

# Short Term Outcome of Urgent Coronary Artery Bypass Grafting (CABG) Surgery

Yousry Shaheen<sup>1</sup>, Mohamed Youssef<sup>1</sup>, Mohamed Saffan<sup>1</sup>, Moataz Rizk<sup>1</sup>, Ashraf Elnahas<sup>1</sup>, Bassem Mofreh<sup>1</sup>, Ahmed Sobhi<sup>1</sup>, Mohamed Elgazar<sup>1</sup>, Sherif Elhendawy<sup>2</sup>, Yosry Thakeb<sup>2</sup>, Ayman Ghoneim<sup>3</sup>, Mahmoud Elemam<sup>1</sup> and Mohamed Alassal<sup>1,2\*</sup>

<sup>1</sup>Benha University Hospitals, Faculty of Medicine, Cardiothoracic surgery department, Egypt

<sup>2</sup>National Heart Institute, Cairo, Egypt

<sup>3</sup>Alazhar University Hospitals, Faculty of Medicine, Cardiothoracic surgery department, Egypt

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**\*Corresponding author:** Mohamed Abdelwahab Alassal, consultant and assistant professor of cardiothoracic surgery, Benha Faculty of Medicine, Benha, Egypt, Consultant of cardiothoracic surgery in PAMCC, Saudi Arabia, Email: dmohamedabdelwahab@gmail.com

## Abstract

**Background and aim of the study:** Outcomes of emergency coronary artery bypass grafting (CABG) for acute coronary syndrome (ACS) due to left main coronary (LM) disease remain unclear. This study aims to assess the short term Outcome for patients undergoing Urgent CABG, due to LM disease; as assessed by relief of symptoms and 6 months improvement of EF.

**Methods:** This study included 60 patients that underwent urgent coronary artery bypass grafting. Patients were divided into three groups according to the pre operative ejection fraction (EF). The three groups were compared regarding preoperative, operative, and postoperative Echo measurement of Ejection fraction and relief of symptoms.

**Results:** 70% of our cases were male with mean age of 52.2 yr (range,  $\pm 7.19$  years), no clinical significance between preoperative comorbidities in relation between 3 groups and the postoperative outcome, the risk factors for our patients are Preoperative myocardial infarction (MI), hemodynamic (HD) instability specially in group C and in turn intraoperative risk is; prolonged Cardiopulmonary bypass time and cross clamp time, while during the intensive care unit stay; postoperative bleeding, MI, prolonged ventilation time and extended ICU stay. The total mortality rate is 8.3% form our patients. Postoperative echocardiography just before discharge and 6 months later showed significant improvement of EF especially for patient showing preoperative instability and MI.

**Conclusion:** The present study demonstrated that patients undergoing Urgent CABG have a significant higher preoperative risk especially with myocardial impairment, despite the higher mortality rate 12%, a favorable clinical outcome can be expected if patients survive.

**Key words:** Urgent CABG, LM disease, ACS, LV impairment.

**Abbreviations:** ACS: acute coronary syndrome; CABG: Coronary artery bypass surgery; CASS: Coronary Artery Surgery Study; CCS: Canadian Cardiovascular Society; COPD: Chronic obstructive lung disease; DM: Diabetes Mellitus; EF: Ejection fraction; HD: Hemodynamic; HTN: Hypertension; IABP: intra-aortic balloon pump; LAD: left anterior descending artery; LCX: left circumflex artery; LM: left main coronary artery disease; LV: Left ventricle; MI: Myocardial infarction; NYHA: New York Heart Association; PCI: percutaneous coronary intervention; RCA: Right Coronary Artery; WMSI: wall motion score index.

## Introduction

Although cardiologists and cardiac surgeons commonly perform urgent CABG in most patients with LMCA stenosis, there is no consensus regarding the ideal interval between the angiographic diagnosis and surgery [1].

Urgent LM surgery is defined as a Procedure required during the same hospitalization in order to minimize chance of further clinical deterioration. Examples of clinical deterioration include but are not limited to: worsening of the symptoms, resistant anginal pain, CHF, progression to acute myocardial infarction (AMI), critical distal LM lesion, requirement of IABP insertion due to chest pain and/or instability, unstable angina (UA) with

intravenous (IV) nitroglycerin (NTG) or rest angina [2, 3].

Significant LM disease is defined as the lesion in the main stem of the LCA greater than 50 percent in the coronary angiography or ostial LAD and LCX involvement (equivalent LM) [4, 5].

The indications for revascularization in patients with Severe Coronary Artery Disease are, improvement of prognosis, persistence of symptoms despite medical treatment, Ischemia is of prognostic importance in patients with Severe Coronary Artery Disease, particularly when occurring at low workload. It demonstrated a survival benefit from CABG in patients with LM or Severe three-vessel Coronary Artery Disease, particularly when the proximal LAD coronary artery was involved. Benefits

were greater in those with severe symptoms, early positive exercise tests, and impaired LV function. Based on the Coronary Artery Surgery Study (CASS) registry, it has been suggested that two important pathophysiological features mitigate against the success of PCI in LM lesions: (1st) up to 80% of LM disease involves the bifurcation, which is known to be at higher risk of restenosis and (2nd) up to 80% of LM patients also have multi-vessel Severe Coronary Artery Disease, where CABG offers a survival advantage independent of the presence of LM disease [6].

**Patients and Methods**

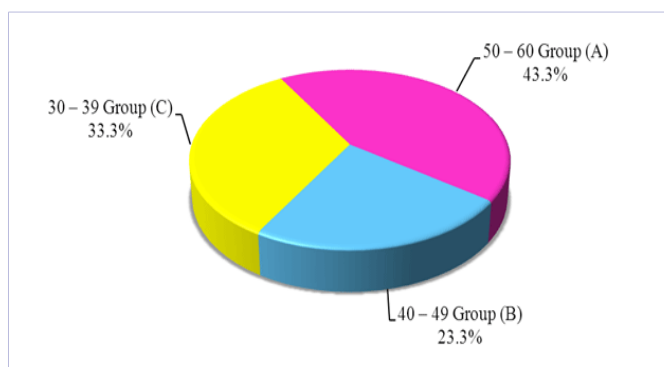
This study was done in the period from December 2014 to July 2016 in three tertiary centers in Egypt (Benha university hospital, National heart institute and Alazhar university hospitals).

It included 60 patients with significant LM disease or LM equivalent underwent urgent CABG, According to society of thoracic surgeon we chose urgent CABG in order to minimize the chance of further clinical deterioration: examples include, worsening general condition, sudden chest pain, acute myocardial infarction, intra-aortic balloon pump insertion, and unstable angina with intravenous nitroglycerin or rest angina.

Also included patients with critical distal LM lesion or significant LM disease with ACS. We excluded patient with accompanied mechanical complications post MI like ventricular septum rupture, acute ischemic mitral regurgitation due to papillary muscle rupture or LV free wall rupture. Patients with previous sternotomy or history of open-heart surgery were also excluded.

**Table 1:** Distribution of the studied cases according to preoperative Ejection Fraction (n=60)

EF	No.	%
50 – 60% Group (A)	26	43.3
40 – 49% Group (B)	14	23.3
30 – 39% Group (C)	20	33.3



**Figure 1:** Distribution of the studied cases according to preoperative Ejection Fraction

Patients were divided into three groups according to their Ejection fraction (Table 1, Figure 1). The three groups were compared regarding preoperative, operative, and postoperative data. Urgent conventional CABG was performed under antegrade cardioplegic arrest with cardiopulmonary bypass. We used the

left internal thoracic artery (LITA) to LAD, saphenous vein (SVG) to OM ± Diagonal and RCA, and 6 patients we used radial artery (RA) as a conduit to tight OM lesion.

**Results**

The male gender was 42 cases (70%) while the female was 18 cases (30%), with mean age of 52.21±7.19 (Table 2).

Baseline demographic data and risk factors prevalence of the study population shown in table 3.

The preoperative data showed that the comorbidities among the three groups were not significant (Table 3 and Figure 2).

**Table 2:** gender distribution and mean age of our patients

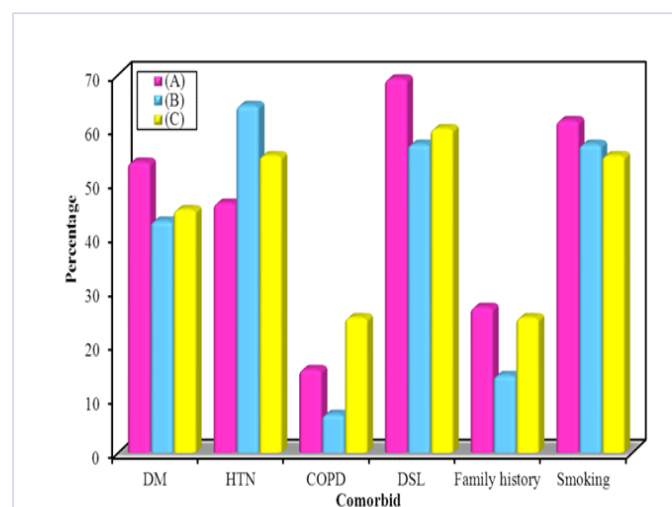
Demographic data	Total (N=60)
<b>Sex</b>	
Male	42 (70%)
Female	18 (30%)
<b>Age (years) Range [Mean±SD]</b>	45-65 [52.21±7.19]

Preoperative symptomatology distribution showed statistical significance as recent MI is higher in-group C, 11\17 patients who had previous MI with significant P-value of 0.002.

According to New York Heart Association classification (NYHA), group A has 12 patients with NYHA class I while 1 patient only in-group C with P-value 0.009. There are zero patients from group A with NYHA class III while 7 patients in group B and 10 in group C with significant P-value of <0.001 (Table 4, Figure 3).

According to Canadian Cardiovascular Society (CCS) grading of angina pectoris there is significant difference with CCS Class III and class IV as there with group 3 there are 7 patients with class III and 11 with class IV.

There were 12 patients that came with hemodynamic instability 9 of them from group C while 2 from group B and 1 from group A with P-value =0.001 showing statistical significance.



**Figure 2:** Preoperative co-morbidities according to 3 groups

**Table 3:** Preoperative co-morbidities according to 3 groups

	Total (n=60)		EF						$\chi^2$	p
			(A) (n = 26)		(B) (n = 14)		(C) (n = 20)			
	No.	%	No.	%	No.	%	No.	%		
<b>DM</b>	29	48.3	14	53.8	6	42.9	9	45.0	0.574	0.751
<b>HTN</b>	32	53.3	12	46.2	9	64.3	11	55.0	1.236	0.539
<b>COPD</b>	10	16.7	4	15.4	1	7.1	5	25.0	1.765	MCp= 0.414
<b>Hyperlipidemia</b>	38	63.3	18	69.2	8	57.1	12	60.0	0.716	0.699
<b>Family history</b>	14	23.3	7	26.9	2	14.3	5	25.0	0.824	MCp= 0.735
<b>Smoking</b>	35	58.3	16	61.5	8	57.1	11	55.0	0.209	0.901

 $\chi^2$ , p:  $\chi^2$  and p values for Chi square test<sup>MC</sup>p: p value for Monte Carlo for Chi square test**Table 4:** Preoperative symptomatology distribution according to the groups

	Total (n = 60)		EF						$\chi^2$	p
			(A) (n = 26)		(B) (n = 14)		(C) (n = 20)			
	No.	%	No.	%	No.	%	No.	%		
<b>AMI</b>	17	28.3	2	7.69	4	28.57	11	55	12.460*	0.002*
<b>NYHA</b>										
<b>I</b>	17	28.3	12	46.15	4	28.57	1	5	9.429*	0.009*
<b>II</b>	11	18.3	1	3.85	1	7.14	9	45	12.587*	<sup>MC</sup> p=0.001*
<b>III</b>	17	28.3	0	0.0	7	50.0	10	50.0	18.140*	<0.001*
<b>CCS</b>										
<b>I</b>	15	25	9	34.62	4	28.57	2	10.0	3.777	0.151
<b>II</b>	6	10	4	15.38	2	14.29	0	0.0	3.553	<sup>MC</sup> p=0.148
<b>III</b>	10	16.7	0	0	3	21.43	7	35.0	11.255*	<sup>MC</sup> p=0.001*
<b>IV</b>	13	21.7	0	0	2	14.29	11	55.0	20.535*	<sup>MC</sup> p<0.001*
<b>HD instability</b>	12	20.0	1	3.85	2	14.29	9	45.0	11.524*	<sup>MC</sup> p=0.001*
<b>Needs for intropes</b>	11	18.3	0	0	2	14.29	9	45.0	15.359*	<sup>MC</sup> p<0.001*
<b>Needs for IABP</b>	6	10.0	1	3.85	1	7.14	4	20.0	3.034	<sup>MC</sup> p=0.215

 $\chi^2$ , p:  $\chi^2$  and p values for **Chi square test**<sup>MC</sup>p: p value for Monte Carlo for Chi square test

\*: Statistically significant at p ≤ 0.05

N.B there were 15 patients free of symptoms

Patients needed inotropic support preoperatively were 12 patients 9 from Group C, 2 from group B and no one from group A needed inotropic support with P-value <0.001 showing statistical significance.

Patients needing preoperative IABP were 6 patients 4 from group C, 1 from group B and 1 from group A with P-value 0.215 (Table 4).

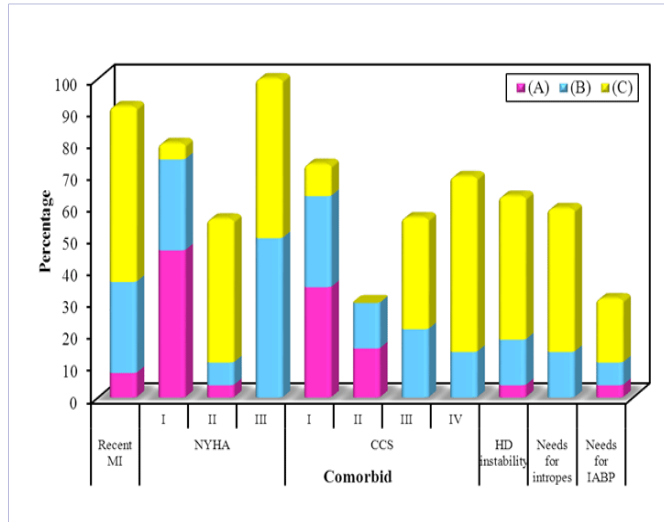


Figure 3: Preoperative symptomatology distribution according to groups

Bypass time and Clamp time were higher with group C while the number of grafts used didn't show significant difference between all groups (Table 5, Figure 4).

Mean Ventilation time and ICU stay were higher with group C.

Total mortality was 5 patients which is 12% of all patients, 1 patient died intraoperative and 4 patients died during the ICU period; 4 patients were from group C and 1 patient from group B with P-value 0.025 (Table 7, Figure 6).

Postoperative complications didn't show statistically difference between the 3 groups (Table 7, Figure 6).

The inotropic support postoperatively showed statistical significance, as there were 34\60 patients on inotropic support postoperatively; 16 patients from group C, 9 patients from group B and 9 from group A with P-value 0.003. Showing statistical significance

IABP was used postoperatively in 11\60, 7 from group C and 2 from group B and 2 from group A with P-value 0.004. Showing statistical significance

Reopened cases were 3; 2 patients from group C reopened due to post operative bleeding and 1 patient from group B reopened due to postoperative MI to recheck the grafts (Table 8, Figure 7).

Postoperative echocardiography follow up was done before discharge and 6 months postoperatively being compared to baseline ECHO done prior to surgery to respective to the 3 groups and showed statistically significant difference (Table 9, Figure 8).

Table 5: Intraoperative data according to EF

	Total (n = 60)		EF						Test of Sig.	p
			(A) (n = 26)		(B) (n = 14)		(C) (n = 20)			
	No.	%	No.	%	No.	%	No.	%		
No. of distal grafts anastomosis										
2G	12	20	6	23.08	3	21.43	3	15	$\chi^2=$ 1.268	$^{MC}p=$ 0.907
3G	32	53.3	12	46.15	8	57.14	12	60		
4G	16	26.7	8	30.77	3	21.43	5	25		
Cardiopulmonary bypass time (CPB) (min.)	60 - 213		60 -120		60 -170		90 -213			
Clamp time (min.)	40 - 160		40 - 100		50 -130		70 -160			
$\chi^2$ , p: $\chi^2$ and p values for Chi square test										
$^{MC}p$ : p value for Monte Carlo for Chi square test										

Regarding the 26 patients of group A; the pre-discharge echo 20\26 patients remained with EF of 50-60% while 6\26 patients had decreased EF.

After 6 months; 4 patients regained the EF 50-60% total (24\26) while 2 of them remained with EF less than 50-60% (Table 10, Figure 9).

In-group B patients; the pre-discharge echo showed

5\13 cases EF increased to 50-60 % and 7\13 remained with EF of 40-49% while 1\13 decreased to 30-39%,

6 months later 4\13 patients showed EF of 50-60%, and 1 patient of the increased EF decreased again to 40-49% and the 2 patients, which showed EF 30-39%, increased to 40-49% (Table 11, Figure 10).

In group C; the pre-discharge echo showed 8\17 patients with increased EF while 8\17 patients remained with EF of 30-39%,

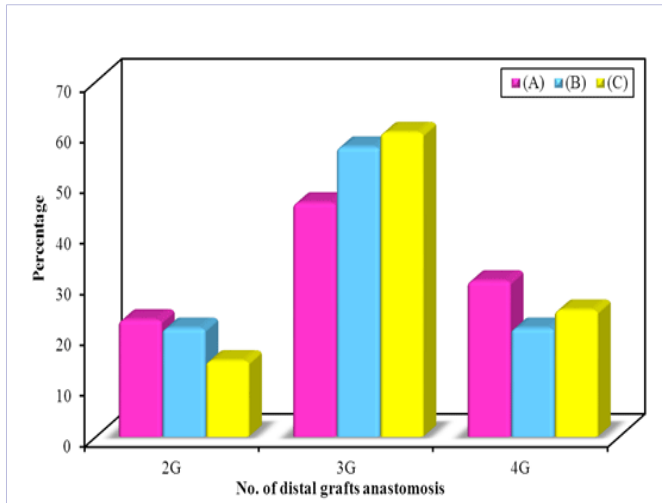


Figure 4: Intraoperative data according to EF

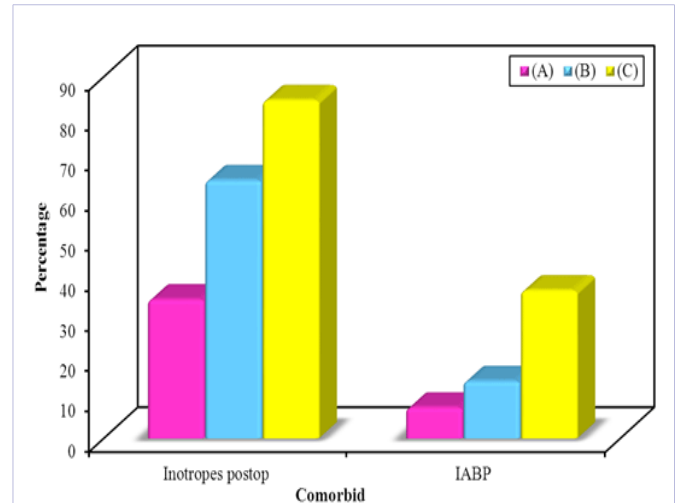


Figure 5: Post op. Data According of all patients acc. to 3 groups (NB: 1 patient died intraoperative)

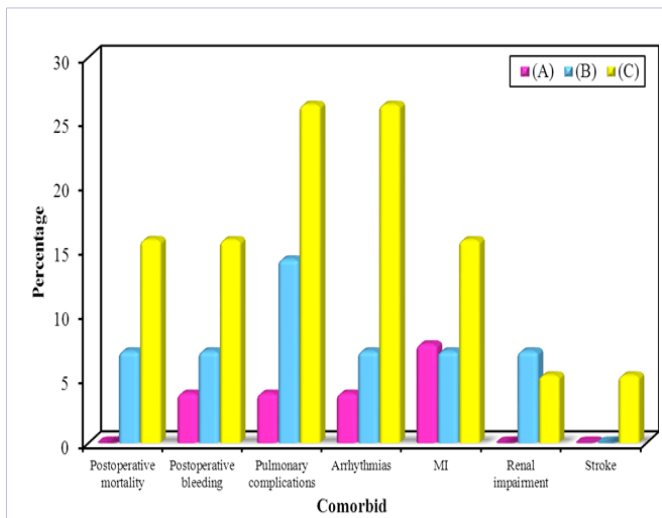


Figure 6: Postoperative Complications according of all patients acc. to 3 groups

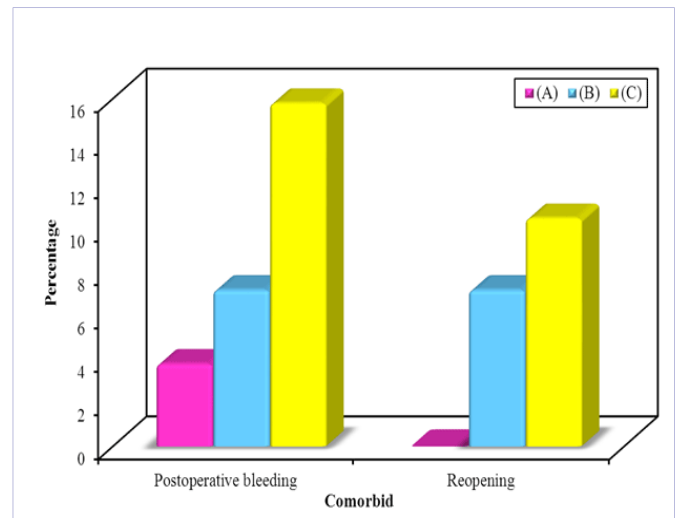


Figure 7: Postoperative Reopening

Table 6: Post op. Data According of all patients acc. to 3 groups

	Total (n = 59)		EF						Test of Sig.	p
			(A) (n = 26)		(B) (n = 14)		(C) (n = 19) #			
	No.	%	No.	%	No.	%	No.	%		
Inotropes postop	34	57.6	9	34.62	9	64.29	16	84.21	$\chi^2=11.391^*$	0.003*
IABP	11	18.6	2	7.69	2	14.29	7	36.84	$\chi^2=5.803^*$	<sup>MC</sup> p=0.044*
Mean Ventilation time	6 – 168		6 – 30		9 – 50		9 – 168			
ICU stay	2 – 12		2 – 3		2 – 4		5 – 12			

$\chi^2$ , p:  $\chi^2$  and p values for Chi square test

<sup>MC</sup>p: p value for Monte Carlo for Chi square test

\*: Statistically significant at p ≤ 0.05

**Table 7:** Postoperative Complications According of all patients acc. to 3 groups

	Total (n = 59)		EF						Test of Sig.	p
			(A) (n = 26)		(B) (n = 14)		(C) (n = 19) <sup>#</sup>			
	No.	%	No.	%	No.	%	No.	%		
Postoperative mortality	4	6.8	0	0	1	7.14	3	15.8	$\chi^2=4.334$	<sup>MC</sup> p=0.077
Postoperative bleeding	5	8.5	1	3.85	1	7.14	3	15.79	$\chi^2=1.979$	<sup>MC</sup> p=0.429
Pulmonary complications	8	13.6	1	3.85	2	14.29	5	26.32	$\chi^2=4.627$	<sup>MC</sup> p=0.097
Arrhythmias	7	11.9	1	3.85	1	7.14	5	26.32	$\chi^2=4.855$	<sup>MC</sup> p=0.066
MI	6	10.2	2	7.69	1	7.14	3	15.79	$\chi^2=0.995$	<sup>MC</sup> p=0.649
Renal Dysfunction	2	3.4	0.0	0.0	1	7.14	1	5.26	$\chi^2=2.121$	<sup>MC</sup> p=0.308
Stroke	1	1.7	0.0	0.0	0	0.0	1	5.26	$\chi^2=2.016$	<sup>MC</sup> p=0.559

**Table 8:** Postoperative Reopening

	Total (n = 59)		EF						$\chi^2$	p
			(A) (n = 26)		(B) (n = 14)		(C) (n = 19)			
	No.	%	No.	%	No.	%	No.	%		
Postoperative bleeding	5	8.5	1	3.8	1	7.2	3	15.8	1.979	0.428
Reopening	3	5.1	0	0	1	7.2	2	10.5	2.84	0.246

**Table 9:** Postoperative before discharge and 6 Months follow up According of all patients acc. to 3 groups

	Total (n = 55)		EF						$\chi^2$	<sup>MC</sup> p
			(A) (n = 26)		(B) (n = 13) <sup>s</sup>		(C) (n = 16) <sup>#</sup>			
	No.	%	No.	%	No.	%	No.	%		
<b>Postop before Discharge</b>										
50 – 60	27	49.1	20	76.92	5	38.46	2	12.5	23.384*	<0.001*
40 – 49	17	30.9	4	15.38	7	53.85	6	37.5		
30 – 39	11	20.0	2	7.69	1	7.69	8	50.0		
<b>6 months Follow up</b>										
50 – 60	30	54.5	24	92.31	4	30.77	2	12.5	34.606*	<0.001*
40 – 49	21	38.2	1	3.85	9	69.23	11	68.8		
30 – 39	4	7.3	1	3.85	0	0.0	3	18.8		

$\chi^2$ , p:  $\chi^2$  and p values for **Chi square test**  
<sup>MC</sup>p: p value for Monte Carlo for Chi square test  
\*: Statistically significant at p ≤ 0.05

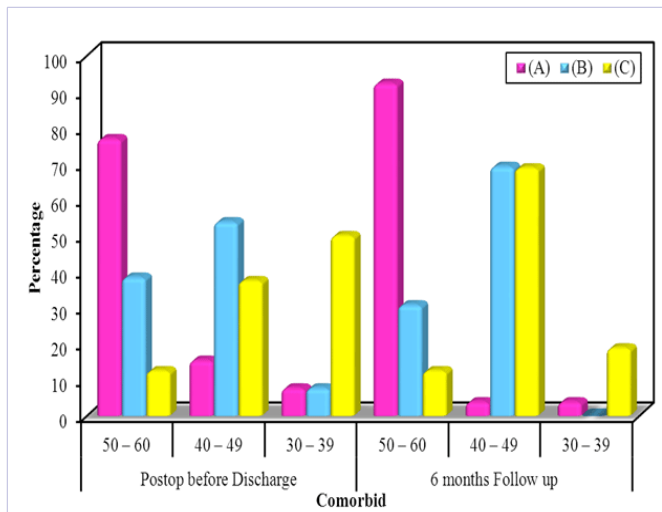


Figure 8: Postoperative before discharge and 6 Months follow up According of all patients acc. to 3 groups NB there are 3 patients died in hospital

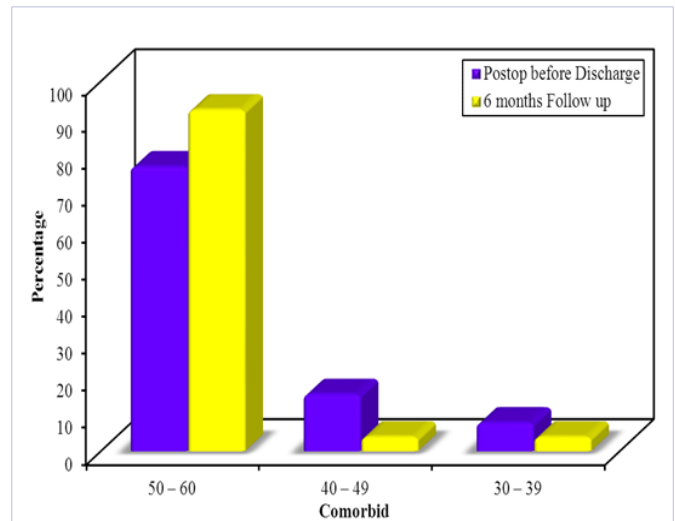


Figure 9: Postoperative and 6 Months follow up According of all patients acc. to group A

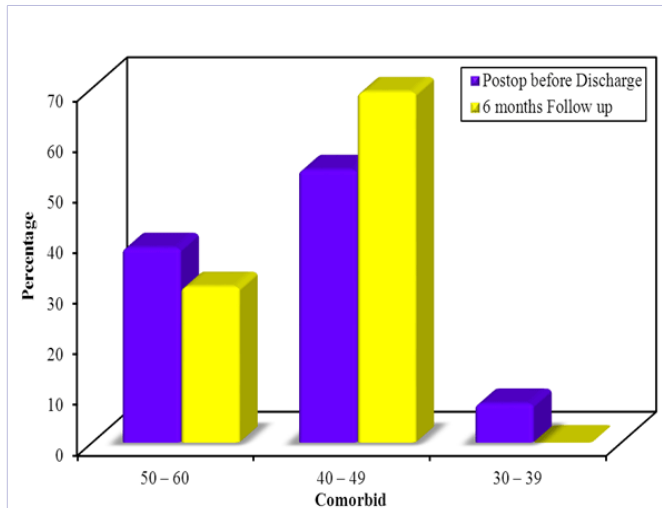


Figure 10: Postoperative and 6 Months follow up According of all patients acc. to group B

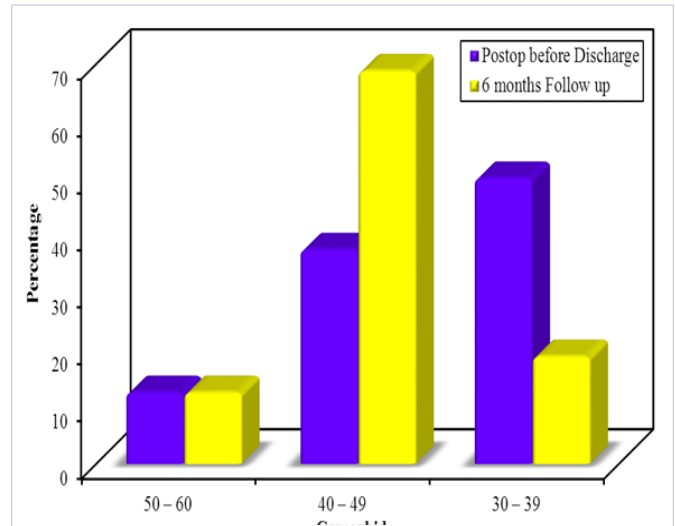


Figure 11: Postoperative and 6 Months follow up According of all patients acc. to group C

Table 10: Postoperative and 6 Months follow up According of all patients acc. to group

Group A	A			
	Postop before Discharge		6 months Follow up	
	No.	%	No.	%
50-60	20	76.92	24	92.31
40-49	4	15.38	1	3.85
30-39	2	7.69	1	3.85

Table 11: Postoperative and 6 Months follow up According of all patients acc. to group

Group B	B			
	Postop before Discharge		6 months Follow up	
	No.	%	No.	%
50-60	5	38.46	4	30.77
40-49	7	53.85	9	69.23
30-39	1	7.69	0	0

**Table 12:** Postoperative and 6 Months follow up According of all patients acc. to group

C				
Group C	Postop before Discharge		6 months Follow up	
	No.	%	No.	%
50 – 60	2	12.5	2	12.5
40 – 49	6	37.5	11	68.8
30 – 39	8	50	3	18.8

and 6 months later; 13\17 patients showed increase EF while only 3\17 patients remained with EF between 30-39% (Table 12, Figure 11).

## Discussion

Actually most of the literature is talking about the timing of the urgent surgery for revascularization of cases with significant LM coronary disease or significant LM equivalent but only a few articles were talking about the follow up and postoperative outcome of urgent CABG.

This attracted and encouraged us to do our study for follow up of these cases and to analyze their outcomes.

In our study patients were stratified into three groups according to EF A 50-60% , B 40-49 % , C 30-39 % while other authors considered EF below 40 % as an independent risk factor for predicting the outcome after CABG surgery [7, 8].

The use of preoperative IABP in our study was in 6\60 patients (10%) while with other authors this percentage climbed to approximately ~ 30 % [7, 9].

We shared the same methodology for patient choice as with most articles in the literature, ranging from 1-14 days according to number of cases and priority in wanting list as well as availability of surgical spots , our mean time for surgery was  $4.3 \pm 1.86$  days, the priority for surgery is discussed by cardiology and cardiac surgeons according to clinical status and angiography, some patient with intractable chest pain or critical anatomy are scheduled on operating list on the same day or next day, other patients scheduled according to priority and also dependent on triage status (incorporating clinical status) and operating room availability [9-12].

Many priority scales were applied in many studies, Ontario and New Zealand priority score are used to define priority [10]. The standard Time frame to urgent CABG varies depending on different reports, Kim et al [7] reported that most of his urgent cases done within 2- 8 hours from diagnosis, while Tomasco B, et al, [10] reported time from 1-3 days as urgent, Deyell et al, [11], consider 2-7 days as urgent also Naylor D, et al, [12] reported up to 14 days as urgent, we agreed to the consensus that all revascularization should be done in the same hospital admission..

In our study we observed long ventilation time  $22.45 \pm 14.36$  hours with range from 6-168 hour, Chen Y, et al [13] reported lower ventilation hours with mean of 16 hours with range from (1-695) hours in the review of his cases.

In our study, Cholesterol levels above 200 mg/ml were considered as hyperlipidemia, total of 38 patients showed hyperlipidemia out of 58 patients as 2 patients were missed.

In our study post operative renal Dysfunction occurred in 2 cases which represents 3.4% of our cases, one case from group B and the other from group C, while in Kim A. Eagle et al [14] showed that Postoperative renal dysfunction occurs in as many as 7.7% of patients.

Renal dysfunction, defined as postoperative Scr of at least 2.0 mg/dL accompanied by an increase of at least 0.7 mg/dL from preoperative baseline [15].

In our study 7 patient showed postoperative arrhythmias 11.6% of all cases, 5 patients had post operative AF were cordarone infusion started as a loading and then maintained and subsided pre-discharge without starting warfarin, 1 patient with SVT without HD instability, and 1 patient with persistent VF and died during the ICU stay.

In our study mortality was 5\60 patients (12%) of all patients, 1 patient died intraoperative and 4 patient died during the ICU period, 4 patients was from group C and 1 patient from group B, while the mortality in other studies like study of Kim and his co-authors they reported mortality of 17.3% (18\104) and considered that EF less than 40% is a risk factor for mortality while Hirose H, et al [16] demonstrated (11\47) 23.4% mortality in his group of urgent CABG and he considered that an ejection fraction < 50% is a risk factor for death after MI.

In our group all patient had LIMA and Saphenous vein graft only 6 patients had radial artery graft, 53% of patients underwent CABG with 3 grafts while 16% with 4 grafts and 12% with 2 grafts the number of grafts used didn't show significant difference between all groups. CPB time, AXC time, and total OR time were longer with group C; this mostly attributed to that many of our patients having difficulty to wean off bypass machine or required re-bypass again.

Generally our results in the same line with results of, Järvinen O, et al [17], which showed significant improvement in functional capacity and NYHA class during the 1st year after CABG.

We lost 5/60 of our patient population representing about 8.3% mortality, 55 patients were discharged free of symptoms with a pre-discharge ECHO measurement of their ejection fractions as follows

For group A 26 patients initial EF 50-60%, 4 had transient decrease of EF to become between 40-49%, 2 patients EF temporary decreased to 30-39% at pre discharge ECHO however at 6 months ECHO follow up all EF patients were between 50-60%, 1 between 40-49% and another 1 between 30-39%

As for group B 13 patients, initial EF 40-49%, 5 had increase of EF to 50-60%, 7 remained same as pre-op EF and 1 decreased to 30-39 % and at 6 months follow up 9 patients remained at 40-49% while 4 patients improved to 50-60%

As for group C 16 patients with initial EF 30-39%, 2 patients EF increased to 50-60%, 6 increased to 40-49% while 8 remained at EF 30=39%, at 6 months follow up 2 patients increased to EF 50-60%, 11 patients improved EF to 40-49% and only 3 patients remained at EF 30-39 %



Aronson S, et al [18] showed that CABG surgery contributes to improved regional and global left ventricular function in patients with left ventricular dysfunction with or without angina and infarction. Revascularization of viable but dysfunctional myocardium perfused by markedly obstructed vessels can reduce the threat to the myocardium and improve left ventricular function. Furthermore, it has been demonstrated that up to 50% of patients with a previous infarction may have areas of hibernating tissue mixed with areas of scar tissue, even in the presence of Q waves on the electrocardiogram. Douki ZE, et al [19], they reported improving in functional status early and late after CABG even with elderly patients, at least on NYHA class improving at early period. Søråas C, et al [20] reported early improvement of myocardial contractility and improvement of WMSI. Most of these studies confirmed that the early improvement of contractility and WMSI associated with good long-term outcome, in contrary deterioration of WMSI early after CABG is associated with poor outcome as reported by Swaminathan M, et al [21].

## Conclusion

Our study demonstrated that the patients undergoing Urgent CABG have a significant higher preoperative risk especially with myocardial impairment. Despite the higher mortality rate 8.3%, a reasonable and favorable clinical outcome can be achieved when those patients tolerate the surgery and survive. Also we assume that establishing hemodynamic stability in conjunction with the cardiologist prior to surgery significantly influences the surgical outcome.

## Study limitations

We can put on-hand on some limitations for this study such as:

The potential bias of any retrospective study and sometimes we couldn't get full detailed information from some patient's files (e.g. some operative details or missed post-operative follow up) that may affect the outcome so these patients were excluded from the study.

We also don't have information on the number of patients who may have not survived after presentation with significant LM lesion or LM equivalent and therefore never received a CABG.

Our study was done in two tertiary centers only, and may require bigger patient volume for more precise evaluation and statistical assessment.

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## Author's contributions

YS and MY wrote the studies, participated in the sequence alignment, drafted the manuscript and were in charge of overall direction and planning. MR and MS collected the data and carried

out the statistics. AE and BM participated in the surgical part and conceived the presented idea. AG, ME, MA and AS participated in the design of the study and performed the statistical analysis. YS and MH conceived of the study, and participated in its design and coordination and helped to draft the manuscript.

SE, AE and YT helped supervise the project and shared in data collection and verified the analytical methods. AG, MA and MM contributed to the final version of the manuscript, supervised the project. All authors read and approved the final manuscript.

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