In-hospital adverse clinical outcomes of ST elevation myocardial infarction patients with renal dysfunction

Insights from the Saudi Project for Assessment of Coronary Events

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ABSTRACT

الأهداف: معرفة القيمة التخمينية لمعدل الترشيح الكبيبي لدى المرضى السعوديين الذين يعانون من احتشاء القلب الحاد وأثر ذلك على العلاجات المقدمة في المستشفى.

الطريقة: تم تحليل بيانات مرضى الإحتشاء القلبي الحاد الذين يعانون من ارتفاع مستوى الكرياتين في الدم والمسجلين في المشروع السعودي لتقييم الحوادث التاجية. تم إجراء الدراسة في مناطق عديدة في المملكة العربية السعودية خلال الفترة من ديسمبر 2005م إلى ديسمبر 2007م. تم تصنيف المرضى بناءً على معدل الترشيح الكبيبي إلى المستويات التالية: (أكبر من 90.1 ملل/دقيقة، وظائف الكلى طبيعية، و من 90-60.1 في حدود المعدل الطبيعي واعتلال بسيط في الكلى، و60-30 اعتلال متوسط في وظائف الكلى، أقل من 30 ملل/دقيقة اعتلال شديد في وظائف الكلى.

النتائج: ضمت الدراسة 2058 مريض مناسب لهذه الدراسة. كان لدى 1058 مريض اعتلال في الكلى. كان المرضى المصابين بالاعتلال الكلوي كبار في السن، مع ارتفاع اصابتهم بتصلب الشرايين وتصلب الأوعية الدموية. وبالمقارنة مع المرضى ذو الوظائف الكلى الطبيعية أو الذين يعانون من اعتلال وظائف الكلى البسيط، كان المرضى المصابين باعتلال وظائف الكلى المتوسط أو الشديد لديهم استعداد أقل للعلاج بمحصرات مستقبلات الفا، ومثبطات إنزيم الانجيوتسين، والاستاتينات، والخضوع للمعالجة الدوائية أو إعادة التروية التاجية. كما وجدت نتائج عكسية أثناء العلاج في المستشفى لدى المرضى الذين كان معدل الترشيح الكبيبي لديهم منخفض. كانت نسبة احتمالات الوفاة المعدلة في المستشفى لدى المرضى الذين يعانون من اعتلال شديد في وظائف الكلى (أقل من 30) 5.3 (95% CI, 1.15-25.51، p=0.0383).

خاتمة: أن انخفاض معدل الترشيح المبدئي لدى مرضى احتشاء القلب الحاد يعد مؤشراً مستقلاً لكل النتائج القلبية الوعائية العكسية الخطرة ودليل للتدخل علاجي

Objectives: To explore the prognostic value of baseline estimated glomerular filtration rate (eGFR) in Saudi patients presenting with ST elevation myocardial infarction (STEMI), and its impact on hospital therapies.

Methods: The STEMI patients with a baseline serum Creatinine enrolled in the SPACE (Saudi Project for Assessment of Coronary Events) registry were analyzed. This study was performed in several regions in Saudi Arabia between December 2005 to December 2007. Based on eGFR levels, patients were classified into: more than 90.1 ml/min (normal renal function), 90-60.1 (borderline/mildly impaired renal function), 60-30 (moderate renal dysfunction), and less than 30 ml/min/1.73 m^2 (severe renal dysfunction).

Results: Two thousand and fifty eight patients qualified for this study. Of these, 1058 patients had renal dysfunction. Patients with renal dysfunction were older, and had a higher prevalence of risk factors for atherosclerosis. Patients with moderate or severe renal dysfunction were less likely to be treated with beta blockers, angiotensin converting enzymes inhibitors, statins, or reperfusion therapies. Significantly worse outcomes were seen with lower eGFR in a stepwise fashion. The adjusted odds ratio of in-hospital death in patients with eGFR less than 30ml/min was 5.3 (95% CI, 1.15-25.51, p=0.0383).

Conclusion: A low baseline eGFR in STEMI patients is an independent predictor of all major adverse cardiovascular outcomes, and a marker for less aggressive in-hospital therapy.

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The association between cardiovascular disease and renal dysfunction has been extensively explored.[1,2] Numerous studies have documented that renal insufficiency is an independent predictor for both short and long term cardiovascular morbidity and mortality.[3-10] Baseline moderate renal dysfunction in ST elevation myocardial infarction (STEMI) patients is associated with a 3 to 24-fold increase in mortality.[4,5] The prognostic impact of baseline estimated glomerular filtration rate (eGFR) in patients presenting with STEMI has not been studied in the Saudi population. Accordingly, our main objective was to determine whether baseline eGFR calculated using the newly validated Chronic Kidney Disease Epidemiology Collaboration Formula (CKD-EPI) formula[11] in patients with STEMI, is an independent predictor for in-hospital adverse cardiovascular events. Moreover, the relationship between renal dysfunction in STEMI patients and the delivery of hospital therapies was explored.

Methods. The SPACE (Saudi Project for Assessment of Coronary Events) study is a prospective, multicenter, observational study of all consecutive acute coronary syndrome (ACS) patients (a diagnosis of STEMI, non-STEMI, and unstable angina) that were admitted to the participating hospitals. This study was conducted from December 2005 to December 2007. The full description of the study design was described in a previous study.[12] Seventeen hospitals across the Kingdom of Saudi Arabia (KSA) participated in this registry. Ethical approval was obtained from the institutional review board of individual hospitals. The diagnosis of STEMI, as well as all other adverse endpoints analyzed in this study were based on the definitions of the Joint Committee of the European Society of Cardiology (ESC)/American College of Cardiology (ACC) published in December 2001.[13]

Data collection was performed using a standardized paper Case Report Form (CRF) in phase I, and an Internet electronic CRF in phase II. Collected data included: patient's demographics; past medical history; provisional diagnosis on admission and final discharge diagnosis; ECG findings; laboratory investigations; medical therapy; use of cardiac procedures and interventions; in-hospital outcomes; and overall mortality. Patients included in this study were those with a diagnosis of STEMI who have a baseline serum creatinine level. All other forms of ACS were excluded. Serum creatinine measurement was performed locally at each participating hospital, and was obtained within 24 hours of hospital admission. The kidney function was stratified by eGFR levels using the CKD-EPI formula.[11] This formula was used instead of the abbreviated Modification of Diet in Renal Disease (MDRD) formula, as it has been shown to be more accurate and suffers less bias, especially at higher eGFR levels.[14] Patients were classified according to their GFR level at baseline into 4 groups: more than 90 ml/min/1.73 m^2 or normal kidney function; 90-60.1 ml/min/1.73 m^2 or borderline/mildly impaired kidney function; 60-30 ml/min/1.73 m^2 or moderate kidney dysfunction; and less than 30 ml/min/1.73 m^2 or severe kidney dysfunction. Baseline characteristics, clinical presentations, and in-hospital therapies were compared across the different GFR groups. The study in-hospital adverse outcomes included: in-hospital all cause mortality; re-infarction; heart failure; cardiogenic shock; stroke; and major bleeding.

Categorical data were summarized with absolute numbers and percentages. Continuous data were summarized with means and standard deviations (SD), or medians and inter-quartile ranges (IQR). Comparisons among different groups were performed using Chi-square test, or Fisher's exact test for categorical variables, and analysis of variance or Kruskal-Wallis test for continuous variables. Multiple logistic regression was used to estimate the adjusted odds ratios. Adjustments were made for age, gender, smoking, dyslipidemia, diabetes, history of hypertension, heart rate, systolic blood pressure, past coronary artery disease (CAD), serum cardiac markers, heart failure on presentation, diagnostic coronary angiography, percutaneous coronary intervention (PCI), coronary artery bypass surgery (CABG), and all pharmacological therapies. All analyses were performed using SAS/STAT software, version 9.1.3 (SAS Institute Inc, Cary, NC, USA).

Results. Of the 5,055patients admitted with ACS, 2083 (41.2%) patients had STEMI and a baseline creatinine level. The mean age for this study cohort was 55.4 ± 13.1. The mean creatinine level was 101.16 micromol/L ± 52.76, and mean eGFR was 77.56 ml/min/1.73 m^2 ± 23.6. Seven hundred and twenty-seven patients (34.9%) had normal eGFR defined as more than 90 ml/min/1.73 m^2, while 1358 (65.1%) had renal dysfunction. **Table 1** depicts the baseline characteristics and the number of patients in each eGFR category. Patients were significantly older, more likely to be woman, Saudi nationals, and were more likely to have risk factors for atherosclerosis with worsening renal function in a stepwise fashion. In addition, previous

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history of vascular disease was significantly more in patients with moderate and severe kidney dysfunction.

Clinical presentation. Patients with the worst kidney function categories were more likely to present with tachycardia and hypotension. In addition, they were more likely to present beyond 12 hours from the onset of chest pain to the emergency room. Moreover, they were more likely to present with heart failure, low ejection fraction (less than 35%), and to have a high-risk coronary anatomy defined, as either severe 3 vessels or left main stem coronary artery disease (**Table 1**).

Hospital therapies. Therapies were equally given across all eGFR categories with some exceptions. Beta (ß)-blockers, angiotensin-converting enzyme inhibitors (ACEI), statins, and glycoprotein IIb/IIIa inhibitors were significantly less utilized with decreasing eGFR. Patients with moderate or severe renal dysfunction were less likely to receive thrombolytic therapy (**Table 2**). The door to needle time (DNT), and door to balloon time (DBT) were significantly longer in patients with moderate or severe renal dysfunction. In addition, the proportion of patients achieving a DBT less than 90 minutes was less in patients with moderate to severe renal dysfunction. Diagnostic coronary angiography and PCI were performed less frequently with declining eGFR. Moreover, the median hospital length of stay was significantly longer for moderate (6 [7]), or severe renal dysfunction (5.5 [8]).

In-hospital outcomes. **Table 3** shows in-hospital outcomes stratified by eGFR group in Saudi nationals, and **Figure 1** depicts in-hospital outcomes in the overall study cohort. Decreasing eGFR was associated with significantly higher in-hospital adverse outcomes. With the reference group being eGFR more than 90 ml/min/1.73 m^2, patients with renal dysfunction had a significantly higher odds ratios for all cause mortality, re-infarction, heart failure, cardiogenic shock, major bleeding, and stroke/TIA. Multivariate analysis adjusting for important confounders confirmed that eGFR remained an independent predictor for all adverse in-hospital outcomes, except for stroke/ transient ischemic attacks (TIA) (**Table 4**). The adjusted odds ratio for

Table 1 - Baseline characteristics of STEMI patients according to estimated glomerular filtration rate (eGFR) category.

Variables	eGFR				*P*-value
	Normal function N=725	Mild dysfunction N= 910	Moderate dysfunction N=378	Severe dysfunction N=70	
	n (%)				
Age (mean ± SD)	48.2 ± 10.3	56.6 ± 12.2	64.6 ± 12.6	65.5 ± 12.3	<0.001
Males	656 (90.2)	775 (85.2)	276 (73.0)	55 (78.5)	<0.001
Saudi	523 (72.1)	685 (75.3)	309 (81.8)	60 (85.7)	0.001
Diabetes	340 (46.9)	462 (50.8)	236 (62.4)	50 (71.4)	<0.001
Hypertension	232 (31.9)	357 (39.3)	218 (58.1)	49 (69.0)	<0.001
Dyslipidemia	176 (24.2)	248 (27.3)	120 (31.9)	15 (21.4)	0.121
Smoking	418 (57.5)	367 (40.4)	93 (24.7)	19 (27.1)	<0.001
Prior CAD	142 (19.5)	194 (21.4)	109 (28.9)	24 (34.3)	<0.001
Prior CABG	6 (0.8)	16 (1.8)	8 (2.1)	2 (2.8)	0.181
Prior PAD	29 (4.0)	39 (4.3)	27 (7.2)	10 (14.2)	<0.001
Prior CVA	11 (1.5)	35 (3.9)	37 (9.8)	7 (9.9)	<0.001
BMI (mean ± standard deviation)	27.3 ± 4.7	27.5 ± 4.8	28.2 ± 4.8	28 ± 6.1	0.063
Mean creatinine (mcmol/dl)	74.4 ± 12.1	94.9 ± 13.1	128.8 ± 23.7	306.6 ± 145.9	<0.001
Mean eGFR	101.63 ± 10.6	75.1 ± 8.2	48.2 ± 8.1	19.7 ± 7.1	<0.001
HR more than100 bpm	79 (10.9)	111 (14.3)	61 (16.1)	11 (15.7)	0.038
SBP less than 90 mm Hg	15 (2.1)	37 (4.1)	31 (8.2)	6 (8.6)	<0.001
Heart failure on admission	85 (11.7)	134 (17.4)	103 (27.2)	20 (28.6)	<0.001
Symptoms onset more than 12 hours (median, IQR)	103 (21.7)	136 (23.3)	82 (33.9)	21 (30.0)	<0.001
Anterior wall MI	326 (45.0)	406 (44.6)	169 (44.7)	27 (38.6)	0.565
LVEF% (less than 35%)	245 (33.8)	373 (41.0)	184 (48.7)	35 (50.0)	<0.001
3VD/LM disease	115 (15.9)	181 (20.0)	88 (23.3)	7 (10.0)	<0.001

CAD - coronary artery disease, CABG - coronary artery bypass surgery, PAD - peripheral arterial disease, CVA - cerebrovascular accidents, BMI - body mass index, HR - heart rate, SBP - systolic blood pressure, STEMI - ST elevation myocardial infarction, LVEF - left ventricular ejection fraction, 3VD/LM - 3 vessel disease/left main stem coronary disease, IQR - inter quartile range

Table 2 - In-hospital management in ST elevation myocardial infarction patients according to estimated glomerular filtration rate category.

Category	eGFR Normal function N=725	Mild dysfunction N= 910	Moderate dysfunction N=378	Severe dysfunction N=70	*P*-value
	n (%)				
Aspirin	718 (98.9)	894 (98.2)	368 (98.1)	68 (95.8)	0.216
Clopidogrel	577 (79.5)	738 (81.2)	308 (82.1)	55 (77.5)	0.615
Beta-blockers	604 (83.2)	705 (77.5)	269 (71.7)	40 (56.3)	<0.001
Statins	687 (94.6)	837 (92.0)	342 (91.2)	60 (84.5)	0.006
ACEI	565 (77.8)	665 (73.1)	280 (74.7)	44 (62.0)	0.011
ARB	17 (2.4)	20 (2.2)	7 (1.8)	1 (1.4)	0.930
Heparin	586 (80.6)	719 (79.2)	303 (80.4)	47 (66.2)	0.037
GP IIb/IIIa inhibitors	224 (30.8)	285 (31.4)	106 (28.1)	8 (11.3)	0.004
Thrombolytic use	432 (59.5)	508 (55.8)	168 (50.0)	34 (54.0)	<0.001
DNT, min (median, IQR)	56 (54.0)	49 (57.0)	55 (72.0)	84 (167.0)	0.033
DNT less than 30 min	51 (18.4)	70 (22.2)	18 (18.0)	1 (5.6)	0.292
Diagnostic coronary angiography	473 (65.1)	613 (67.4)	221 (58.6)	21 (29.6)	<0.001
Percutaneous coronary intervention	331 (45.8)	404 (44.6)	141 (37.3)	3 (18.3)	<0.001
Primary PCI	48 (6.6)	79 (19.0)	29 (18.8)	1 (5.9)	0.284
DBT, min (median, IQR)	94 (54.0)	113 (69.0)	127 (57.0)	276 (348.0)	0.026
DBT less than 90 min	29 (46.8)	23 (25.6)	7 (23.3)	0	0.019
Coronary artery bypass surgery	33 (4.6)	49 (5.4)	21 (5.6)	2 (2.9)	0.862
Length of hospital stay (median, IQR)	4 (3.0)	5 (4.0)	6 (7.0)	5.5 (8.0)	<0.001

ACEI - angiotensin converting enzyme inhibitors, ARB's - angiotensin receptor blockers, GP - glycoprotein, DNT - door to needle time, DBT - door to balloon time, PCI - percutaneous coronary intervention, IQR - inter-quartile range

Table 3 - Rate of in-hospital adverse cardiac outcomes in Saudi nationals stratified by estimated glomerular filtration rate (eGFR) category.

Cardiac outcomes	eGFR Normal function N=523	Mild dysfunction N=684	Moderate dysfunction N=309	Severe dysfunction N=60	*P*-value
	n (%)				
Death	4 (0.8)	21 (3.1)	39 (12.6)	13 (21.7)	<0.001
Cardiogenic shock	3 (0.6)	21 (3.1)	12 (3.9)	6 (10.0)	<0.001
ReMI	15(10.7)	39 (5.7)	52 (16.8)	20 (33.3)	<0.001
Heart failure	29 (5.5)	80(11.7)	74 (24.0)	16 (26.7)	<0.001
Major bleeding	2 (0.4)	8 (1.2)	10 (3.2)	3 (5.0)	<0.001
Stroke or TIA	6 (1.2)	9 (1.3)	11 (3.6)	**0 (0.0)**	0.025

ReMI - recurrent myocardial infarction, TIA - transient ischemic attacks

in-hospital mortality in patients with moderate renal impairment was 4.9 (95% CI: 1.55-15.88, p=0.0070), and for severe renal impairment was 5.3 (95% CI: 1.15-25.51, p=0.0383).

Discussion. Several key observations were made from this multicenter, observational study. Despite the relative young age of STEMI patients in this registry, a large majority of patients (65.1%) suffered from some degree of renal dysfunction defined as an eGFR less than 60 ml/min/1.73 m^2. The high prevalence of renal dysfunction in this cohort may be related to a higher prevalence of vascular disease risk factors and vascular co-morbidities, all potential precursors of chronic kidney disease.[1] We have also found that in "real world" unselected predominantly Saudi patients with STEMI, in-hospital rates of major adverse cardiac events (MACE) were markedly higher in patients with moderate or severe renal dysfunction compared to patients with normal or mild renal dysfunction. Moreover, GFR estimated by the CKD-EPI formula independently predicted in-hospital mortality. Several important management differences/gaps were noted in our STEMI patients with the worst eGFR categories. Despite the higher risk profile upon presentation in patients with moderate or severe renal dysfunction, namely, heart failure, moderate

Table 4 - Crude and adjusted odds ratios for in-hospital outcomes according to estimated glomerular filtration rate (eGFR) category.

Outcomes	eGFR	*OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
Death	<30	32.4 (12.9-81.5)	<0.0001	5.3 (1.2-25.5)	0.0383
	30-60	14.3 (6.4-3)	<0.0001	4.9 (1.6-15.9)	0.0070
	60.1-90	2.8 (1.2-6.5)	0.0176	1.7 (0.5-5.6)	0.3447
ReMI	<30	19.7 (5.6-69.2)	<0.0001	16.5 (2.5-110.1)	0.0038
	30-60	6.4 (2.1-19.9)	0.0012	4.1 (0.9-18.1)	0.0657
	60.1-90	4.9 (1.7-14.2)	0.0034	3.3 (0.9-12.4)	0.0310
Major bleeding	<30	10.6 (2.1-53.7)	0.0654	10.9 (1.4-85.7)	0.0229
	30-60	7.2 (2.0-26.1)	0.0331	6.6 (1.2-36.4)	0.0286
	60.1-90	2.7 (0.80-9.8)	0.2443	2.6 (0.5-13.0)	0.2474
Heart failure	<30	5.8 (3.00-10.8)	<0.0001	1.2 (0.4-3.4)	0.7227
	30-60	5.9 (4.00-8.8)	<0.0001	1.9 (1.1-3.6)	0.0266
	60.1-90	2.0 (1.4-3.0)	0.0005	1.2 (0.7-2.0)	0.6346
Cardiogenic shock	<30	17.2 (8.9-33.1)	<0.001	4.7 (1.6-14.1)	0.0055
	30-60	6.9 (4.1-11.4)	<0.001	2.5 (1.2-5.2)	0.0109
	60.1-90	1.9 (1.1-3.2)	0.018	1.38 (0.7-2.4)	0.4484
Stroke/TIA	30-60	4.3 (1.6-11.4)	0.0034	2.2 (0.5-9.4)	0.2826
	60.1-90	1.5 (0.5-4)	0.4484	1.3 (0.4-4.7)	0.6726

OR - odds ratio, CI - confidence interval, ReMI - recurrent myocardial infarction, TIA - transient ischemic attacks. Adjustments were made for age, gender, smoking, dyslipidemia, diabetes, history of hypertension, heart rate, systolic blood pressure, past coronary artery disease, serum cardiac markers, heart failure on presentation, diagnostic coronary angiography, percutaneous coronary intervention, coronary artery bypass surgery, and all pharmacological therapies.
*Reference group is eGFR more than 90 ml/min/1.73m^2

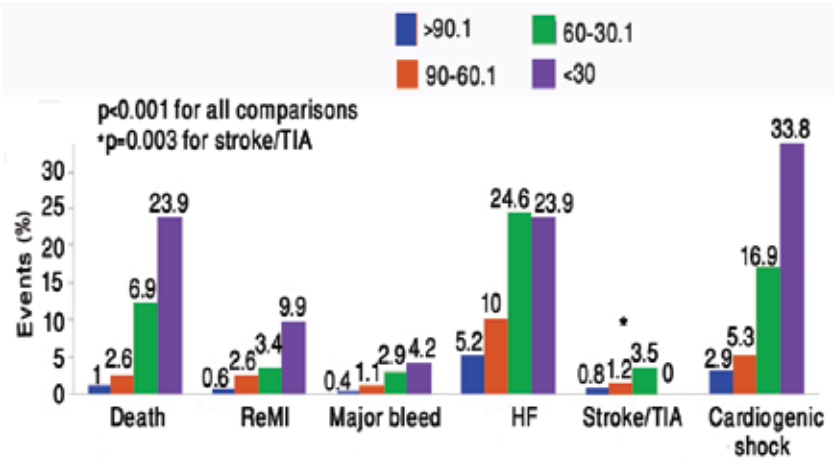

Figure 1 - Rate of in-hospital adverse cardiac outcomes stratified by estimated glomerular filtration rate (eGFR) category. TIA - transient ischemic attacks, HF - heart failure, ReMI - recurrent myocardial infarction.

or severe LV systolic dysfunction, and a higher risk coronary anatomy, there was a lower rate of PCI and CABG. This lower use of PCI and CABG could be explained on the basis of extensive/diffuse CAD, which is often more appropriate for medical therapy, as well as their past vascular disease, such as prior stroke and PAD, in addition to other potential comorbidities that have not been collected in the CRF.[15] In addition, deferral of PCI is possibly an attempt to avoid the risk of contrast-induced nephropathy. Medical therapy gaps/differences seen with lower GFR categories in this study have also been demonstrated in previous similar registries.[4,8,16] Reperfusion therapies, both pharmacological and mechanical were given far less in patients with a lower eGFR, and once given, its delivery was delayed. Patients with renal dysfunction are often older, more likely females and have diabetes, which are all known factors in atypical or delayed clinical presentation of STEMI.[15] Some of the care gaps in pharmacological therapies may be "appropriate" gaps, and could be justified by certain relative, or absolute contraindications seen more commonly in our study

cohort with renal dysfunction, such as hypotension (in the case of ß blockers or ACEI), risk of nephrotoxicity (ACEI), acute heart failure (ß blockers), lower renal clearance, and higher risk of bleeding (glycoprotein IIb/IIIa inhibitors), or risk of Rhabdomyolysis (statins).

The higher MACE with lower GFR in our study confirm the findings of previous reports.[3,4,5,7,8,10,16,17] Our patients with moderate or severe renal dysfunction had a 12.2-23.9% mortality rates, and were almost 5 times more likely to die compared to other patient groups after adjusting for all potential confounders. This mortality rate seen in our study is lower than in the GREECE registry (13-37%),[5] comparable to the Gulf RACE registry (15-27%),[7] and higher than in the GRACE registry (8-18.1%).[4] Differences in mortality rates could be in part related to differences in demographics and baseline risk profile of patients. For example, the GREECE registry patients were far older than our patients, and had diabetes rates that exceeded 40%.[5] On the other hand, although the GRACE registry patients were older than ours, their diabetes rates did not exceed 35%,[4] compared to the staggering 60-70% in our registry. The rate of coronary angiography was generally low in the Gulf RACE registry, and was 10-14% in the severe and moderate renal dysfunction categories, potentially explaining the slightly higher mortality rates in their registry.[7]

Major bleeding episodes were almost 10 folds higher in patients with severe renal dysfunction. This is higher than what was reported in previous registries, however the absolute number of bleeding episodes was small.[4,5,8] Bleeding risk increases progressively with lower GFR.[4,8] Plausible explanations include decreased platelets function in patients with CKD combined with further platelets function inhibition by antiplatelets agents, such as clopidogrel, in addition to the underestimation of the degree of renal dysfunction when only assessing serum creatinine rather than creatinine clearance, potentially leading to dosing errors of antithrombotic agents, and glycoprotein IIb/IIIa inhibitors commonly used in ACS patients.[18,19]

Our study has several limitations. This was an observational, non-randomized study, therefore, inherent biases in this study design could not be avoided but potentially reduced by the use of multivariate analysis, and being a "real life" representation of clinical care in Saudi Arabia. The GFR was calculated but not measured. Calculated GFR however is practical, and validated in various patient populations. Data on the use of renal replacement therapy and long-term outcomes was not prospectively collected in our registry, therefore this was not included as an outcome measure in this analysis.

In conclusion, our findings add to the growing body of evidence of the deleterious effects of baseline renal dysfunction in patients presenting with STEMI. Most of our patients had some degree of renal dysfunction on admission, and therefore systematic assessment of eGFR is essential in risk stratifying patients, tailoring therapy, and early and aggressive management. Future research should focus on prospectively evaluating the effect of aggressive therapy in this high-risk group.

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