ORIGINAL ARTICLE

A Prospective, Observational Trial on the Association of Chronic Kidney Disease and Anemia with Acute Coronary Syndrome

Mukesh Verma[1], Saumya Gupta[2], Keemi Dalal[3]

Authors' affiliations: [1]Senior Resident, Dept. of Medicine, Lady HardingeMedical College, New Delhi; [2]Assistant Professor, Dept. of Medicine, Institute of Medical Sciences, BHU, Varanasi; [3]Senior Resident, Dept. of Dermatology, Lady Hardinge Medical College, New Delhi
Correspondence: Dr. Saumya Gupta, Email: g_saumya@yahoo.com

ABSTRACT

Introduction: Chronic kidney disease and anemia, both independently have been shown to be a causative factor in the development of Cardiovascular diseases. The aim of the study is to establish that both CKD and Anemia are risk factors for adverse CVD outcomes in the general population.

Methods: This cross-sectional, observational, single-centre, study comprising of 108 patients. A diagnosis of acute coronary syndrome was made in each patient after obtaining an ECG and cardiac biomarkers (Troponin-T/ Troponin-I) when indicated. Normality of data was tested by Kolmogorov-Smirnov test. If the normality was rejected, then a nonparametric test was used. A p value of <0.05 was considered statistically significant.

Results: Out of 108 patients, 38(35%) were diagnosed with Chronic kidney disease, whose proportion was higher in patients with STEMI (55.81%) and NSTEMI (33.36%) than those with unstable angina (13.95%) ($p=0.001$). The mean hemoglobin level in non-CKD patients was 11.67 gm/dl while in CKD patients it was 9.72 gm/dl. In patients with acute coronary syndrome, 78 patients (72.22%) were anemic, a much higher proportion than general population.

Conclusion: Overall, our study shows that both CKD and Anemia are risk factors for adverse CVD outcomes in the general population. There is a high prevalence of CVD in subjects with CKD. Therefore regular evaluation for renal disease, should be included as routine investigations for patients with, or at a higher risk for CVD. Anemia is associated with increased cardiovascular morbidity. It appears play a causative role in the progression of CVD, especially in patients with CKD. Microcytic type was the most common. Hence large scale iron supplementation programs may have a significant benefit in reducing the cardiovascular mortality too.

Key words: Acute Coronary Syndrome, Chronic Kidney Disease, Anaemia, Cardiovascular risk factors.

INTRODUCTION

Cardiovascular diseases (CVDs) have now become the leading cause of mortality in India [1]. Chronic Kidney Disease (CKD) is an important modifiable risk factor, and its association with Acute Coronary Syndrome (ACS) is gaining importance. CKD is a spectrum of pathophysiologic disturbance that leads to abnormal renal function and a progressive decrease in glomerular filtration rate (GFR), whose stages are now classified according to both estimated glomerular filtration rate (eGFR) and extent of albuminuria [2]. Depending on these stages of CKD, the increased risk of CVD ranges from 10 to 20 times in ESRD when compared to age and sex matched general population [3]. Mortality rate was higher in younger patients with an odds ratio of 7.58 in comparison to 4.75 for old patients and 3.5 for very elderly patients [4].

Since CVD is more severe in patients with elevated serum creatinine levels [9-11], early identification and treatment of CVD in patients with CKD may reduce the severity of disease, thereby improving the outcomes of those who reach ESRD treatment. This increase in prevalence can be attributed to various traditional risk factors [12] and nontraditional factors [13-20]. Oxidant stress and inflammation together with abnormal calcium & phosphorus metabolism could be the principal intermediary that leads to development of left ventricular remodelling[21,22] & vascular remodelling [23]after MI.Cardiac troponin (cTn) markers can be elevated in CKD without any evidence of ACS that hampers the diagnosis in this population, so serial measurements are more informative[24]. Dis-

eased/damaged kidneys are unable to make enough Erythropoietin, thereby causes Anemia[25]. Various trials suggested that anemia is associated with higher mortality, re-infarction and adverse outcomes after ACS [25-29].This is primarily due to the oxygen supply-demand mismatch and further increases cardiac work and make it more vulnerable to ACS[31].The long term risk of anemia in ACS by various other pathways ultimately, influence atherothrombosis [35].

Few studies were done investigating anemia and CKD. As there is a paucity of literature in the Indian population, we planned to conduct this study.

MATERIALS AND METHODS

This cross-sectional, observational, single-centre, study was conducted at a tertiary care hospital. Both outpatient and inpatients fitting into the classical presentation of ACS along with documented ECG and biochemical changes were included, totalling 108 patients. A written, informed consent was obtained from each participant, and the ethical approval for this human study was obtained from the ethical committee, University of Delhi. Besides the basic history taking and investigations, additional studies included Iron profile, Ultrasonography (USG) – abdomen. Specific investigations were done if in preliminary investigation some particular lead is obtained. While taking history, the following cardiovascular risk factors were noted: Age of the patient, presenting symptoms and their duration, history, and treatment being taken for hypertension, CKD, and diabetes, past history of acute coronary syndrome or of having undergone PCI/CABG/dialysis.

Then, a general physical examination was done, followed by a thorough system-wise review. Particular care was taken to find out any signs of left or right-sided heart failure, which was used to classify the patients under Killip class I to IV, according to the following criteria [36]:

- Class I: No evidence of heart failure
- Class II: Findings of mild to moderate heart failure (S3 gallop, rales < half-way up lung fields or elevated jugular venous pressure
- Class III: Pulmonary edema (rales > half-way up the lung fields)
- Class IV: Cardiogenic shock defined as systolic blood pressure < 90mmHg (with/without signs of hypoperfusion such as oliguria, cyanosis, and sweating).

A diagnosis of acute coronary syndrome was made in each patient after obtaining an ECG and cardiac biomarkers (Troponin-T/ Troponin-I) when indicated. Non-ST-elevation ACS (NSTEACS) was diagnosed if there were related signs or symptoms, along with new ECG changes suggestive of ischemia, such as ST depression, labile ST-T changes, T wave inversions, etc.; but no ST segment elevation. A Trop-T test was done after 6 hours of onset of the symptoms. For patients with known renal failure or apparent congestive heart failure, a Troponin-I kit was used. Once the diagnosis of STEMI/ NSTEMI/ UA was made, appropriate treatment was instituted.

Categorical variables were presented in number and percentage (%), and continuous variables were presented as mean ± Standard Deviation (SD) and median. Normality of data was tested by Kolmogorov-Smirnov test. If the normality was rejected, then a nonparametric test was used. A p value of <0.05 was considered statistically significant. The results thus obtained, are as following.

RESULTS

Out of the 108 patients studied, their ages varied from 35 years to 85 years. 63.8% of them were 51-70 years old, with the median age being 59 years. The group consisted of 74 males (68.5%) and 34 females (31.4%). The most common presenting symptoms were chest pain (n=107, 99%), anxiety/trepidation (n=102, 94.4%), perspiration (n=67, 62%), palpitation (n=56, 51.8%) and dizziness (n=44, 41.6%). Majority of patients were in Killip's class I (46, 42.59%), 36 patients (33.33%) belonged to class II, 22 patients (20.37%) were in class III, and only four patients (3.7%) were in class IV. Only 24 patients (22.22%) had a past history of MI/ACS. Out of this, only 11 patients (10.19%) underwent intervention with PCI/CABG. Out of 108 cases, 62 (57.41%) were a known case of hypertension, and 43 (39.81%) had diabetes. Both these co-morbidities were shared by 29 (26.85%) of enrolled cases. STEMI was diagnosed in 43 patients (39.81%), Unstable Angina in 42 patients (38.88%) and NSTEMI in 23 patients (20.37%).

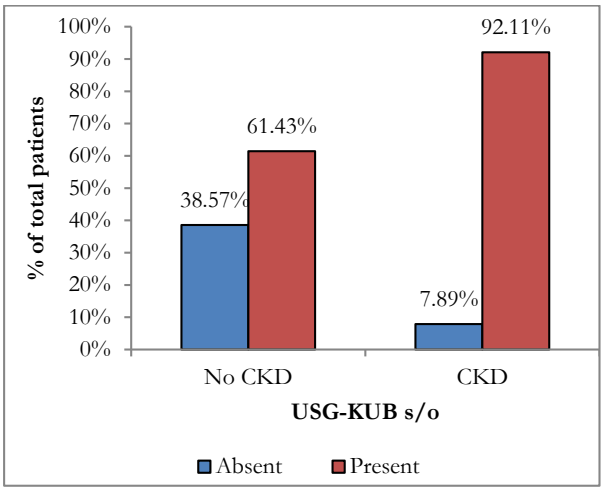

Figure 1: Distribution of Frequency of USG Finding and Presence of Anemia

Table 1: Correlation of Hemoglobin Levels and USG Findings

Hb	USG-KUB s/o	
	No CKD	CKD
Sample size	70	38
Mean ± SD	11.67 ± 2.6	9.72 ± 1.78
Median	11	9.3
Min-Max	8-17	7-15.4
Inter quartile Range	10 – 14	9 - 10

P value 0.0001

In the sample 78 patients (72.22%) were anemic. Out of these 78, 27 were females (79.41%) while 51 were males (68.91%). The peripheral smear revealed a microcytic picture; macrocytic picture and normocytic picture in 69 (63.89%); 5(4.63%) and 34 (31.48%) patients respectively. The mean hemoglobin level in non-CKD patients was 11.67 gm/dl while in CKD patients it was 9.72 gm/dl. The various data points of hemoglobin in both groups are shown in (**Table 1).**

Table 2: Correlation of USG Finding and Diagnosis

USG-KUB s/o	Diagnosis			Total	P value
	NSTEMI	STEMI	UA		
No CKD	14 (63.64%)	19 (44.19%)	37 (86.05%)	70 (64.81%)	0.0003
CKD	8 (36.36%)	24 (55.81%)	6 (13.95%)	38 (35.19%)	
Total	22 (100.00%)	43 (100.00%)	43 (100.00%)	108 (100.00%)	

Table 3: Correlation of Anaemia and Diagnosis

Anemia	Diagnosis			Total	P value
	NSTEMI	STEMI	UA		
Absent	3 (13.64%)	5 (11.63%)	22 (51.16%)	30 (27.78%)	0.0001
Present	19 (86.36%)	38 (88.37%)	21 (48.84%)	78 (72.22%)	
Total	22 (100.00%)	43 (100.00%)	43 (100.00%)	108 (100.00%)	

Table 4: Studies showing mortality rate in ACS patients with CKD

Source	Acstype	Number	Follow-up	Mortality rate in CKD (%)	Non-CKD Mortality (%)
Herzog et al (1998)[45]	STEMI	34189	In hospital	26	-
			1 year	59	
			2 year	73	
			3year	81	
			5year	90	
			10year	97	
Mc Cullough et al (2000)[46]	STEMI NSTEMI	9544	27 month	54.5	22.7
Shlipak et al (2002)[47]	STEMI	130099	1year	46	24
Berger et al(2003)[48]	STEMI	146765	30 days	29	18.3
Ane vekar et al (2004)[49]	STEMI	14527	3 years	45.5	20.5
Gibson et al (2004)[50]	UA/NSTEMI	13307	6 months	3.8	2.5
Han et al(2006) [51]	UA/NSTEMI	45343	-	9	3.6
Fox et al (2007)[52]	STEMI	20479	30 days	31.1	7.1
Summer et al (2009)[53]	NSTEMI	23262	1year	38.2	5.8
Mehran et al (2009) [54]	UA/NSTEMI	12939	1year	7.9	2.8
Fox et al (2010) [55]	STEMI	19089	-	8.8	2.3
Fox et al (2010) [55]	NSTEMI	30462	-	4.8	1.8
Hanna et al (2011) [56]	NSTEMI	40074	-	2.8	0.6

Out of all the enrolled patients, 21(19.44%) had a prior diagnosis of CKD. In the ultrasound KUB, 38 patients (35.19%) had evidence of CKD while 70 patients (64.81%) did not show such findings. Of the 38 patients with CKD on USG, 21 were known cases of CKD while 17 patients were diagnosed during the current admission for ACS. Amongst the CKD patients, 92.11% had anemia while only 61.43% of patients without CKD had anemia, which was statistically significant (p=0.001). This is graphically represented in (**Figure 1**). There was a larger proportion of patients with CKD features on USG, with STEMI and NSTEMI as the final diagnosis (**Table 2**). Similarly, Anemia was more common amongst the patients with MI (**Table 3**).

Table 5: Prevalence, short term and long term mortality in patients of ACS with Anemia in studies

Source	Number	Duration	Prevalence
CB Arant et al Florida (2004)[26]	936 women	3.3years	21%
Amal jamee et al Palestine (2014)[27]	300	3 month	60%
Mamas et al UK (2016)[25]	422855	4 years	27.7%
Syed et al India(2015)[28]	162	In hospital	62.96%
Penta et al India (2016)[29]	130	In hospital	51.5%

DISCUSSION

Several studies have shown an increased mortality risk in cardiovascular patients with concomitant CKD (**Table 4**). Various studies have also investigated the prognostic impact of hemoglobin levels in context with ACS, both in the short term and long term (**Table 5**).

With this background, we studied the presentation of ACS patients coming to a tertiary care centre in northern India along with the prevalence and impact of the risk factors CKD and Anemia in ACS. Mean age and distribution in various age groups in our study was similar to previous Indian studies [37,38]. The second most common presenting complaint of subjects in our study was anxiety/trepidation, symptoms which Indian clinicians are well versed of, which was not considered earlier. A significantly higher proportion (57.49%) of patients presented with Killip class >1. As old age remains a strong predictor of ACS and majority of ACS in elderly patients are complicated by CHF, patients usually present with failure. Moreover, our study recruited a relatively large proportion of cardiac biomarker positive ACS, so there was an increased likelihood of deteriorating clinical condition at presentation. In our study, around 22.22% patients had a previous history of MI/ACS and this prevalence was nearly similar to the CREATE registry in which about 18% patients had such history at the time of presentation[38].However, only about half of the patients were able to get the intervention. An explanation to this can be that our hospital primarily caters to the lower middle/lower socio-economic class and patients pursue non-interventional medical management due to economic constraints. Nearly half the patients in our study had some pre-existing co morbidity, either hypertension or diabetes, with a quarter suffering from both. This was around ten percentage points higher than that recorded in CREATE registry, which was completed in 2005 [38]. A probable explanation for the discrepancy is that according to trends available, the prevalence of these non-communicable diseases is increasing in the Indian population, so in the past 12 years since the CREATE study was done, prevalence may have increased. Proportion of patients diagnosed as STEMI was comparable to previous studies whereas ratio of NSTEMI and UA was variable in different studies [29,39].

There was a greater percentage of anemics in patients with ACS.Anemia was more prevalent in females, and it was primarily of a microcytic hypochromic picture. This conforms to the norm of nutritional anemia in our country. The average prevalence of anemia in our study was found to be 72.2% higher than another similar study by Bhavanadhar et al., where it was 51.5% [29]. A possible explanation for the higher prevalence of anemia in our study can be hospital bias. The studies from other countries are given in table 6.A lower prevalence of anemia shown in these studies can be due to a higher prevalence of anemia in our country as compared to these developed nations. The widespread anemia is a cause of concern and prevention of anemia may be a vital key to decreasing ACS burden. However so, aggressive treatment of anemia has not been shown to have a positive impact on prognosis[40]. Rao et al. assessed 2401 patients who underwent RBC transfusion during hospitalization for ACS and concluded that although low hemoglobin levels are associated with higher mortality, however correcting them by transfusion proved detrimental [40]. Bassand JP et al. in a retrospective analysis of 32170 patients in OASIS trial, reported baseline anemia in 20.5% patients after excluding malignancies and hemorrhagic diathesis [41]. They were assessed using GRACE cardio-vascular risk score, and a significant inverse correlation with the baseline hemoglobin was observed. Patients with low hemoglobin were older, mainly females, with lower BMI, higher heart rate, lower creatinine clearance and low BP. They also tend to have more co-morbidities like CAD, hypertension, DM or heart failure.

A surprising fact emerged in studying anemia in different subgroups of ACS. Unlike our study, in a previously reported study done by Bindra et al., STEMI was more often observed in non-anemic patients, but the accurate mechanisms could not be explained[28]. The possible explanation to this can be the less number of CKD patients in UA group as compared to other two biomarkers positive ACS group patients. Moreover, CKD is itself a strong predictor of the presence of anemia.

In our study, almost half the patients diagnosed with CKD (n=17) on abdominal ultrasound eventually, had no prior history of it. So at the time of discharge, we had 35.19% patients with diagnosed CKD. This proportion was similar to the findings of a study by

Bhavanadhar et al [27]. The percentage of patients with CKD features on USG, with STEMI; NSTEMI and Unstable Anginas were 55.81%; 36.36%, and 13.95% respectively. The correlation of CKD with anemia was found to be statistically significant with p value <0.001. NCDR-ACTION reported CKD prevalence rates of 30.5% among patients with STEMI and 42.9% among patients with NSTEMI[3]. The mean hemoglobin levels in CKD patient was found to be significantly low (p value 0.0001). Anemia has been a frequent associate of advanced renal disease but may also occur in lesser degrees of renal impairment because of reduced erythropoietin production and impaired hematopoietic response to this hormone [42]. Furthermore, the combination of renal impairment and anemia resulted in a bad prognosis in severe forms of IHDwith heart failure [43].

A major strength of our study is that it assesses the importance of CKD in conjunction with anemia in CAD patients, not previously considered in the Indian population, with a relatively broad age group of patients. Another surprising output was of a significant number of newly diagnosed patients with CKD that presented with ACS. In our study a statistically significant correlation was found between numbers of variables; there was a positive relationship between anemia; CKD with ACS. This data could thus help in planning further future studies on these lines.

Our study also has several limitations. Our study was a hospital based study and was thus not truly representative of the entire population. Our hospital caters to patients belonging primarily to lower or middle socioeconomic strata, and the data primarily reflects the situation in this cohort. The study population consisted of a predominantly urban population.It is a small scale study with a limited follow-up so results cannot be extrapolated.

CONCLUSIONS

Overall, our study shows that both CKD and Anemia are risk factors for adverse CVD outcomes in the general population. There is a high prevalence of CVD in subjects with CKD. The presence of CKD, which should be confirmed with an abdominal ultrasound in all CAD patients, seems to be an independent risk factor for CVD outcomes, particularly in patients with other comorbidities. These conclusions are congruous with the NKF task force guidance that patients with CKD should be placed in the highest-risk group for CVD events[12].We recommend that regular evaluation for renal disease, like measurement of spot urine albumin-to-creatinine ratio or total protein-to-creatinine ratio, should be included as routine investigations for patients with, or at a higher risk for CVD.

There appears to be a causative role of anaemia in the progression of CVD& increased cardiocasvular morbidity, especially in patients with CKD. Even mild degrees of anemia may precipitate myocardial ischemia, particularly in patients with CAD. Our study concluded that microcytic type was the most common. Hence large scale iron supplementation programs may have a significant benefit in reducing the cardiovascular mortality too.

REFERENCES

1. Dorairaj Prabhakaran, Panniyammakal Jeemon and Ambuj Roy. Cardiovascular Diseases in India. Circulation. 2016;133:1605-20
2. Bargman JM, Skorecki K.Chronic kidney disease. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J. editors. Harrison's principles of internal medicine. 19th Ed New York: McGraw-Hill; 2015.pg 1812.
3. Cardarelli F, Bellasi A, Ou FS, Shaw LJ, Veledar E, Roe MT, et al. Combined impact of age and estimated glomerular filtration rate on in-hospital mortality after percutaneous coronary intervention for acute myocardial infarction (from the American College of Cardiology National Cardiovascular Data Registry). Am J Cardiol. 2009; 103(6):766-71.
4. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kidney Dis. 1998;32 (3):112–9. [PubMed]
5. M.J. Sarnak, A.S. LeveyCardiovascular disease and chronic renal disease: A new paradigm Am J Kidney Dis, 35 (2000), pp. S117-S131
6. U.S. Renal Data System USRDS 2002 Annual Data Report, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases (2002)
7. Centers for Medicare and Medicaid Services. 2001 Annual Report, End-Stage Renal Disease Clinical Performance Measures Project, Department of Health and Human Services, Centers for Medicare and Medicaid Services, Center for Beneficiary Choices, Baltimore, MD (2001)
8. A.J. CollinsCardiovascular mortality in end-stage renal disease. Am J Med Sci, 325 (2003), pp. 163-167
9. B.F. Culleton, P.W. Wilson. Cardiovascular disease: risk factors, secular trends, and therapeutic guidelines. J Am Soc Nephrol, 9 (1998), pp. S5-15
10. A. Levin, O. Djurdjev, B. Barrett, et al.Cardiovascular disease in patients with chronic kidney disease: Getting to the heart of the matter Am J Kidney Dis, 38 (2001), pp. 1398-1407
11. MS Amaresan. Cardiovascular disease in chronic kidney disease. Indian J Nephrol 2005;15: 1-7
12. National Kidney Foundation K/DOQI clinical practice guidelines on managing dyslipidemias in chronic kidney disease. Am J Kidney Dis. 2003; 41 (suppl 3): S1–S77.
13. Boaz M, Matas Z, Biro A, et al. Serum malondialdehyde and prevalent cardiovascular disease in hemodialysis. Kidney Int. 1999; 56: 1078–83.
14. Bostom AG, Shemin D, Verhouf P, et al. Elevated fasting total plasma homocysteine levels and cardiovascular disease outcomes in maintenance dialysis patients: a prospective study. Arterioscler Thromb Vasc Biol. 1997; 17: 2554–58.

15. Mallamaci F, Zoccali C, Tripepi G, et al. Hyperhomocysteinemia predicts cardiovascular outcomes in hemodialysis patients. Kidney Int. 2002; 61: 609–14.

16. Zimmerman J, Herrlinger S, Pruy A, et al. Inflammation enhances cardiovascular risk and mortality in hemodialysis patients. Kidney Int. 1999; 55: 648–58.

17. Wahn F, Daniel V, Kronenberg F, et al. Impact of apolipoprotein(a) phenotypes on long-term renal transplant survival. J Am Soc Nephrol. 2001; 12: 1052–58.

18. Longenecker JC, Klag MJ, Marcovina SM, et al. Small apolipoprotein(a) size predicts mortality in end-stage renal disease: the CHOICE study. Circulation. 2002; 106: 2812–18.

19. Kronenberg F, Neyer U, Lhotta K, et al. The low molecular weight apo(a) phenotype is an independent predictor for coronary artery disease in hemodialysis patients: a prospective follow-up. J Am Soc Nephrol.1999; 10: 1027–36.

20. Himmelfarb J, Stenvinkel P, Ikizler TA, et al. The elephant in uremia: oxidant stress as a unifying concept of cardiovascular disease in uremia. Kidney Int. 2002; 62: 1524–38.

21. Arici M, Walls J. End-stage renal disease, atherosclerosis, and cardiovascular mortality: is C-reactive protein the missing link? Kidney Int. 2001; 59: 407–14.

22. Levin A, Thompson CR, Ethier J, et al. Left ventricular mass index increase in early renal disease: impact of decline in hemoglobin. Am J Kidney Dis. 1999; 34: 125–34.

23. Guerin AP, London GM, Marchais SJ, et al. Arterial stiffening and vascular calcifications in end-stage renal disease. Nephrol Dial Transplant. 2000; 15: 1014–21.

24. Bargman JM, Skorecki K.Chronic kidney disease. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J. editors. Harrison's principles of internal medicine. 19th Ed New York: McGraw-Hill; 2015.page 1811-21.

25. Mamas MA, Kwok CS, Kontopantelis E, Fryer AA, Buchan I, Bachmann MO, et al. Relationship Between Anemia and Mortality Outcomes ina National Acute Coronary SyndromeCohort: Insights Fromthe UK Myocardial Ischemia National Audit Project Registry. J Am Heart Asso.2016; 5(11):e003348.

26. Ducrocq G,Puymirat E, Steg PG, Henry P, Martelet M, Karam C, et al. Blood transfusion, bleeding, anemia, and survival in patient with acute myocardial infarction: FAST-MI registry. Am Heart J.2015; 170(4):726-34.

27. Jamee A, Abed Y. Anemia Prevalence and Sociodemographic Factors among Patient with Cardiovascular Disease in Gaza-Palestine. Am J Cardiovasc Dis. 2014; 2 (1): 4-8.

28. Bindra K,Berry C, Rogers J, Stewart N, Watts M, Christie J, et al. Abnormal haemoglobin levels in acute coronary syndromes. QJM. 2006; 99(12):851-62.

29. Bhavanadhar P, Srinivasan VR, Oruganti SS, Adiraju KP. A Prospective Study on Prevalence and Causes of Anaemia in Patients with Acute Coronary Syndrome. J Clin Diagn Res. 2016; 10(7):1-5.

30. Wu WC, Rathore SS, Wang Y, Radford MJ, Krumholz HM. Blood transfusion in elderly patients with acute myocardial infarction. N Engl J Med. 2001; 345(17):1230-6.

31. Lawler PR, Filion KB, Dourian T, Atallah R, Garfinkle M, Eisenberg MJ. Anemia and mortality in acute coronary syndromes: a systematic review and meta-analysis.Am Heart J. 2013; 165(2):143-53.

32. Anand I, McMurray JJ, Whitmore J, Warren M, Pham A, McCamish MA. Anemia and its relationship to clinical outcome in heart failure. Circulation. 2004; 110(2):149-54.

33. Solomon A, Blum A, Peleg A, Lev EI, Leshem-Lev D, Hasin Y. Endothelial progenitor cells are suppressed in anemic patients with acute coronary syndrome. Am J Med. 2012; 125(6):604-11.

34. Shacham Y, Leshem-Rubinow E, Ben-Assa E, Roth A, Steinvil A. Lower admission hemoglobin level is associated with longer symptom duration in acute ST-elevation myocardial infarction. Clin Cardiol. 2014; 37(2):73-7.

35. Farhan S, Baber U, Mehran R. Anemia and Acute Coronary Syndrome: Time for Intervention Studies. Journal of the American Heart Association: Cardiovascular and Cerebrovascular Disease. 2016;5(11):e004908.

36. Killip 3rd T, Kimball JT. Treatment of myocardial infarction in a coronary care unit. A two year experience with 250 patients. Am J Cardiol. 1967;20(4):457–64.

37. Singh PS, Singh G, Singh SK. Clinical profile and risk factors in acute coronary syndrome. JIACM. 2013; 14(2):130-2.

38. Xavier D, Pais P, Deveraux PJ, Xie C, Prabhakaran D, Reddy KS, et al. Treatment and outcomes of acute coronary syndromes in India (CREATE): a prospective analysis of registry data. Lancet. 2008; 371(9622): 1435–42.

39. Al-Saif SM, Alhabib KF, Ullah A, Hersi A, Alfaleh H, Alnemer K, et al. Age and its relationship to acute coronary syndromes in the Saudi Project for Assessment of Coronary Events (SPACE) registry: The SPACE age study.J Saudi Heart Assoc. 2012;24(1):9–16

40. Rao SV, Jollis JG, Harrington RA, Granger CB, Newby LK, Armstrong PW, et al. Relationship of blood transfusion and clinical outcomes in patients with acute coronary syndromes. JAMA. 2004; 292(13):1555-62.

41. Bassand JP, Afzal R, Eikelboom J, Wallentin L, Peters R, Budaj A, et al. Relationship between baseline haemoglobin and major bleeding complications in acute coronary syndromes. Eur Heart J. 2010; 31(1):505-8.

42. Eckardt K-U. Cardiovascular consequences of renal anaemia and erythropoietin therapy. Nephrol Dial Transplant. 1999; 14(5):1317-23.

43. Berry C, Norrie J, Hogg K, Brett M, Stevenson K, McMurray JJ. The prevalence, nature, and importance of haematologic abnormalities in heart failure.Am Heart J. 2006; 151(6):1313-21.

44. Chobanian AV, Bakris GL, Black HR, et al; National Heart, Lung and Blood Institute Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report.JAMA. 2003; 289: 2560–72.