Impact of Renal Dysfunction on Outcome of Acute Myocardial Infarction

Ashutosh M Somalwar*, Arvind S Singh**

Abstract

Background and Objective:

Renal failure is associated with one of the highest risks but limited information exists on the risks associated with lesser degrees of chronic kidney disease in patients who have had an acute myocardial infarction. With this background in mind, this study was planned to assess renal dysfunction in patients of acute MI and study its impact on outcomes after acute MI.

Methodology:

204 patients above 18 years of age admitted as a case of acute MI as per WHO criteria and treated by standard protocol for treatment of acute MI were selected for this study carried out in a tertiary care teaching institute from October 2010 to December 2012. Systolic BP of less than 90 mm of Hg at presentation, ESRD i.e. eGFR <15 ml/min/1.73metre square and seriously ill patients e.g. patients presenting with shock, arrhythmia and other conditions led to exclusion of cases from study. GFR was calculated by equation from modification of diet in renal disease study (MDRD). Two groups without renal dysfunction (eGFR >90 ml/min/1.73m^2) and with renal dysfunction (eGFR $\leq$ 90 ml/min/1.73m^2) were formed. The distribution of estimated GFR in patients of second group was divided into three categories of mild, moderate and severe renal dysfunction. The outcomes of patients during in-hospital stay were compared amongst the two groups as well as various categories of renal dysfunction as per eGFR

Main outcomes:

The adverse outcomes studied were death, recurrent acute coronary syndromes (reinfarction /post infarct angina), left ventricular failure/ congestive cardiac failure, stroke, ventricular arrhythmia /cardiac arrest and composite cardiovascular end point.

Result:

The composite cardiovascular end point and its individual components were more common among cases with a lower estimated GFR at baseline than among those with the highest estimated GFR. Renal dysfunction (eGFR < 90ml/min/1.73m2) was found to be independently associated with adverse outcomes after acute MI, after controlling for all other risk factors; odds ratio 4.52; 95%C.I (1.189 - 17.19); P value=0.027. In the group with the lowest estimated GFR the adjusted odds ratio for adverse cardiovascular events was 2.42 (95 %CI 1.39 to 4.19; P<0.002), as compared with 2.30 (95 %CI 1.12 to 4.74) in the group with moderate renal impairment

Conclusion:

Adequate preventive measures against CVD should be started early during the natural history of kidney dysfunction. Among patients who have had a myocardial infarction, any degree of preexisting renal impairment should be considered a potent, independent, and easily identifiable risk factor for cardiovascular complications.

Address for correspondence

* Associate professor,** Senior Resident,
Department of Medicine, GMCH, Nagpur
Dr. A M Somalwar, Plot No.264, Bajaj Nagar,
West High Court Road, Nagpur, 440010
Cell: 9850301640;
Email: amsomalwar@gmail.com

Introduction

The presence of coexisting conditions has a substantial effect on outcome of acute myocardial infarction[1]. It has been found that renal dysfunction also affects outcomes of acute MI.

Both traditional and nontraditional risk factors have been implicated in the development of cardiovascular disease in chronic kidney disease.

The National Kidney Foundation defines chronic kidney disease as persistent kidney damage, as reflected by a glomerular filtration rate (GFR) of less than 60.0 ml per minute per 1.73 m^2 of body-surface area for more than three months[2]. Community studies reveal a rising prevalence of cardiovascular disease with declining renal function[3].

Limited information exists on the risks associated with lesser degrees of chronic kidney disease in patients who have had an acute myocardial infarction. The majority of what is known relates to the serum creatinine level, which is an insensitive indicator of renal dysfunction.

Consequently, the National Kidney Foundation uses GFR rather than serum creatinine level to define renal dysfunction.

With this background in mind, this study was planned to assess renal dysfunction in patients of acute MI and study its impact on outcomes after acute MI.

Material and methods

Study Design:

It was a hospital based prospective observational study carried out in our parent institute.

Inclusion Criteria:

Patients above 18 years admitted as a case of Acute MI as per WHO criteria and treated by standard protocol for treatment of acute MI were selected for study.

Exclusion Criteria:

Systolic BP of less than 90 mm of Hg at presentation, ESRD i.e. eGFR <15 ml/min/1.73metresquare and seriously ill patients e.g. patients presenting with shock, arrhythmia and other conditions led to exclusion of cases from study.

Medical History:

Past history of hypertension, diabetes mellitus and coronary heart disease along with history of any major illness was noted. Personal history regarding the habit of smoking, tobacco chewing and alcohol intake was noted.

Measuring proteinuria :

Typical dipstick measures of proteinuria were **none, trace, 1+, 2+, and 3+,** which corresponds to urinary protein concentrations of **< 0.1, 0.1-0.3, 0.31-1.0, 1.01-3.0, and more than 3.0 g/l.** We defined proteinuria as trace or greater protein on baseline dipstick urinalysis (Multistix; Ames Miles Bayer) read automatically.

Calculation of GFR:

By equation from MODIFICATION OF DIET IN RENAL DISEASE STUDY (MDRD)[4]

Two groups were formed

a) Without renal dysfunction (GFR >90 ml/min/1.73m^2)
b) With renal dysfunction (GFR ≤ 90 ml/min/1.73m^2)

The distribution of estimated GFR in patients of group (b) was divided into three categories

1. Mild: 60-90 ml/min/1.73 m^2
2. Moderate: 30-59.9ml/min/1.73m^2
3. Severe: 15-29.9 ml/min/1.73m^2

In-Hospital Adverse Events:

The adverse outcomes studied during in hospital stay were death, recurrent acute coronary syndromes (re-infarction /post infarct angina), left ventricular failure/ congestive cardiac failure (LVF/CCF), stroke and ventricular arrhythmia /cardiac arrest.

The two groups were compared for the adverse outcomes during in-hospital stay.

The outcomes of patients were also compared amongst various categories of renal dysfunction as per eGFR.

Left Ventricular Failure/ Congestive Cardiac Failure:

All patients were considered to have CCF in whom open treatment with diuretics, digoxin, and/or an Angiotensin converting enzyme (ACE) inhibitor was started for typical signs and/or symptoms related to CHF, or in whom hospitalization was prolonged or were hospitalized due to the presence of symptoms of CHF

Stroke:
Stroke was defined as per the World Health Organization (WHO) definition "Rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin"

Statistical Analysis:
Statistical software STATA version 10.0 was used for data analysis. Continuous variables (age, eGFR, serum creatinine) were presented as mean (± SD). Categorical variables (complications, prior IHD hypertension, diabetes, smoking, tobacco chewing, alcoholism, urine protein positive (≥ trace), anterior wall MI, renal dysfunction, age > 60 years) were expressed in numbers and percentages. Categorical variables were compared with complication and without complication by performing Chi Square Test. For small numbers Fisher Exact Test was used wherever necessary. Chi Square Test for linear trend was used to assess the trend for baseline characteristics of patients and complications during in hospital stay across different grades of renal dysfunction. Multiple logistic regression analysis was done to identify the independent predictors of composite end point. Odds Ratio was calculated to assess the risk for composite end point. P value < 0.05 was considered as statistically significant.

Results
Baseline Characteristics
The baseline estimated GFR for the 204 cases was **normally distributed.** The mean (±SD) estimated GFR was **64.87 +/-23.64** ml/min/1.73 m^2 (range**15.06-129.62**). (see fig 1)

In the present study the **mean age** of the cases was **54.62 +/- 11.59 years**. Out of 204 cases **138** were males and **66** were females. The male to female ratio was **2.09: 1.** Thus male dominance was observed.

A total of **32 (15.69%)** cases had an estimated GFR **>90.0** ml/min/1.73 m^2, **172 (84.31%)** cases had an estimated GFR of **≤90.0** ml/min/1.73 m^2 **(renal dysfunction)**. Estimated GFR < 60 ml/min/1.73m^2 suggestive of chronic kidney disease was present in **79(38.73%)** cases.

There were 93(45.59%) cases having an estimated GFR of 60.0 to 90ml per minute per 1.73m^2, 56(27.45%) cases had an estimated GFR of 30.0 to 59.99 ml per minute per 1.73 m^2, and 23(11.27%) cases had an estimated GFR of less than 30.0 ml per minute per 1.73 m^2.

Cases with renal dysfunction were more often old and females. They had the higher rates of hypertension, diabetes, prior ischaemic heart disease. Cigarette smoking +/-tobacco chewing was less frequent among patients with renal dysfunction.

There was a trend for stepwise increase in co-morbidities among patients with normal, mildly impaired, and severely impaired renal function .Characteristics like mean age, female sex (%) and systemic hypertension came out as significant in linear trend, P<0.05 while other co-morbidities were not significant due to small number of patients in subgroups.

Outcomes
The adverse outcomes studied during in hospital stay were LVF/CCF, recurrent ACS, Ventricular Arrhythmia, stroke, death and composite end point of these events.

There were in all 96 adverse events in the study. There were three complication in cases with normal renal function (eGFR>90 ml/min/1.73m^2) while cases with renal dysfunction (eGFR ≤ 90 ml/min/1.73m^2) had 93 adverse events. The most common complication was LVF/CCF, occurring in 52(25.49%) cases overall.

The composite cardiovascular end point and its individual components were more common among cases with a lower estimated GFR at baseline than among those with the highest estimated GFR. P value for the trend was significant for composite cardiovascular end point along with LVF/CCF and death; P<0.05 (fig 1).

In order to study the relationship of renal dysfunction with adverse outcomes after acute MI, a multiple logistic regression analysis was performed with composite end point as a dichotomous outcome variable. Renal dysfunction (eGFR <90ml/min/1.73m2) was found to be independently associated with adverse outcomes after acute MI, after

controlling for all other risk factors; odds ratio 4.52; 95%C.I (1.18983 - 17.19616); P value=0.027. (table 1)

Proteinuria (≥trace), age (>60years), prior ischemic heart disease and smoking and /or tobacco chewing were also independently associated with adverse events during in hospital stay.

Using the group with an estimated GFR of greater than 90.0 ml per minute per 1.73 m^2 as the reference group yielded unadjusted odds ratios for the composite end point that increased as the degree of renal impairment increased.

In the adjusted model, groups with a lower estimated GFR at baseline had worse outcomes than the reference group (Table 2). In the group with the lowest estimated GFR (15-29.99 ml/min/1.73m^2) the adjusted odds ratio for composite cardiovascular end point was 2.42 (95 % CI, 1.39 to 4.19; P<0.002), as compared with 2.30 (95 % CI, 1.12 to 4.74; P<0.024) in the group with moderate renal impairment (eGFR, 30-59.99 ml per min per 1.73 m2).

Discussion

Chronic kidney damage is defined as structural abnormalities of the kidney that can lead to decreased kidney function. The level of glomerular filtration rate (GFR) is accepted as the best measure of overall kidney function in health and disease.

It has been realized in the past 10-15 years that cardiovascular disease is a major contributor to mortality in patients who have kidney disease, such that the mortality of those in their 20s and 30s can be equivalent to that of 80-year-old persons who don't have kidney disease.[5] National Kidney Foundation and the American College of Cardiology/American Heart Association recommend that CKD be considered a CHD risk equivalent. We found that preexisting renal disease was a common and significant independent risk factor for adverse events in patients who had had a myocardial infarction.

In our study 38.73% cases had an eGFR suggestive of chronic kidney disease, a higher incidence than has been reported in previous cardiovascular trials.[6,7] We found that older age and female sex were associated with a worsening estimated GFR.

The presence of mild-to-moderate renal impairment after myocardial infarction increases the rate of adverse outcomes during in hospital stay. After adjustment, a low estimated GFR was independently associated with an increased risk of death and complications from cardiovascular causes, reinforcing the concept that renal disease is a risk factor for cardiovascular events.

Several studies have suggested that cutoff values for an estimated GFR of less than 60.0 ml per minute per 1.73 m^2 are predictive of adverse cardiovascular outcomes.[4,8] Findings in various studies suggest that patients with renal impairment already have an increased risk of cardiovascular events and that this risk increases with worsening renal function. Our study is in agreement with the latter.

The use of Framingham scores underestimates cardiovascular risk in patients with chronic kidney disease, suggesting that other factors are also influential. Various hypotheses have been put forth about pathophysiology of perverse outcomes after acute MI in patients of renal dysfunction. Both traditional and nontraditional risk factors have been implicated in the development of cardiovascular disease in chronic kidney disease.

The incidence and severity of obstructive CAD increases as glomerular filtration rate (GFR) declines.[9]CAD shows a pattern of diffuse multi-vessel involvement with coronary calcification,[10] small angiographic studies suggest that this incidence exceeds 50% in unselected CKD 5D patients. [11] Inflammation and oxidative stress have been linked to the pathogenesis of plaque formation and plaque rupture;both are associated with worse cardiovascular outcomes.[12]The role of mineralocorticoid excess in the development of cardiovascular complications is increasingly recognized.Recent studies have implicated disordered mineral and bone metabolism in the pathogenesis of coronary disease and CVD in CKD patients.[13]

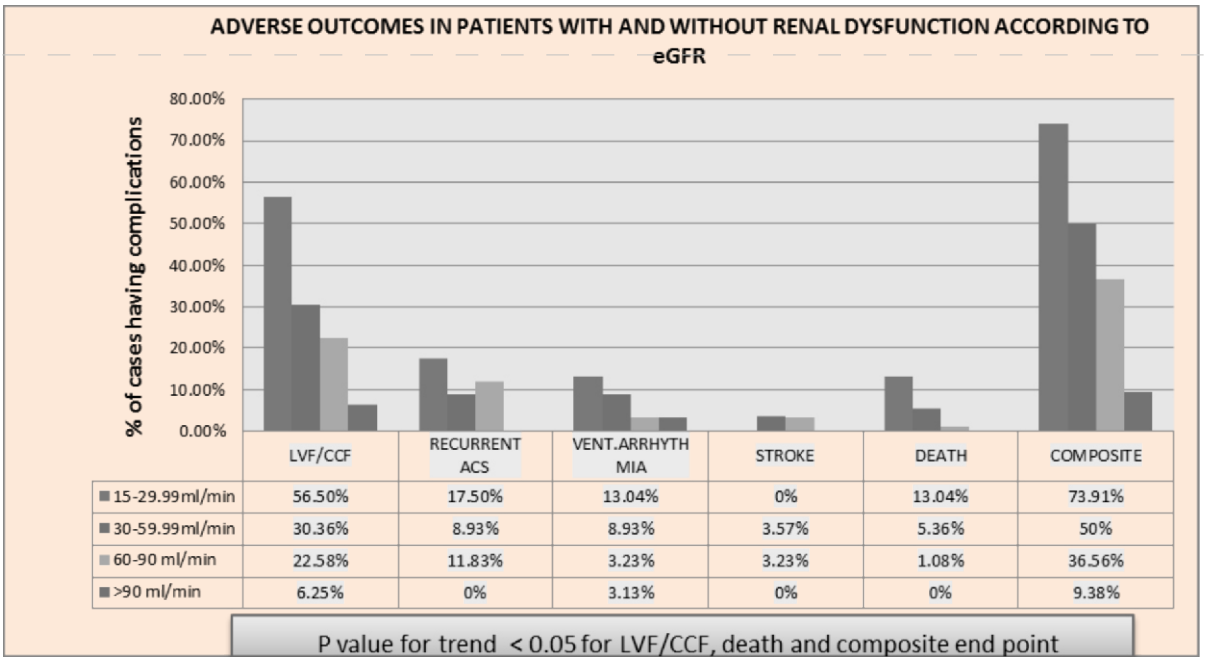
In our cohort, the proportions of patients with hypertension and diabetes mellitus increased with worsening estimated GFR.CVD, CKD, and diabetes can act together as major adverse prognostic factors for morbidity and mortality. [14]CKD is a coronary disease

risk equivalent for the development of cardiovascular events. When CVD and CKD coexist, each disease state amplifies the risk factors of the other. Diabetes and hypertension account for more than two-thirds of CVD risk and they are the 2 primary causes of CKD. Diabetes is the leading cause of kidney failure, accounting for 44% of new cases. Congestive heart failure (CHF) is the leading cardiovascular condition in CKD patients. It can interplay with hypertension and diabetes mellitus to impact CKD and vice versa.

The increasing association of CKD with CVD has given rise to a new definition of cardio-renal syndrome (CRS).The term CRS is used to identify a disorder of the heart and kidneys, whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ.[15]

In conclusion, the present study showed that renal dysfunction is strongly associated with an increased risk of adverse outcome after AMI. Among patients who have had a myocardial infarction, any degree of preexisting renal impairment should be considered a potent, independent, and easily identifiable risk factor for cardiovascular complications.

(fig 1



	LVF/CCF	RECURRENT ACS	VENT.ARRHYTHMIA	STROKE	DEATH	COMPOSITE
15-29.99 ml/min	56.50%	17.50%	13.04%	0%	13.04%	73.91%
30-59.99 ml/min	30.36%	8.93%	8.93%	3.57%	5.36%	50%
60-90 ml/min	22.58%	11.83%	3.23%	3.23%	1.08%	36.56%
>90 ml/min	6.25%	0%	3.13%	0%	0%	9.38%

Fig 1: ADVERSE OUTCOMES IN PATIENTS WITH AND WITHOUT RENAL DY SFUNCTION ACCORDING TO eGFR

Table 1: Multiple Logistic Regression Analysis Showing association of renal dysfunction with composite end point after acute MI£

	Odds ratio (95% Conf.Interval)	P value
Renal dysfunction (eGFR ≤ 90 ml/min/m^2)	4.52 (1.19 - 17.19)	0.027
u. protein (≥ trace)	6.16 (2.99 - 12.68)	0.000
Age(>60years)	3.26 (1.58 - 6.72)	0.001
Ischaemic heart disease	2.25 (1.02 - 4.95)	0.044
Smoking ±Tobacco chewer	2.71 (1.27 - 5.81)	0.010

£ : The covariates used for adjustment were Age (> 60 years), DM, IHD, Hypertension, Smoker ±Tobacco Chewer, Urine Protein +

Table 2: Odds Ratio for Composite Outcomes According to the eGFR at the Baseline

Outcome	eGFR >90. # (N=32)	eGFR 60-90 (N=93)	eGFR 30-59.99 (N=56)	eGFR <30 (N=23)
Composite End Point(%)	9.38%	36.56%	50%	73.91%
Unadjusted Odds Ratio	#1	1.37(1.15-1.68); P=0.003[S]	1.83(1.37-2.48); P=0.0001[HS]	4.95(2.33-10.89); P=0.000[H]
Adjusted Odds Ratio ¥	#1	3.20 (.81-12.6); P=0.09[NS]	2.30(1.12- 4.74); P=0.024 [S]	2.42 (1.39-4.19); P=0.002 [S]

#: reference category; **¥:** the covariates used 0for adjustment were age (>60 years),IHD, DM, Hypertension, smoker ± tobacco chewer, urine protein + (≥trace).

Reference

Anavekar NS

1. McMurray JJ, Velazquez EJ, Solomon SD, Kober L, Rouleau JL et al: Relation between Renal Dysfunction and Cardiovascular Outcomes after Myocardial Infarction N Engl J Med. 2004 Sep 23;351(13):1285-95.
2. National Kidney Foundation. Kidney Disease Outcome Quality Initiative (K/DOQI) clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002;39: Suppl 1:S1-S266.
3. Foley RN, Parfrey PS, Sarnak MJ. Epidemiology of cardiovascular disease in chronic renal disease. J Am Soc Nephrol 1998;9: Suppl:S16-S23.
4. Levey AS, Bosch JP, Lewis Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999; 130:461
5. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kidney Dis. 1998;32(suppl3): S112-S119.
6. Al Suwaidi J, Reddan DN, Williams K, et al. Prognostic implications of abnormalities in renal function in patients with acute coronary syndromes. Circulation 2002;106: 974-80
7. Walsh CR, O'Donnell CJ, Camargo CA Jr, Giugliano RP, Lloyd-Jones DM. Elevated serum creatinine is associated with 1-year mortality after acute myocardial infarction. Am Heart J 2002;144:1003-11.

8. Henry RMA, Kostense PJ, Bos G, et al. Mild renal insufficiency is associated with increased cardiovascular mortality: the Hoorn Study. Kidney Int 2002;62:1402-7.

9. Nakano T, Ninomiya T, Sumiyoshi S , Fujii H, Doi Y, Hirakata H, *et al*. Association of kidney function with coronary atherosclerosis and calcification in autopsy samples from Japanese elders: the Hisayama study. *Am J Kidney Dis* 2010; 55: 21–30.

10. Chonchol M, Whittle J, Desbien A , Orner .M B , Petersen .L. A. ,Kressin. N.R *et al*. Chronic kidney disease is associated with angiographic coronary artery disease. *Am J Nephrol* 2008; 28: 354–360.

11. Joki N, Hase H, Nakamura R , Yamaguchi T. Onset of coronary artery disease prior to initiation of haemodialysis in patients with end-stage renal disease. *Nephrol Dial Transplant* 1997; 12: 718–723.

12. Longenecker JC, Coresh J, Powe NR J, Levey AS, Fink NE., Martin A, *et al*. Traditional cardiovascular disease risk factors in dialysis patients compared with the general population: the CHOICE Study. *J Am Soc Nephrol* 2002; 13: 1918–1927.

13. Giovannucci E, Liu Y, Hollis BW , Rimm EB.*et al*. 25-Hydroxyvitamin D and risk of myocardial infarction in men: a prospective study. *Arch Intern Med* 2008;168: 1174– 1180.

14. National Kidney Foundation Kidney Disease Outcome Quality Initiative (NKF KDOQI). Diabetes and Chronic Kidney Disease. *Am J Kidney Dis*. 2007;49:S1-S179

15. Ronco C, McCullough P, Anker S, Anand I, Aspromonte N, Bagshaw SM et al. Cardio-renal syndromes: report from the Consensus Conference of the Acute Dialysis Quality Initiative. *Eur Heart J*. 2010;31:703-711.