2-vessel CAD	45 (29.4) (n=153)	23 (25.0) (n=92)	.45
3-vessel CAD	50 (32.5) (n=153)	50 (54.3) (n=92)	.001
PCI	113 (68.9) (n=164)	61 (41.2) (n=148)	<.0001
In-hospital medication, n (%)			
Aspirin	165 (100.0)	141 (90.9)	<.0001
Clopidogrel	154 (93.3)	144 (92.9)	.87
LWMH	163 (98.8)	144 (94.1)	.02
Beta-blockers	160 (97.6)	142 (91.6)	.01
ACE	150 (92.0)	126 (81.8)	.007
Statins	143 (87.2)	107 (69.9)	<.0001
Immediate treatment	148 (89.7)	115 (74.2)	<.0001
In hospital death	1 (0.61)	5 (3.25)	.11

Females had on average a longer hospitalization than males, regardless of RD [Figure 6].

[Figure 6.The length of hospitalization by gender and RD].



Mean GFR scores at admission, at the creatinine peak and discharge are provided in figure 2 for patients with and without RD. The RD group had more extension of coronary disease, 54.3% of them had 3-vessel lesion. Moreover the percentile increases with the CKD progression (49.3% in CKD stage 3 vs. 73.7% in CKD stages 4 and 5) (Table 2 and 3).

Table 2. *Baseline characteristics in the four groups*						
	GFR≥60 (n=165) **A**	GFR 59-30 (n=105) **B**	GFR 29-15 (n=38) **C**	GFR <15 (n=12) **D**	p-value	Post-hoc significant pairwise comparisons
Age (mean, SD) – y	66.3 (11.3)	81.8 (7.4)	86.2 (5.6)	71.2 (13.8)	<.0001	A < B, C; C > D; B < C
In hospital days (mean, SD)	5.3 (4.1)	7.0 (6.1)	7.8 (7.0)	9.2 (5.8)	<.0001	A vs. C
Male, n (%)	129 (78.1)	55 (52.3)	14 (36.8)	4 (33.3)	<.0001	A>B,C,D
History of lipid disorders, n (%)	99 (60.0)	60 (57.1)	14 (36.8)	7 (58.3)	.07	
History of diabetes, n (%)	45 (27.3)	34 (32.7)	14 (36.8)	7 (58.3)	.11	
History of hypertension, n (%)	120 (73.2)	85 (80.9)	31 (81.6)	10 (83.3)	.38	
History of PAD, n (%)	8 (4.8)	13 (12.5)	6 (15.8)	5 (41.7)	<.0001	D>A
Prior myocardial infarction, n (%)	54 (32.9)	55 (52.9)	25 (65.8)	7 (63.6)	<.0001	B,C>A
Prior stroke/TIA, n (%)	12 (7.3)	17 (16.2)	8 (21.0)	3 (25.0)	.02	B,C,D>A
Presentation characteristics, n (%)						
Heart failure	24 (14.5)	30 (28.6)	20 (52.6)	2 (16.7)	<.0001	C>A
Left ventricular dysfunction (EF<=40) n (%)	24 (14.5)	25 (23.8)	13 (34.2)	2 (16.7)	.03	C>A
In hospital markers, n (%)						
Troponin I	6.9 (15.1)	5.5 (9.6)	11.4 (26.0)	9.2 (11.9)	.056	
C-reactive protein (CRP)	1.31±2.64	2.45±3.75	5.47±7.82	3.59±4.57	<.0001	A<C,A<B(.051)
Uric acid	6.2 (2.0)	7.1 (2.1)	8.2 (2.5)	7.3 (2.7)	<.0001	B,C>A
Angiographic findings, n (%)						
Coronarography	155/164 (94.5)	72/99 (72.7)	10/37 (27.0)	5/12 (41.67)	<.0001	A>C,D
1-vessel CAD	50 (32.9)	14 (19.4)	0	0	.009	
1-vessel CAD	45 (29.4)	20 (27.4)	3 (25.0)	0	.4	
3-vessel CAD	50/153(32.5)	36/73 (49.3)	7/12 (58.3)	7/7 (100.0)	<.0001	
PCI	113 (68.9)	52 (52.5)	6 (16.2)	3 (25.0)	<.0001	A>C,D
In-hospital medication (%)						
Aspirin	165 (100.0)	100 (95.2)	31 (81.6)	10 (83.3)	<.0001	A>C,D
Clopidogrel	154 (93.3)	101 (96.2)	33 (86.8)	10 (83.3)	.12	
LWMH	163 (98.8)	98 (94.2)	34 (91.9)	12 (100.0)	.07	
Beta-blockers	160 (97.6)	99 (94.3)	31 (81.6)	12 (100.0)	.001	A>C
ACE	150 (92.0)	93 (89.4)	28 (73.7)	5 (41.7)	<.0001	A>C,D
Statins	143 (87.2)	80 (77.7)	22 (57.9)	5 (41.7)	<.0001	A>C,D
Immediate treatment	148 (89.7)	86 (81.9)	21 (55.3)	8 (66.7)	<.0001	A>C
In-hospital death	1 (25.0)	2 (1.9)	3 (7.9)	0	.02	A<C

When patients were classified into 4 groups according to the CKD stages, further differences emerged. Stage 5 patients (GFR<15) were younger than stage 3 and 4 patients (Table 2). The proportion of females increased across stages, and the length of in hospital stay increased with increasing CKD stage.

A history of cardiac disease was more common in stage 3 to 4 patients compared to non RD patients. Similarly, mean CRP and uric acid levels were significantly higher in stages 3 to 4 - 5 patients compared to non RD patients.

The stage CKD 5 was a very small simple size, thus we included the patients in 4 and 5 CKD stages in a single group (Table 3).

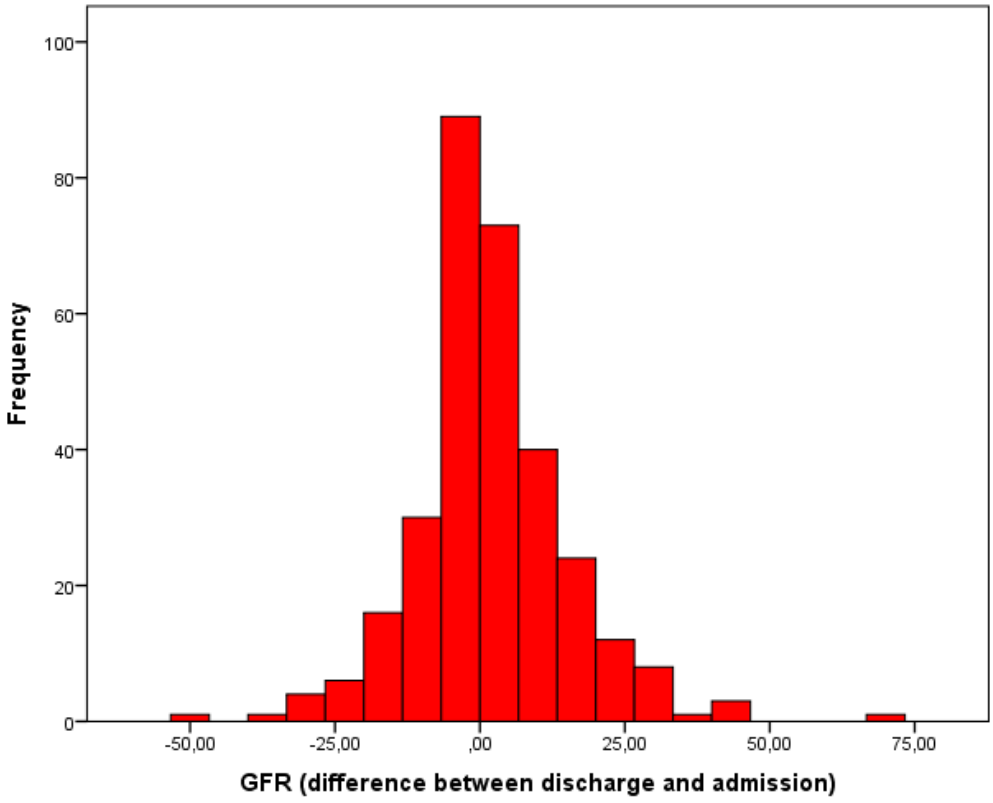
Table 3. *Baseline characteristics in non RD patients and CKD stages patients*

	GFR≥60 (n=165) **A**	GFR 59-30 (n=105) **B**	GFR <30 (n=50) **C**	p-value	Post-hoc significant pairwise comparisons
In hospital markers, n (%)					
Troponin I	6.9 ±15.1	5.5 ±9.6	10.9 ±23.3	.056	
C-reactive protein (CRP)	1.31±2.64	2.45±3.75	4.99 ±7.14	<.0001	A<C,A<B
Uric acid	6.2 ±2.0	7.1 ±2.1	7.95±2.55	<.0001	B,C>A
Angiographic findings, n (%)					
Coronarography	155/164(94.5)	72/99(72.7)	15/49 (30,6)	<.0001	A>C,D
1-vessel CAD	49/152 (32.2)	15/72 (20.8)	0	.006	A>C, B>C
2-vessel CAD	46/153 (30.1)	19/73 (26.3)	3/19 (15.8)	.4	
3-vessel CAD	50/153 (32.5)	36/73 (49.3)	14/19(73.7)	0.001	A>B (0.52), A>C

4.2 Estimated GFR

Examination of the change in GFR levels from admission to discharge was carried out in 310 patients, excluding the 10 undergoing dialysis. The change in GFR levels was computed by subtracting the value at baseline from the value at discharge. Therefore, a positive change indicates an improvement from baseline and a negative change a worsening from baseline [Figure 7].

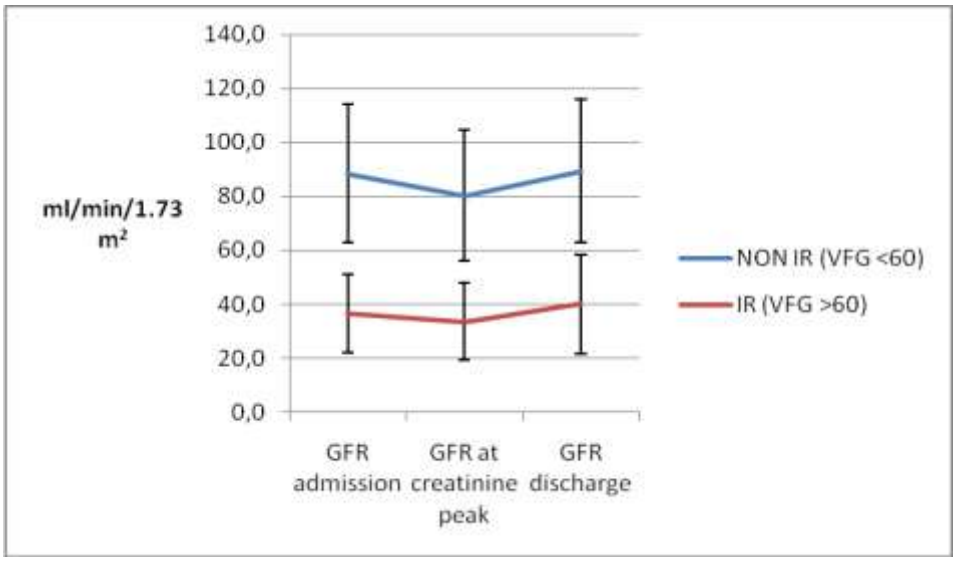
[Figure 7. Frequency distribution of the difference between discharge and admission GFR score (ml/min/1.73 m^2]



On average, in the overall sample the GFR improved 2.2 ml/min/1.73 $m^2$from baseline to discharge, with a standard deviation of 13.3 ml/min/1.73 m^2, indicating a large variability among individuals. In order to try to explain this variability, a generalized linear model was used that included the change in GFR as the dependent variable and gender, age, length of hospitalization in days, RD (coded as yes or no), appropriate treatment (coded as yes or no) as independent variables. The interaction term RI * appropriate treatment was included in the model under the hypothesis that patients with renal insufficiency would be more likely to receive an immediate treatment.

The results indicate that the model explains a very low percentage of variability (4%, Table 3) and that the only variable significantly associated with the change in GFR is age (p=0.011), while RD reaches only borderline significance (p=0.085). Patients with increasing age have a little improvement during hospitalization. After controlling for the effect of age, gender and length of hospitalization, i.e. *ceteris paribus*, the GFR of RD patients treated appropriately (immediate therapy) increases on average by 5.5 ml/min/1.73 m^2 and that of RI patients treated inappropriately (non immediate therapy) increases 4.9 ml/min/1.73 m^2 [Figure 8]. But, we already mentioned that we utilized the creatinine on admission for estimated GFR. Thus, we included a number the patients who have the acute kidney injury.

[Figure 8. GFR levels in RD and non-RD at admission, creatinine peak and discharge]



4.3 In-hospital therapy

About 3 in 4 (74.2%) RD patients received an immediate in-hospital treatment. This proportion was significantly lower than in non-RD patients (89.7%). In particular, RD patients were less likely to be treated with statins (69.9%), ACE inhibitors (81.8%), beta-blockers (91.6%), aspirin (90.9 %), and LWMH (94.1%). No statistical difference in regard with clopidogrel therapy between two groups. This trend remained also in the four groups, the patients in advanced CKD stages were less likely to receive a guideline recommended therapy, except the use of clopidogrel (Table2).

4.4 In-hospital outcome

The in hospital mortality was higher in the RD group (3.25%) than non RD patients (0.61%), but without statistical significance. The length of in hospital stay was higher in the RD patients with un average by 2.6 days and increased with the stages of CKD (respectively 7.0 ±6.1 in stage 3; 7.8 ±7.0 in stage 4 and 9.2±5.8 in stage 4).

5. Discussion

The percentage of patients with a GFR value <60 ml/min/1.73 m^2 in the study sample (48.4%) is considerably higher than in the general population, confirming the known relationship between cardiovascular diseases and CKD [CDC, 2010]. Previous studies had already shown the high incidence of the CKD in patients with acute coronary syndrome. In the CRUSADE Registry 15% of the patients with NSTEMI had CKD, and in the study conducted by Fox et al the proportion was higher, about 40% NSTEMI patients had CKD [Han JH, 2006; Fox C, 2010].

Patients with CKD are known to have poor outcomes after myocardial infarction [Wright RS, 2002]. In our study the short term mortality (in hospital) was higher in the RD patients than they without RD, but without statistical significance. Our results were similar to their reported by a previous study [Khambatta S, 2012]. This result could be explained by the small number of simple size. It is widely accepted that CKD is one of the strongest independent predictors of the mortality and the adverse events after acute coronary syndrome. The risk of mortality among the subjects with CKD increases to 10- to 20 fold after an ACS [Foley RN, 2005]. In our study patients with GFR <60 ml/min/1.73 m^2 have more prior MI, prior stroke/TIA, peripheral artery disease (PAD) as consequence of accelerated atherosclerosis. In addition, these patients have more severe symptoms on emergency room presentation that can explain the poor prognosis in this group (heart failure).

The RD patients have a longer hospitalization than non RD group and the length of stay increased with increasing CKD stage, suggesting that these patients need more time to reach symptom stabilization. Similarly to other studies the RD population was older than this without RD and the age increases with CKD stage [Rogers WJ, 2000], except the stage 5 of CKD. These patients were younger than they included in CKD stage 3 o 4 (with an average by 10 years). We performed a multivariate analysis and the only variable significantly associated with the change in GFR was the age. Older patients have a little improvement of their GFR during hospitalization. It is known that there is an age-related decrease of GFR [Douville P, 2009], and the age is an important determinant of outcomes for patients with acute coronary syndromes. The pathophysiological processes like the decrease on arterial compliance, changes in afterload, and left ventricular diastolic dysfunction could only in part explain that [Lakatta E, 1997].

Also, the proportion of females increased across stages, so that two thirds of the most severe patients were female. Our results are consistent with the other studies [Fabbian F, 2013; Muiesan ML, 2012; Rao Mk, 2013]. The proportion of women in the CKD is also age-related. NMRI 2 and 4 have shown that the absolute number of the women with ACS increases related to the trend of general population ageing [Rogers WJ, 2000].

The inflammation is another important risk factor for both ACS and CKD. Inflammatory markers are also important predictors of outcomes in ACS.

In our study the levels of CRP was higher in the patients with renal dysfunction then without that, with on average by 1,95 mg/dl. With the progression of the renal disease the levels of CRP have increased, thus the patients of CKD stage 4 and 5 have the higher levels (4.9 ± 7.1). It is known that the systemic micro-inflammation determine a damage of vascular endothelium and the CKD is recognized that a persistent a low degree of inflammation disease. Moreover, recently, researchers focused on the role of inflammatory markers as links between cardiovascular and kidney disease. Activation of the inflammatory cells is an important pathogenic factor in ACS [Libby P, JACC 2009; Hansson GK.NEJM 2005]. C-reactive protein (CRP), a very sensitive marker of inflammation has high levels in ACS patients. Recent evidence has shown the direct effect of CRP on modulating endothelial cells. For example, CRP impairs the ability of endothelial progenitor cells to defend themselves against oxidant stresses and increases the rate of endothelial progenitor cell apoptosis [Fujii H, 2006]. This effect of CRP may directly impair endothelial function and accelerate the development of atherosclerosis. The number of disrupted coronary plaques correlates with systemic CRP levels [Avanzas P, Heart 2004; Tanaka A, JACC 2005]. Widespread acute coronary inflammation is, the likely cause of multiple complex stenoses coronary artery branches.

Several studies have shown that patients with ACS and increased CRP levels have a worse outcome than patients with a similar severity of coronary atherosclerosis but normal levels of inflammatory markers [Kaski JC, Eur Heart J 2010]. Thus CRP is also an important predictor in ACS. An immune dysregulation may produce renal damage but it, also may play a role in further damaging myocytes. Inflammatory activation may have a role in heart failure by contributing to both vascular dysfunction and fluid overload in the extravascular space (McCullough PA 2003). This mechanism could be a cause for inadequate renal perfusion pressures, peritubular edema, pathological reduction of glomerular filtration, and finally, mixed inflammatory and ischemic tubular damage [Ronco C, JACC 2012]. That can explain why the heart failure on admission was more frequently in our patients with CKD, and directly related with the CKD stage.

The inflammatory status after discharge may help in the identification of patients at higher risk of recurrence of coronary instability [Crea F, JACC 2013].

Many previous studies have shown that increased uric acid (UA) levels are associated with obesity, raised of blood pressure, lipid disorders, glucose intolerance, all of which play a causal role in the pathogenesis of cardiovascular disease [Milionis HJ, 2004; Cappuccio FP, 1993].

However, there is increasing epidemiological, experimental, and clinical evidence that uric acid

may play a role in the pathogenesis of kidney injury [Ejaz AA, 2007]. Uric acid induces renal vasoconstriction, impairs autoregulation, has proinflammatory and anti-angiogenic properties, and has important roles in both innate and adaptive immune responses [Kang DH, 2005; Kono H, 2010]. Also uric acid is both an antioxidant and a prooxidant agent, depending on its serum concentration, cellular location, and milieu. Uric acid is an antioxidant only in the hydrophilic environment, but reactions of uric acid with oxidants may produce other radicals that propagate radical chain reaction and oxidative damage to cells [Sautin YY, 2008]. Increased activation of the renin-angiotensin system and decreased bioavailability of nitric oxide are among the mechanisms responsible for the reduction in renal function [Yu MA, 2010]. In the patients with renal dysfunction uric acid is associated with uremia and has been associated with atherosclerosis and cardiovascular death in multiple studies [Dikow R, 2010; Feig DI, 2008].

Two previous study have observed that contrast agents had a uricosuric effect, as consequence of an increase in the renal tubular secretion of uric acid []. Hyperuricemia was significantly associated with the risk of contrast-induced acute kidney injury in patients who underwent coronary angiography [Park SH, 2011]. Contrast-induced acute kidney injury has been recognized as a serious complication of percutaneous coronary intervention (PCI) and may cause an increase in mortality.

The lowering of uric acid levels has been found to reduce signs of systemic inflammation such as circulating levels of high-sensitivity C-reactive protein and tumor-necrosis factor-α [Ogino K, 2010].

Moreover, observational studies of patients with gout and heart failure or angina have shown that allopurinol is associated with improved outcomes [Noman A, 2010; Thanassoulis G, 2010]. Randomized trials suggest that lowering uric acid may influence the natural history and symptoms of both CKD and cardiovascular disease [Goicoechea M, 2010]. Thus, uric acid may be a potentially modifiable risk factor.

In our population study, uric acid has high levels, with statistically significance between non renal and renal dysfunction patients (6.28±1.99, respectively 7.36±2.31). The difference has increased with the progression of CKD stage, thus the levels were higher especially in patients with GFR <30 ml/min/1.73 m^2 (7.9 ± 2.5).

Our results are consistent with previous studies which found that patients with NSTEMI and renal dysfunction have higher baseline risk and more extensive and diffuse coronary artery disease (CAD) [Hanna EB, 2012; Hachinohe D, 2011]. Thus, 54.3% of patients with GFR < 60 ml/min/1.73 m^2 have 3-vessel CAD. Furthermore, the percentage increase with the progression of CKD, 49.3% in the stage 3 of CKD, respectively 73.7% in CKD stage 4-5. Despite extensive CAD, these patients

have received in a lower proportion reperfusion therapy (PCI). That support previous findings of another studies [McCullough PA, 2009]. The preference for conservative medical management over aggressive intervention in patients with CKD because of the diffuseness of their CAD and because the presence of comorbidities led to a perception of high reperfusion risk. Also, that may indicate the concern of the increased risk of coronary angiography for contrast-induced acute kidney injury in addition to the preexistent lesion.

Thus, the use of invasive procedures may be limited in part by a desire to avoid worsening kidney function. End-organ protection for CKD patients at risk (GFR < 60 ml/min/1.73 m^2) can be thought of in two realms: renal protection and vascular protection. Prevention measures have to be done before PCI include hydration, measures to reduce the direct cellular toxicity of the contrast, and, measures to reduce the intrarenal vasoconstriction and oxidative stress that occur uniquely in CKD patients when exposed to iodinated contrast [McCullough PA, 2001].

There are several leading explanations for why CKD is a potent risk factor for adverse outcomes, including contrast induced nephropathy, after cardiovascular events: more comorbidities in CKD patients, including older age and female sex; underused organ protective strategies in CKD patients; excess toxicities from conventional therapies used including radiocontrast material.

The use in hospital medications (aspirin, betablockers, LMWH, statins, ACE-inhibitors) was lower among patients with CKD. Despite their higher risk the CKD patients received less cardioprotective medications then without CKD. Despite the population with CKD have a major number of coronary lesions, were less likely to receive statin therapy. Is well known that statin is effective as secondary prevention in CKD as well as act to slow the progression of renal disease [Koren MJ, 2009]. Therefore, the 4-D Trial, which enrolled patients with diabetes mellitus and end-stage renal disease on dialysis, demonstrated increased risk of fatal stroke among those randomized to statin therapy versus placebo [Wanner C, 2005]. Interestingly, we do not observe any statistically differences between the RD group e non RD group in regard with the use of clopidogrel. Moreover, the important proportion of the patients in CKD 4 and 5 has received clopidogrel. The use of clopidogrel among patients with ACS have been adopted by the American College of Cardiology guidelines for the management of ACS and provided a class I recommendation [Anderson JL, 2007]. The CURE trial has shown that the benefit from Clopidogrel Therapy in NSTEMI patients [Yusuf S, 2001].

Also, the patients with GFR< 60 ml/min/1.73 m^2 received in the lower proportion the association of aspirin, clopidogrel, LWMH and betablockers (which we defined as an immediate therapy o appropriately therapy) in the first 24 hours from hospital admission than they with GFR>= 60 ml/min/1.73 $m^{2.}$ In a multivariate statistical model after adjustment for age, gender and length of

hospitalization, the GFR of RD patients treated appropriately (immediate therapy) increased on average by 5.5 ml/min/1.73 m^2 and that of RD patients treated inappropriately (non immediate therapy) increases by 4.9 ml/min/1.73 m^2 .Therefore, this difference not was with statistical significance.

On average in the overall study population the GFR improved with 2.2 ml/min/1.73 m^2 from baseline to discharge with a high standard deviation, indicating a large variability among individuals. Because of, we cannot have the creatinine values before on hospital admission we performed the analyses with creatinine levels on the day of admission**.** But a number of patients, especially they with heart failure, had an acute kidney injury (AKI) as consequence of the acute cardiac event. These patients with cardiorenal syndrome tip 1, after the treatment of the ACS improved their renal function. That condition were been reflected in the trend of GFR from admission to discharge.

6. Conclusions

1. The proportion of patients with a GFR value <60 ml/min/1.73 m^2 was higher than in the general population
2. RD patients were older, more likely to be female and had more comorbidities than without RD, and these are directly related to CKD stages.
3. RD patients have more prior MI, prior stroke/TIA, peripheral artery disease (PAD) as consequence of accelerated atherosclerosis.
4. The levels of CRP were higher in the patients with renal dysfunction then without that. Moreover, with the progression of the renal disease the levels of CRP have increased, thus the patients of CKD stage 4 and 5 have the higher levels.
5. Uric acid has high levels with statistically significance between non renal and renal dysfunction patients. The difference has increased with the progression of CKD stage, thus the levels were higher especially in patients with GFR <30 ml/min/1.73 $m^{2.}$
6. The RD group have more extensive and diffuse coronary artery disease Thus, over half of patients with GFR < 60 ml/min/1.73 m^2 have 3-vessel CAD. Furthermore, the percentage increases with the progression of CKD.
7. Patients with GFR <60 ml/min were less likely to receive guideline-therapies and reperfusion therapy despite your more severe conditions.
8. The RD patients have a longer hospitalization than non RD group and the length of stay increased with increasing CKD stage.
9. The in hospital mortality not was significantly difference among the patients with a GFR value ≥60 ml/min/1.73 m^2, and patients with a GFR value <60 ml/min/1.73 m^2.
10. The GFR of patients with renal dysfunction improves with immediate therapy, but under our estimation (not was a difference with statistical significance between CKD patients treated appropriately and they treated inappropriately).

However, the study in the current form has some limitations. Because of its retrospective, observational nature, the conclusions are limited in their application and do not allow statements on causality. Another limitation is the relatively small simple size. But the most important we cannot exclude the patients with cardio-renal syndrome tip 1 and we had the bias in estimated GFR.

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