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Clinico-Angiographic Profile and Short Term Outcomes in Elderly Patients (>75 Years) with Acute Coronary Syndrome

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Abstract

Background: As elderly remain a vastly understudied population with significant differences from the younger patients, we aimed to study the profile of acute coronary syndrome (ACS) exclusively in elderly along with short-term outcomes.

Methods: This prospective observational study enrolled 100 elderly ACS patients and studied their demographic, clinical and angiographic profile. After any coronary intervention as indicated, they were followed-up for a period of 3 months for occurrence of death due to any cause and major adverse cardiovascular events.

Results: Average age of study population was 80 years with majority being male (69%). Dyslipidemia, family history of CAD, diabetes, hypertension and smoking constituted 9%, 9%, 22%, 30% and 61% of patients respectively. STEMI was the commonest presentation (53%). LAD was the most common artery involved (79%) and ostio-proximal left circumflex (LCx) involvement (32%) was common (p-value < 0.05). Multivessel disease was associated with elevated serum homocysteine and hs-CRP level (p-value < 0.05). Cardiac cause accounted for 80% of total mortality. Serum homocysteine level of 16.63±5.26 µmol/L, LVEF <35%, presence of mitral regurgitation (MR), involvement of left main (LM), LCx or right coronary artery (RCA) and triple vessel disease (TVD) showed a significant association with mortality (p-value < 0.05) .

Conclusions: Elderly patients with ACS commonly have a multivessel disease which correlates with elevated serum homocysteine and hs-CRP level. The important predictors of short-term mortality include higher serum homocysteine level, LVEF < 35%, significant MR, involvement of LM and presence of TVD.

Keywords: Elderly, Acute Coronary Syndrome, Profile, Mortality

INTRODUCTION

Global improvement in life expectancy has led to increased incidence and prevalence of coronary artery disease (CAD) in older individuals. However, the elderly patients, especially those with acute coronary syndrome (ACS) remain an underrepresented population in most clinical studies either because exclusion of patients of more than 65 years of age [1,2] or their representation was not more than 10% [3]. Further the profiles of ACS in elderly tend to differ from younger patients in many aspects, especially with reference to clinical presentation, risk factor and angiographic profile. The relative accumulation of risk factors with increasing age and increase in extent and severity of coronary artery disease further alters the prognosis in elderly. Angiographic studies have shown that extent and

severity of CAD in older patients is more than in younger patients. Despite the fact that elderly patients form a high risk group and various studies have proved significant benefits of percutaneous coronary intervention (PCI) in these patients, [4–6] the invasive procedures are performed relatively less frequently in the elderly. Evaluating the age-related differences in prevalence, pathophysiology and risk factor profile of CAD and their clinical significance is important for better understanding and management of the disease. Thus we aimed to conduct this study to evaluate the demographic, clinical and angiographic profiles of elderly patients presenting with acute coronary syndrome along with immediate and short term outcomes at 3 months of follow up.

MATERIAL AND METHODS

This observational study was carried out between March 2019 and May 2020 at a tertiary care institute in Northern India. Patients of either sex, aged >75 years, presenting with acute coronary syndrome (ACS) and fulfilling the inclusion criteria were eligible for recruitment. ACS spectrum included patients diagnosed as unstable angina (UA), non-ST elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI), in accordance with American College of Cardiology/American Heart Association (ACC/AHA) definitions and all patents were treated as per ACC/AHA guidelines [7,8].

Inclusion Criteria: For the assigned period of study, a total of 100 consecutive elderly patients (>75 years age) of either sex, presenting with acute coronary syndrome (UA/NSTEMI /STEMI) and admitted to coronary care unit at our hospital, undergoing coronary angiography followed, if indicated by PCI were included in the study as per protocol.

Exclusion Criteria: Patients were excluded if they had history of prior ACS, Chronic stable angina or associated congenital heart disease, valvular heart disease and hypertrophic cardiomyopathy. Patients were also excluded if they had acute infections, severe renal insufficiency (creatinine clearance <30 ml/min), chronic inflammatory disorders or were not willing to participate in the study.

Outcomes: These patients were studied for their demographic, clinical and angiographic profiles and the distribution of various risk factors for CAD. After the angiography or PCI, these patients were observed in the hospital and followed up for a period of 3 months after discharge for occurrence of any death or Major Adverse Cardiovascular Event (MACE). MACE included cardiovascular death, non-fatal myocardial infarction, stroke, target vessel revascularization, stent thrombosis and heart failure requiring hospitalization. The first and second follow up visit was at 40 and 90 days respectively. They were also contacted telephonically in between as per the need. At each follow-up visit, echocardiographic assessment of left ventricular function was also done.

Laboratorial Investigations: Baseline investigations including complete hemogram, blood sugar, serum electrolytes, blood urea, serum creatinine, and lipid profile were done. Patients were also evaluated for the presence of novel markers of atherosclerosis in the form of serum homocysteine and high sensitivity - C Reactive Protein (hs-CRP) level. Angiographic profile including stenosis location, severity, type of lesion, and the number of arteries involved were analyzed. Significant CAD was defined by luminal stenosis of more than 50% for the left main coronary artery and more than 70% for the remaining major epicardial coronary arteries.

Ethical Considerations: The study was approved by Institutional Ethics Committee (Intramural) and conducted according to the ethical principles stated in the latest version of Helsinki Declaration, and the applicable guidelines for good clinical practice. A written informed consent was obtained from all the participants.

Statistical analysis: Patient characteristics and outcome measures data were presented using numbers and percentages for categorical variables and Mean (±SD) for quantitative variables. Normality of the measurable data over the various outcomes was checked using Kolmogorov test. Depending upon the normality of the measurable data over the various outcomes, comparisons between 3 or more groups were conducted using ANOVA followed by post-hoc tests, Kruskal-Wallis followed by Mann Whitney tests and comparisons between 2 groups were conducted using Student's t-test and Mann Whitney tests. For classified/categorical data, Chi-Square test or exact Fisher test, depending on the nature of the variables were applied to find the

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association of various classified/categorical data with the outcome parameter(s). A p-value of <0.05 was considered statistically significant.

RESULTS

The baseline characteristics of study population are presented in Table 1. The mean age of the patients was 80.03 ± 3.46 (mean ± SD) years and 69% were male

Table 1: Baseline Characteristics of Study Population

Variable		Frequency (n)/ or mean	Percentage/ or mean ± SD
Sex	Male	69	69%
	Female	31	31%
	Age (years)	80.03	80.03 ± 3.46
Risk Factors	Diabetes Mellitus	22	22%
	Smoking	30	30%
	Hypertension	61	61%
	Family history of IHD	09	09%
	Dyslipidaemia	09	09%
	Obesity	06	06%
	PAD	01	01%
	Alcohol	21	21%
	Previous aspirin use	05	05%
	Atrial Fibrillation	04	04%
	Prior stroke	02	02%
	CKD without dialysis	06	06%
	Prior PCI	05	05%
Symptoms	Chest pain	74	74%
	Dyspnoea	50	50%
	Diaphoresis	69	69%
	Palpitation	14	14%
Blood Pressure	Systolic BP (mm Hg)	133.42	133.42 ± 23.678
	Diastolic BP (mm Hg)	80.30	80.30 ± 12.058
Clinical	UA	22	22%
Diagnosis	NSTEMI	25	25%
	STEMI	53	53%
	Cardiogenic Shock	6	6%
	CHF/LVF	8	8%
STEMI	AWMI	28 (53)	52.8%
	IWMI	25 (53)	47.16%
	THROMBOLYSED	21 (53)	39.6%
LVEF	>35%	74 (100)	74%
	<35%	26 (100)	26%
Left Ventricular Diastolic dysfunction		33 (100)	33%
Mitral	Present	47 (100)	47%
Regurgitation	Mild	30 (100)	30%
	Moderate	14 (100)	14%
	Severe	3 (100)	3%
Angiographic Characteristics			
Access	Femoral	26	26%
	Radial	74	74%
Number of	SVD	31	31%
diseased	DVD	36	36%
vessels	TVD	26	26%

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Insignificant CAD	7	7%
Severe Calcifications	16	16%
Thrombus	14	14%
Diffuse disease	38	38%

Abbreviations:- IHD- Ischemic Heart Disease, PAD- Peripheral Arterial Disease, CKD- Chronic Kidneys Disease, PCI- Percutaneous Coronary Intervention, BP- Blood Pressure, UA- Unstable Angina, NSTEMI- Non ST Elevation Myocardial Infarction, STEMI- ST Elevation Myocardial Infarction,, LVEF- Left Ventricular Ejection Fraction, CHF- Congestive Heart Failure, LVF- Left Ventricular Failure, AWMI- Anterior Wall Myocardial Infarction, IWMI- Inferior Wall Myocardial Infarction, SVD- Single Vessel Disease, DVD- Double Vessel Disease, TVD- Triple Vessel Disease, CAD- Coronary Artery Disease.

Demographic profile: The majority of the patients (62%) were from urban areas and 38% of patients were from rural areas.

Clinical Profile:

Risk Factors: Diabetes, smoking and hypertension was present in 22%, 30% and 61% respectively in this study. A family history of ischemic heart disease (IHD) in the first-degree relative was present in 9% of patients and an equal percentage of patients had dyslipidemia. One fifth of patients were alcohol consumer. Atrial fibrillation and prior stroke was observed in 4% and 2% of patients respectively. The mean serum (±SD) concentration (mg/dL) of Total Cholesterol, Triglyceride, HDL and LDL was 192.91±29.656, 184.43±58.186, 45.22±6.983 and 104.10±25.249 respectively. The serum level (mean±SD) of homocysteine and hs-CRP in study population was 13.001±5.3531 µmol/L and 4.7690±3.5881 mg/L respectively.

Clinical Presentation: In addition to chest pain, diaphoresis was the major symptom observed in approximately 70% of patients. Although, the history of hypertension (treated or untreated) was present as most common risk factor but the blood pressure was controlled in the study population. The presenting diagnosis was UA, NSTEMI and STEMI in 22%, 25% and 53% of ACS patients respectively. Whereas 52.8% of STEMI patients had anterior wall infarction, inferior wall myocardial infarction, was diagnosed in 47.2% patients. 6% and 8% of patients had cardiogenic shock and left ventricular failure respectively at presentation.

Echocardiographic Parameters: Patients were divided into 4 groups according to left ventricular ejection fraction (LVEF) at presentation i.e. patients having EF >55%, 45-54%, 35-44%, and < 35% .30% were having EF 45-54%, 29% had EF of 35-44%, 26% had EF < 35%, and 15% of the patients had EF >55%. However, for the convenience of comparison, patients with LVEF > 35% were grouped together. 47% patients had mitral regurgitation (MR) at presentation of which (63.82%) had mild, 29.78% had moderate and 6.38% of the patients had severe MR.

Angiographic Findings: The radial artery access for coronary angiography was used in 74% cases. The most common form of CAD was double vessel disease (DVD) in 36% followed by single vessel disease (SVD) in 31%, and triple vessel disease (TVD) in 26% of patients. Chronic total occlusions were seen in 15% and 16 % patients had calcified vessels on fluoroscopy. Angiographically visible thrombus was seen in 14% of the patients. 13% and 38% patients had eccentric lesions and diffuse disease respectively. The left main (LM) coronary artery was significantly stenosed in 10 cases (10%). While significant stenosis in left anterior descending (LAD) was observed in 79% of patients, 43%, 55%, and 5% of patients had significant stenosis in left circumflex (LCx), Right coronary artery (RCA), and Ramus respectively. The LCx demonstrated a significantly more common involvement of ostio-proximal segments (32%) over mid-distal segments (17%) (p-value < 0.05).

Correlation of risk factors with angiographic severity of CAD: As shown in Table 2, serum HDL showed a statistically significant reverse correlation with the severity of CAD, with significantly lower HDL levels observed in patients with TVD as compared to those with single vessel disease (SVD) (p < 0.05). The serum level (Mean ±SD) of homocysteine was 10.72±5.33 µmol/L, 12.11±4.97 µmol/L and 17.57±3.5 µmol/L in patients with SVD, DVD and

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TVD respectively with the significant difference found between TVD and DVD ($p < 0.05$), & TVD and SVD ($p < 0.05$). Similarly ,the hs-CRP level (Mean ±SD) was 3.79±2.97 mg/L in patients with SVD, 4.21±2.55 mg/L in DVD and 6.32±3.93 mg/L in patients with TVD with significant difference observed between TVD and DVD ($p < 0.05$), & TVD and SVD ($p < 0.05$) **(Table 2)**.

Table 2: Biochemical Parameters and CAD Severity

Parameter	SVD	DVD	TVD	p- value
TG (mg/dL) (mean±SD)	179.9±62.02	179.31±56.22	194.27±57.34	0.556
Cholesterol(mg/dL)(mean±SD)	183.81±29.49	192.53±29.6	200.42±25.25	0.93
HDL(mg/dL) (mean±SD)	46.97±6.48	45.22±6.96	42.38±6.99	0.05
LDL (mg/dL) (mean±SD)	101.65±26.72	101.19±23.75	109±21.94	0.403
Serum Homocysteine µmol/L (mean ± SD)	10.72±5.33	12.11±4.97	17.57±3.5	0.001
hs-CRP (mg/L) (mean±SD)	3.79±2.97	4.21±2.55	6.32±3.93	0.007

Abbreviations:- SVD - Single Vessel Disease, DVD - Double Vessel Disease, TVD - Triple Vessel Disease, TG -Triglyceride, HDL - High Density Lipoproteins, LDL - Low Density Lipoproteins, hs-CRP - High Sensitivity C-Reactive Protein

Follow-up and Short Term Outcomes: Physical and or telephonic follow up was done at 40th day and at 90th day from the day of first presentation and their echocardiographic parameters, death or any MACE were recorded.

Echocardiographic Outcomes: For the convenience of comparison, the patients were divided into the two groups i.e. with EF <35% and EF >35%. 74% of patients had EF >35% at presentation, which increased to 83.52% and 91.11% of at 40 and 90 days respectively. 26% of total patients at presentation had EF <35%, which decreased to 16.48% and 8.88% at 40 days and 90 days follow up respectively **(Figure 1**).

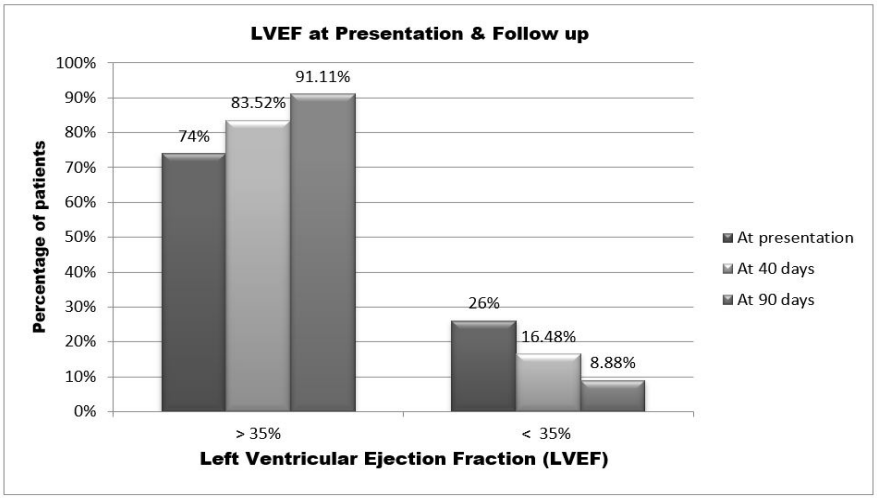

Figure 1. Left Ventricular Ejection Fraction (LVEF) at presentation, 40 days and 90 days follow up. The bar graph show progressive increase in the percentage of patients with LVEF >35% during follow up.

Overall MR was observed in 47% of the patients at presentation which decreased to 42.9% and 36.7% on follow up at 40 and 90 days respectively. Significant MR decreased from 17% at presentation to 3.33% at 90 days **(Figure 2**).

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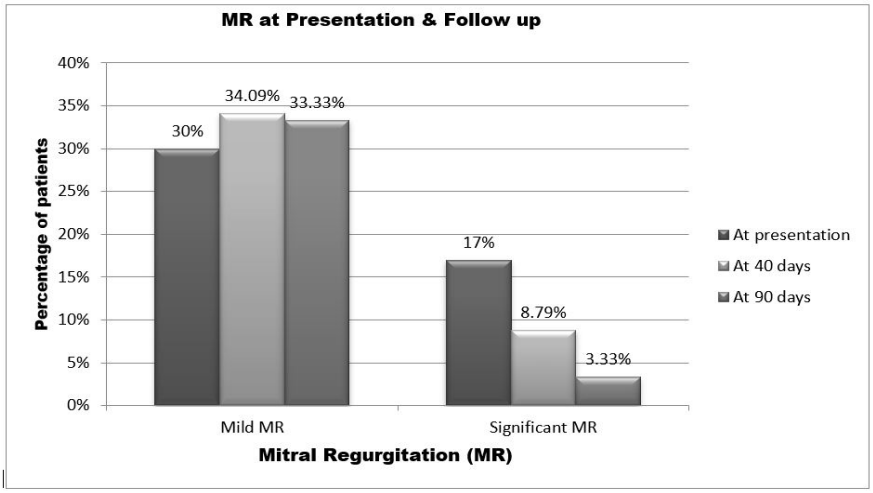

Figure 2. Mitral regurgitation (MR) at presentation, 40 days and 90 days. There is a progressive decrease in the severity of significant MR during follow up.

Death and MACE: (Table 3) A total of 10 deaths occurred by 3 months of follow up. Out of which 8 deaths were due to cardiac cause and two deaths were non-cardiac including one due to stroke and the other due to sepsis associated with multiorgan dysfunction. Of the cardiac causes, four patients died during index hospitalization (one patient each due to acute decompensated heart failure, refractory cardiogenic shock, refractory ventricular tachycardia before angiogram could be done and one due to probable ST). Four patients died after discharge from the hospital (Two post-PCI patients died due to probable stent thrombosis and two patients died at home possibly due to recurrent ACS while awaiting coronary artery bypass surgery).Congestive Heart failure was also seen in one patient (1%) at first follow up which recovered after hospitalization.

Table 3: Death and MACE at follow up

Variable	Death/MACE by the end of 40 days (First follow up)		Death/MACE between 40 to 90 days (Second follow up)		Overall Death/MACE during study period (at 90 days)	
	Number (n=100)	Percentage	Number (n=91)	Percentage	Number (n=100)	Percentage
Death due to any cause	9	9%	1	1.09 %	10	10%
Cardiac cause	7 (9)	77.77%	1(1)	100 %	8 (10)	80%
Non-Cardiac cause	2 (9)	22.22%	Nil	Nil	2 (10)	20%
Stroke (Haemorrhagic)	1	1%	Nil	Nil	1	1%
ISR	Nil	Nil	nil	Nil	Nil	Nil
ST Probable	3	3%	Nil	Nil	3	3%
Definite	Nil	Nil	Nil	Nil	Nil	Nil
TVR	Nil	Nil	Nil	Nil	Nil	Nil
Non-fatal MI	Nil	Nil	Nil	Nil	Nil	Nil
CHF	1	1%	1	1.09%	2	2%

Abbreviations:- MACE - Major Adverse Cardiovascular Events, ISR- In stent restenosis, ST- Stent Thrombosis, TVR- Target vessel revascularization, MI- Myocardial Infarction, CHF- Congestive Heart Failure

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Factors associated with short term (90 days) mortality in Elderly (> 75 years) patients with ACS (Table 4)

Although the presence of atrial fibrillation at admission had a high odds ratio of 3.222 for death but the association was non-significant (p-value = 0.307). High serum homocysteine level (mean±SD) of 16.63±5.26 µmol/L was significantly associated with mortality (p-value < 0.05) compared to a level of 12.6±5.24 µmol/L among the survivors. The hs-CRP and serum lipid level was not found to be associated with the mortality in our study population (p-value =NS).LVEF <35% had a high odds ratio (8.719) and a significant association with mortality (p-value < 0.05). Similarly presence of any degree of MR as well as significant MR was significantly associated with mortality (p-value < 0.05 and odds ratio of 18.6), although presence of mild MR was not (p-value =0.146). Angiographically, the presence of LM involvement, RCA involvement, LCx involvement as well as the presence of TVD had a high odds ratio and significant association with mortality (p < 0.05) whereas presence of SVD was associated with a better survival (p < 0.05).

Table 4: Factors Associated with 90 days Mortality

VARIABLE		Death (n=10)	Surviving (n=90)	p-value	Odds ratio
Male		7 (70%)	62 (68.9%)		
Female		3 (30%)	28 (31.1%)	0.943	1.054
Diabetes Mellitus		1 (10%)	21 (23.3%)	.334	0.365
Smoking		3 (30%)	27 (30%)	1.000	1.000
Hypertension		6 (60%)	55 (61.1%)	.946	0.955
Family History of IHD		0	9 (10%)	.295	-
Dyslipidaemia		1(10%)	8 (8.88%)	.907	1.139
Alcohol		2 (20%)	19 (21.1%)	.935	0.934
Previous Aspirin Use		0	5 (5.55%)	.444	-
Atrial Fibrillation		1 (10%)	3 (3.33%)	.307	3.222
CKD		1 (10%)	5 (5.55%)	.575	1.889
Prior PCI		0	5 (5.55%)	.444	-
BMI (> 25 Kg/m2)		5 (50%)	41 (45.5%)	0.789	.837
UA		1 (10%)	21 (23.3%)	.334	2.739
NSTEMI		4 (40%)	21 (23.3%)	248	.457
STEMI		5 (50%)	48 (53.3%)	.841	1.143
Cardiogenic Shock		1(10%)	5 (5.55%)	.575	.529
CHF/LVF		2 (20%)	6 (6.7%)	.140	.286
Serum Homocysteine level (µmol/L)		16.63±5.26	12.6±5.24	0.02	-
hs-CRP(mg/L)		4.62±2.09	4.79±3.73	0.89	-
LVEF(at presentation)	>35%	3 (30%)	71 (78.9%)	-	-
	<35%	7 (70%)	19 (21.1%)	0.001	8.719
LV Diastolic dysfunction		3 (30%)	30 (33.3%)	0.832	.857
MR	Present	8 (80%)	39 (43.3%)	0.028	5.231
	Mild	1(10%)	29 (32.2%)	0.146	0.234
	Significant	7 (70%)	10 (11.11%)	0.001	18.667
Diseased Vessel	LM	3 (30%)	7 (7.7%)	0.026	5.082
	LAD	10 (100%)	69 (76.7%)	0.086	-
	LCx	8 (80%)	35 (38.9%)	0.013	6.286
	RCA	10 (100%)	45 (50%)	0.003	-
	Ramus	0	5 (5.55%)	.444	-
Number of diseased Vessels	SVD	0	31 (34.4%)	.025	-
	DVD	2 (20%)	34 (37.8%)	.267	0.412
	TVD	8 (80%)	18 (20%)	.001	16.000
Severe Calcifications		2 (20%)	14 (15.5%)	.716	1.357
CTO		3 (30%)	12 (13.3%)	.161	2.786

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Visible Thrombus	3 (30%)	11 (12.2%)	.124	3.078
Diffuse disease	5 (50%)	33 (36.7%)	.410	1.727

Abbreviations:- IHD- Ischemic Heart Disease, **CKD**- Chronic Kidneys Disease, **PCI**- Percutaneous Coronary Intervention, **BMI**- Body Mass Index, **UA**- Unstable Angina, **NSTEMI**- Non ST Elevation Myocardial Infarction, **STEMI**- ST Elevation Myocardial Infarction, **CHF**- Congestive Heart Failure, **LVF**- Left Ventricular Failure, **hs-CRP**- High Sensitivity C-Reactive Protein, **EF**- Ejection Fraction, **LV**- Left Ventricle, **LM**- Left Main, **LAD**-Left Anterior Descending, **LCx**- Left Circumflex, **RCA**- Right Coronary Artery, **SVD**- Single Vessel Disease, **DVD**- Double Vessel Disease, **TVD**- Triple Vessel Disease, **CTOs** - Chronic Total Occlusions, MR-Mitral Regurgitation

DISCUSSION

This prospective observational study done exclusively among patients more than 75 years of age presenting with ACS and undergoing coronary angiography with or without PCI observed significant differences in demographic, clinical and angiographic profile of CAD in elderly.

Demographic Profile: The predominant male population in our study can be due to the additive effect of the higher prevalence of modifiable risk factors among males along with their higher gender susceptibility to CAD. Although the male preponderance is maintained in elderly patients with ACS but proportion decreases with advancing age [9,10]. In the study by Bhatia et al, the male to female ratio in the younger patients was 3.43:1 while it was 1.27:1 in elderly [10].We observed a male to female ratio of 2.22 in the current study. This reduction in the gender ratio among the ACS population with increasing age is also contributed by equalization of risk factors among males and females with advancing age. Majority of our patients (62%) were from the urban area. The various epidemiological studies conducted in India have demonstrated the relatively higher prevalence of CAD in urban population [11–13].However Wander et al. found a significant increase in the prevalence of CAD in the rural population of Punjab from 1994 to 2014, especially in the elderly (from 6.2%to 8.9 %) [13]. This increase in the prevalence of CAD in the rural population is attributed to increase in risk factors due sedentary lifestyle as a result of mechanization. This study also, has more than 1/3rd of the patient from rural areas.

Clinical Profile: In our study, the most common presenting symptoms were chest pain in 74% closely followed by diaphoresis in 69% and dyspnea in nearly 50% of patients. The symptoms of ACS usually differ in elderly compared to young. Presentation with atypical chest pain or no chest pain, dyspnea, fatigue, syncope is more common in the elderly patients, although chest pain still remains the most common symptom in both age groups [10]. Goch A et al observed that in patients ≥ 75 years, dyspnoea or fatigue was more frequent than the typical chest pain when compared with patients of ≤ 75 years of age [14]. Atypical symptoms are associated with increased in-hospital mortality (13% vs 4%) because of delay in diagnosis and management, underscoring the significance of early and proper assessment of these symptoms in the elderly [15,16].In our study, half of the patients had dyspnoea and an approximately 2/3rd of the patients presented with diaphoresis. The diaphoresis was more commonly associated with STEMI than Non-ST-elevation ACS. In one of the studies by Gokhroo RK et al sweating can be an important predictor for diagnosis of STEMI [17].

In our study, hypertension was the most common (61%) risk factor followed by smoking and diabetes mellitus (30% and 22% respectively). In the ISACS-TC registry too, among patients of age ≥ 80 years, hypertension was present in 73.9%, followed by diabetes and smoking (25.6% and 5.7%) respectively [18]. Goch A et al found a history of IHD, hypertension, diabetes to be a common risk factor in elderly patients (>75 years) as compared to the obesity, family history of IHD, hyperlipidemia, and smoking which were more prevalent in patients aged <75 years [14]. Other important, although less common risk factors found in the present study were family history of IHD, dyslipidemia, alcohol consumption, prior PCI, chronic kidney disease and peripheral arterial disease. IHD in family might be attributed to similar dietary habits and lifestyles. Although history of hypertension was most common risk factor, the mean systolic blood pressure at

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presentation in current study was 133.42 ± 23.67 mm Hg and diastolic blood pressure was 80.30 ± 12.05 mm Hg. Various factors such as presence of left ventricular dysfunction, hypovolemia and drugs can contribute to the lower blood pressure in patients presenting with ACS. Thus despite a history of hypertension in majority of the patients, the mean blood pressure at presentation was not in the hypertensive range as defined by International Society of Hypertension guidelines [19].

Angiographic Profile: Insignificant CAD and SVD were seen in 7% and 31% of our patients. Multivessel disease (62%) was more commonly seen in our elderly (>75 Years age) ACS patients. Mattos LA et al in their study found that the prevalence of multi-vessel disease (MVD) was 44% in the age group 60-69 years, 49% in the age group 70-79 years, and 65% in the age group of ≥ 80 years [20]. The higher prevalence of MVD in elderly patients as found in the current study has been supported by previous studies [21,22]. All this data including ours highlight**s** the increase in extent or severity of CAD with advancing age. Further, the most common involvement of LAD observed in the present study is also supported by other studies [23,24]. On segmental analysis of coronary arteries, the LCx demonstrated a significantly more common involvement of ostio-proximal segments (32%) compared to mid-distal segments (17%) in our study ($p < 0.05$). The proximal disease occurs early in the progression of CAD, followed by the involvement of the distal segments as the disease progresses [25,26]. Although statistically insignificant, we also noticed a more common involvement of distal LM as compared to the ostio-proximal, as reported in a study by Ezhumalai B et al [22]. No significant difference in segmental involvement for other vessels was observed in our study. In contrast, the earlier published data shows that the proximal segment involvement is more commonly observed in the LAD, LCx, and RCA [27,28]. However, our exclusive study population of elderly patients with a higher prevalence of multivessel disease and the increased severity of CAD might explain the lack of a normally observed difference in ostio-proximal segment involvement over mid distal segments in the coronaries except for LCX. This is in agreement with some studies which reported more common involvement of distal segments with increased atherosclerotic burden [25,26]. Primary angioplasty is the preferred reperfusion strategy in elderly patients. TRIANA trial showed a mortality reduction at 30 days with primary PCI as compared to fibrinolysis [29]. Although 70% of the patients in our study underwent invasive therapy; primary PCI rate was lower because of delayed presentation.

Novel Markers of Atherosclerosis: We studied the correlation of the various traditional and some novel risk factors such as homocysteine and hs-CRP with severity of CAD **(Table 2)**. The traditional risk factors were not found to correlate with severity of CAD. This lack of correlation has been noted in some previous studies [30,31]. Veeranna et al in their study found that only diabetes have an independent association with the severity of CAD [30].Another study found no significant association between traditional risk factors and CAD except for hypertension [31].These conventional risk factors are more potent predictors of outcome in younger patients than in the elderly [32,33].The advancing age per se an independent risk factor for the CAD. Thus the conventional risk factor profile of younger patients cannot be applied directly to the elderly patients because of many confounding factors. Out of the various types of lipoproteins, only serum HDL showed a significant correlation with the severity of CAD in our study. Statistically significant lower HDL levels were observed in patients with TVD as compared to those with SVD. Despite the lack of correlation with other lipoproteins, this finding supports the protective role of HDL as observed by Bordalo AD et al in their study in elderly patients of CAD [34].

Our study demonstrated a significant correlation of both serum homocysteine levels and the hs-CRP levels with the severity of CAD in patients more than 75 years of age, based on the significant differences in the levels of both serum homocysteine and hs-CRP between the groups of patients with TVD,DVD and SVD (p value < 0.05) **(Table 2).** Karadeniz M et al, studied the hyper-homocysteinemia and its correlation with the severity of the CAD in relation to the syntax score [35]. In their study, patients were divided in three groups, each with increasing syntax score. Patients were of mean age 69.89 ±13 years in group III, 63.62±12.4 in group II and 59.62±12.2 in the group I. They found a significant difference in the

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levels of homocysteine in group II and III compared to the group I, and the homocysteine levels also demonstrated significant correlation with the severity of CAD .The role of inflammation in the inception of the coronary plaques is well established. The hs-CRP has shown inconsistent results for its correlation with the severity of CAD in the previous studies. Razbanet al in their study, demonstrated no significant correlation of hs-CRP with the severity of CAD using Gensini scoring system [36]. Badran HM et al studied the correlation of serum hs-CRP level in three groups of patients with different age profiles, with group III having elderly patients of ≥65 years of age [23]. Despite the lack of a significant association of serum hs-CRP with CAD severity in younger patients, the elderly (≥65 years) demonstrated a significant correlation of hs-CRP levels with severity of CAD. This can be further substantiated from the present study which showed that serum homocysteine and hs-CRP, as novel markers of atherosclerosis, correlate well with the severity of CAD even in elderly population of more than 75 years of age .

Predictors of Short Term (90 Day) Mortality:

Age per se is one of the strongest risk factor for mortality in patients with ACS, with elderly patients having 1 in 10 chance of dying during index hospitalization [15]. Our study observed a short term mortality of 10% among elderly patients presenting with ACS. Besides age, we found various clinical and angiographic variables associated with short term mortality in our elderly patients with ACS. The important clinical factors include raised serum homocysteine levels, left ventricular ejection fraction less than 35% and presence of significant mitral regurgitation. Angiographic factors include involvement of left main, left circumflex or right coronary artery and presence of triple vessel disease.

Whereas both serum homocysteine and hs-CRP levels correlated significantly with the severity of the CAD, only serum homocysteine level depicted a significant positive correlation with the mortality in the current study, while hs-CRP level did not. The mean serum homocysteine level among the deceased (16.63±5.26 micromols/L) was significantly higher than the level (12.6±5.24 micromol/L) found in those who survived ($p \leq 0.05$). Similarly, Matetzky S et alin their study found that serum concentration of homocysteine >2.7 mg/L was associated with recurrent adverse cardiovascular events (36% versus 17%, p-value 0.04) and with increased long term mortality (18% versus 5%, p-value 0.05) (Odds ratio 3.8; 95% CI,1.3-11.0) [37]. A significant positive correlation of serum homocysteine with short term mortality in elderly demonstrated in our study adds to the results of the previous studies [38,39].

Majority (70%) of the patients who died in our study had LVEF less than 35%. As a well-established predictor of mortality in variety of clinical situations [40,41]. Our study also observed the presence of severe left ventricular dysfunction to be a predictor for mortality in elderly patients with ACS. Presence of significant MR was another echocardiographic factor associated of mortality in our study. Out of the 10 deaths, 8 (80%) patients had MR at presentation.MR was moderate or severe in the majority of the patients who died whereas majority of the surviving patients had mild MR. Li S et al in their study found that in patients aged ≥ 80 years with ACS, presence of MR was associated with mortality irrespective of the degree [42]. Pant S et al showed that mild functional MR following ACS most commonly occurred in the setting of STEMI and did not affect the immediate mortality (10 days) [43]. Although a larger study is required to evaluate the exact prognostic impact of various degrees of MR in this patient population, presence of MR was associated with increased mortality in our study.

The involvement of the LM (30% in deceased, 7.7 % in survived) and the presence of TVD (80% in deceased, 20% in survived) were significantly associated with the mortality (p-value ≤ 0.05 for both) in our study. Similar results were reported in patients with ACS on a multivariate analysis [44].On the other hand, presence of SVD in the present study was associated with higher chances of survival. No patient with the SVD died in our study as also observed in the study by Nazzaro et al [45]. Additionally RCA and LCx involvement were found to have a significant association with death in our study. Surprisingly, isolated LAD involvement was not associated with increased mortality. The most possible explanation for this paradox is that LAD being the most common artery involved was diseased in both the groups of patients who died or survived diluting any statistical significant difference. Involvement of RCA and LCx in patients with LAD

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involvement establishes diagnosis of TVD which is associated with significantly higher mortality than SVD. However, a larger study is required to clarify this issue.

CONCLUSIONS

This exclusive study of elderly patients showed that ACS patients aged more than 75 years commonly have multivessel disease and serum homocysteine and hs-CRP level correlate significantly with the angiographic extent of the disease. Cardiac cause is the most common reason of short term mortality in such patients. The important predictors of short term mortality observed in our study include higher serum homocysteine level, presence of severe left ventricular dysfunction, presence of significant mitral regurgitation, involvement of left main, right or left circumflex coronary artery and presence of triple vessel disease. Traditional risk factors like, diabetes, hypertension, smoking, lipid levels were not found to be associated with mortality among elderly ACS patients. These results would help in better prognostication and management of such highly under-studied elderly population with ACS.

LIMITATIONS

The main limitation of the study is the small sample size. Further, as only those consecutive elderly patients of ACS undergoing coronary angiography (with or without subsequent PCI) were included, the demographic and clinical data may not be entirely representative of the profile of ACS in the elderly. Further being a single-center study, the findings may not be generalizable to a larger population.

ABBREVIATIONS:

ACS - Acute coronary Syndrome, ACC - American College of Cardiology, AHA - American Heart Association, CAD - Coronary Artery Disease, LVEF - Left Ventricular Ejection Fraction, HDL - High Density Lipoproteins, hs-CRP - High Sensitivity C-Reactive Protein, IHD - Ischemic Heart Disease, LAD - Left Anterior Descending, LCx - Left Circumflex, LDL - Low Density Lipoproteins, LM - Left Main, MACE - Major Adverse Cardiac Event, MR - Mitral Regurgitation, MVD - Multi Vessel Disease, UA - Unstable Angina, NSTEMI - Non ST Elevation Myocardial Infarction, STEMI - ST Elevation Myocardial Infarction, PCI - Percutaneous Coronary Intervention, RCA - Right Coronary Artery, SVD - Single Vessel Disease, DVD- Double Vessel Disease, TVD - Triple Vessel Disease

Ethics approval and informed consent

The study was approved by Institutional Ethics Committee (Intramural) of Post Graduate Institute of Medical Education and Research, Chandigarh, India wide reference number NK/5277/DM/468 and conducted according to the ethical principles stated in the latest version of Helsinki Declaration, and the applicable guidelines for good clinical practice. A written informed consent was obtained from all the participants. All participants gave consent for anonymous use of data for scientific purpose.

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