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Impact of Metabolic Syndrome on Mortality and Morbidity After Coronary Artery Bypass Grafting Surgery

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Background: The prevalence of Metabolic syndrome (MetS) has been increased in Asian countries. It represents a cluster of cardiovascular risk factors including obesity, insulin resistance, lipid abnormality and hypertension.
Objectives: The purpose of this study was to assess the association between MetS and outcome in patients undergoing coronary artery bypass grafting surgery (CABG).
Patients and Methods: This prospective study was performed on patients scheduled for coronary artery bypass grafting surgery (CABG). All the patients were followed up in hospital and three months afterward. Patients were excluded if they were younger than 18 years or had severe comorbidities, a history of valvular heart disease, and low ejection fraction.
Results: A total of 235 patients (135 women) with a mean age of 59 ± 9.3 years were included. MetS was more prevalent in women ($P < 0.001$). The most prevalent complications were bleeding [20 (8.5%)] and dysrhythmia [18 (7.7%)]. At three months follow-up, the frequency rates of readmission [24 (10.2%)] and mediastinitis [9 (3.8%)] were higher than other complications. Diabetes and MetS were risk factors for a long ICU stay (> 5 days) and atelectasia ($P < 0.05$). Significant associations were observed between diabetes and pulmonary embolism ($P = 0.025$) and mediastinitis ($P = 0.051$).
Conclusions: Identification of MetS before CABG can predict the surgery outcome. Patients with MetS have increased risks for longer ICU stay and atelectasia.

Keywords: Metabolic Syndrome; Coronary Artery Bypass Graft; Outcome

1. Background

Metabolic syndrome (MetS) is estimated to have affected 35% to 40% of the population of industrialized countries in the recent years (1). Recent studies have demonstrated a dramatic rise as 50.8% in the prevalence of MetS in the Iranian population (2-5) and Asian countries (6). Patients with MetS have increased risks for developing coronary artery disease, stroke, peripheral vascular disease, and type II diabetes mellitus as well as greater mortality from coronary disease and other causes (7-10). Metabolic syndrome increases the risk of coronary artery disease up to four times (11, 12) and can predict the likelihood of diabetes (8, 13, 14). Metabolic syndrome represents a cluster of related cardiovascular risk factors including central obesity, insulin resistance, atherogenic lipid profile, and hypertension. There are several definitions for MetS and whilst they share core components, they differ in detailed criteria required to diagnose the syndrome. Amongst these, the World Health Organization definitions and the National Cholesterol Education Program Adult Treatment Panel III are the most widely accepted ones (15, 16).

Insulin resistance is the cornerstone of MetS as it induces hyperinsulinemia, hyperglycemia, sodium retention, and vasoconstriction impairment and increases VLDL, triglyceride, Apo B1, and small LDL and decreases HDL. MetS per se is associated with a two-fold risk of the presence of diabetes. It has been postulated that low-grade inflammation and prothrombin state (12) in particular, is related to the pathogenesis of MetS and associated with cardiovascular diseases (17-21).

2. Objectives

The aim of this study was to assess the association between MetS and outcome in patients undergoing coronary artery bypass grafting surgery (CABG).

3. Patients and Methods

3.1. Study Population

This prospective study was conducted on patients sched-

uled for isolated CABG in Cardiovascular Medical and Research Center, Tehran, Iran ,which is a tertiary health care center for cardiovascular patients between March 2009 and February 2010. Preoperative and operative data of all patients undergoing CABG in our hospital were prospectively collected and entered a computerized database. The anesthetic and surgical techniques were standardized for all patients (midline sternotomy, hypothermia below 30°C, and antegrade cold blood cardioplegia). Baseline data including demographic characteristics, clinical information, and ICU sheets in addition to data on risk factors, medication, and function status, were obtained by trained personnel supervised by a researcher nurse. Postoperative complications were recorded prospectively by a researcher, and all major adverse events were prospectively validated by an experienced cardiac surgeon according to the standard definitions. All the patients were followed in hospital for three months; follow-up was completed for all patients.

Patients were excluded if they were younger than 18 years or had severe comorbidities, a history of valvular heart disease, and low ejection fraction (EF < 35%) on admission confirmed by echocardiography. Those undergone concomitant procedures were also excluded. The study was approved by the institutional ethics committee, and informed consent was obtained from all the patients.

3.2. Clinical, Anthropometrical, and Laboratory Measurements

The patients' characteristics including age, sex, mean blood pressure, body mass index (BMI), waist circumference, type II diabetes mellitus, systemic hypertension, obesity, and smoking were collected.

Weight was measured using a calibrated digital scale (Seca GmbH & Co. kg. Germany). A stadiometer (Seca GmbH & Co. kg. Germany) calibrated before each measurement, was used for height measurement. These measurements were used for calculating BMI. Waist circumference was assessed by a trained nurse, using a cloth tape. The waist was defined at the midpoint between the highest point of the iliac crest and the lowest part of the costal margin in the midaxillary line.

Type II diabetes mellitus was defined as taking diabetes medication or fasting plasma glucose concentration of ≥ 110 mg/dL. Subjects were considered to have hypertension if they were taking antihypertensive medications or had a systolic blood pressure of ≥ 130 mm Hg or a diastolic blood pressure of ≥ 85 mm Hg.

Reviewers extracted the following outcomes: all-causes mortality, cardiovascular disease mortality, myocardial infarction, cardiogenic shock, preoperative need for inotropic or diuretic agents, requirement for an intra-aortic balloon pump, aortic cross-clamp time, units of blood transfused, reoperation for homeostasis, prolonged intubation, level of cardiac enzymes, new-onset atrial fibrillation, sternal wound infection, new neurological deficits, renal dysfunction, and death.

3.3. Definition of Metabolic Syndrome

Clinical identification of patients with the features of MetS was based on the criteria proposed by the NCEP-ATPIII (National Cholesterol Education Program Adult Treatment Panel III) (10). Patients were considered to have MetS when three of the following five criteria were met: 1) waist circumference ≥ 102 cm in men and 88 cm in women; 2) fasting hyperglycemia ≥ 110 mg/dL or using diabetes medications; 3) triglycerides ≥ 150 mg/ dL or taking triglyceride-lowering agents; 4) HDL cholesterol < 40 mg/dL for men, < 50 mg/dL for women or taking cholesterol-lowering agents; and 5) hypertension (systolic blood pressure ≥ 130 diastolic blood pressure ≥ 85) or using antihypertensive medication.

3.4. Outcome Follow-up

The primary endpoint of our study was operative mortality, defined as death from any cause within three months after the operation. Cardiac and noncardiac morbidities constituted the secondary endpoint. Cardiac morbidities were cardiac arrhythmias, myocardial infarction, heart failure, tamponade and cardiogenic shock (systolic blood pressure < 90 mm Hg with no or poor response to fluids and requiring administration of inotropic infusions to maintain the blood pressure). Noncardiac morbidities were atelectasia, long ICU stay (more than 5 days), prolonged mechanical ventilation (more than 72 hours) reintubation, gastrointestinal bleeding, renal failure, sepsis, wound and lung infection, mediastinitis, pressure ulcer, pulmonary embolism, and readmission.

The criterion for lung infection was a positive result in sputum culture associated with a radiological infiltration. The criterion for postoperative renal failure was a 50% increase in the baseline serum creatinine level. The criterion for postoperative sepsis was the presence of a positive blood culture. Mediastinitis was diagnosed when a deep sternal infection was present, necessitating an opening of the wound with the excision of the tissue and treatment with antibiotics. Mortality was defined as in-hospital death and death within a three-month period after the operation. All of the follow-up data were collected when the patient died or was discharged until three-month period after the operation.

3.5. Statistical Analysis

The data was described as mean ± standard deviation for the interval and count (%) for the categorical variables. The two groups were compared using the Student t-test and between more than two groups using One-way analysis of variance (ANOVA) models.

Nominal data were compared between the two groups using Pearson chi square or Fisher exact test and ordinal variables were compared between the two groups using

Mann-Whitney U-test. Effect modifications of diabetes and MetS on the study outcomes were investigated using two-way analysis of variance (ANOVA) models for the interval outcomes and the Mantel-Haenszel method for the binary outcomes. A P value < 0.05 was considered statistically significant. SPSS 15 for Windows (SPSS Inc. Chicago, Illinois, the USA) was applied for statistical analysis.

4. Results

4.1. Background Data

A total of 235 patients, including 135 women, with a mean age of 59 ± 9.3 years were recruited. Descriptive results are presented in Table 1. Diabetes, hypertension, and different types of hyperlipidemia were more prevalent amongst women. Laboratory findings demonstrated that serum fasting glucose and total cholesterol levels were higher in women at the time of data collection.

Table 1. Descriptive Statistics of the Study Population (n = 235) [a]

	Descriptive Statistics
Age, y	59 ± 9.3
Sex, F/M	135/100
Underlying Diseases	
Diabetes (History)	121 (51.5)
Hyperlipidemia (History)	107 (45.5)
Hypercholesterolemia (> 200 mg/dL)	74 (31.5)
LDL Dyslipidemia (> 130 mg/dL)	30 (12.8)
HDL Dyslipidemia (men: < 50 mg/dL; women: < 40mg/dL)	191 (81.3)
Hypertriglyceridemia (> 150 mg/dL)	139 (51.9)
Hypertension	136 (57.9)
Body Mass Index, kg/m²	27 ± 4.2
Waist Circumference, cm	101 ± 14.7
Paraclinical Findings	
Fasting Serum Glucose (mg/dL)	145 ± 60.4
Total serum Cholesterol (mg/dL)	174 ±53.8
Serum High Density Lipoprotein (mg/dL)	39.8 ± 54.9
Serum Low Density Lipoprotein (mg/dL)	90.3 ± 37.4
Serum Triglyceride (mg/dL)	201 ± 142.8
Hemoglobin A1C (g/dL)	6.2 ± 1.9
Serum Creatinine (mg/dL)	1.3 ± 0.3
Medications	
ACE inhibitors	144 (61.3)
Beta Blockers	196 (83.4)
Calcium Channel Blockers	41 (17.4)
Involved Coronary Artery	
Left main	6 (2.6)
Left Anterior Descending	235 (100)
Left Circumflex	203 (86.4)
Right Coronary Artery	202 (86)

[a] Data are presented as Mean ± SD or No. (%).

The associations between the patients' characteristics and MetS are presented in Table 2. MetS was more prevalent in women (P value < 0.001). According to the definition and criteria for MetS, an association was found between this syndrome and diabetes, dyslipidemia, BMI, waist circumference, serum glucose level, and lipid profile.

Table 2. Association Between Patients' Characteristics and Metabolic Syndrome [a]

	Metabolic Syndrome		
	No (n = 50)	Yes (n = 185)	P value
Age, y	59 ± 11.1	60 ± 8.8	0.771
Sex, F/M	16/34	119/66	< 0.001
Underlying Diseases			
Diabetes	11 (22)	110 (59.5)	< 0.001
Hyperlipidemia (History)	15 (30)	92 (49.7)	0.013
Hypercholesterolemia (> 200 mg/dL)	16 (32)	58 (31.4)	0.930
LDL Dyslipidemia (>130 mg/dL)	9 (18)	21 (11.4)	0.211
HDL Dyslipidemia (men: < 50 mg/dL; women: < 40mg/dL)	26 (52)	165 (89.2)	< 0.001
Hypertriglyceridemia (> 150 mg/dL)	13 (26)	126 (68.1)	< 0.001
Hypertension	14 (28)	122 (65.9)	< 0.001
Body Mass Index, kg/m²	24.6 ± 3.7	28 ± 4.1	< 0.001
Waist Circumference, cm	89.9 ± 13.9	104.3 ± 13.4	< 0.001
Paraclinical Findings			
Fasting Serum Glucose, (mg/dL)	111 ± 44.8	145 ± 60.9	< 0.001
Total serum Cholesterol (mg/dL)	184.5 ± 55.2	171.5 ± 53.3	0.131
Serum High Density Lipoprotein (mg/dL)	41.9 ± 13.6	39.3 ± 61.5	0.761
Serum Low Density Lipoprotein (mg/dL)	98 ± 32.3	88 ± 38.5	0.096
Serum Triglycerides (mg/dL)	139 ± 61.4	218 ± 153.6	< 0.001
Hemoglobin A1C (g/dL)	5.9 ± 1.5	6.3 ± 2	0.068
Serum Creatinine (mg/dL)	1.3 ± 0.3	1.3 ± 0.3	0.316
Medications			
ACE inhibitors	28 (56)	116 (63)	0.364
Beta Blockers	38 (76)	158 (85.9)	0.093
Calcium Channel Blockers	9 (18)	32 (17.4)	0.920
Involved Coronary Artery			
Left main	2 (4)	4 (2.2)	0.611
Left Anterior Descending	50 (100)	184 (99.5)	> 0.99
Left Circumflex	43 (86)	160 (86.5)	> 0.99
Right Coronary Artery	43 (86)	159 (85.9)	>0.99

[a] Data are presented as Mean ± SD or No. (%).

Descriptive results of mortality and surgery complications are depicted in Table 3. After three months of follow-up, the frequency of readmission [24 (10.2%)] and mediastinitis [9 (3.8%)] were higher than other complications.

4.2. Immediate Complications

Diabetes and MetS are considered as risk factors for a long ICU stay (> 5 days) and atelectasia (P < 0.05). The most prevalent complications were bleeding [20 (8.5%)] and dysrhythmia [18 (7.7%)]. Moreover, MetS was more frequent in patients with myocardial infarction (12 vs. 0, P = 0.052). Table 4 demonstrates the effect of diabetes and metabolic syndrome on immediate complications.

4.3. Late Complications

Table 5 shows the effect of diabetes and metabolic syndrome on late complications. The incidence of complications after three months of follow-up was low. Still, significant associations were observed between diabetes and pulmonary embolism (P = 0.025) and mediastinitis (P = 0.051). No association existed between MetS and complications (Table 6). At third month of follow-up, the frequency of readmission [24 (10.2%)] and mediastinitis [9 (3.8%)] were higher than other complications.

Table 3. Complications Before and After Three Months of Surgery [a]

	Immediate	Third Month
Surgery Complications		
Dysrhythmia	18 (7.7) [a]	0
Sepsis	3 (1.3)	0
Heart Failure	2 (0.9)	-
Cardiac Shock	2 (0.9)	1 (0.4)
Atelectasia	16 (6.8)	1 (0.4)
Reintubation	3 (1.3)	-
Renal Failure	2 (0.9)	1 (0.4)
Intra-aortic Balloon Pump	9 (3.8)	-
Bleeding	20 (8.5)	-
Wound Infection	9 (3.8)	4 (1.7)
Mediastinitis	8 (3.4)	9 (3.8)
Lung Infection	4 (1.7)	2 (0.9)
Tamponade	3 (1.3)	-
Myocardial Infarction	12 (5.1)	3 (1.3)
Pulmonary Embolism	3 (1.3)	8 (3.4)
Readmission	-	24 (10.2)
Mortality	4 (1.7)	3 (1.3)

[a] Data are presented as No. (%).

Table 4. Effect Modification of Diabetes and Metabolic Syndrome on Immediate Complications

	Group [a,b]				P value	Common OR [CI 95%]
	G1 (n = 150)	G2 (n= 20)	G3 (n = 35)	G4 (n = 30)		
Pump Time, min	101 ± 57	98 ± 54.7	95 ± 61.3	104 ± 44	0.569 [c]	-
Cross - Clamp Time, min	57 ± 43.8	58 ± 43.2	53 ± 50.3	56 ± 34.3	0.865 [c]	-
Mechanical Ventilation ≥ 72 hours (n = 8)	5 (3.3)	0	2 (5.7)	1 (3.3)	0.670	2.92 [0.28 – 30.57]
ICU stay ≥ 5 days (n = 63)	48 (32)	4 (20)	8 (22.9)	3 (10)	0.143	2.15 [0.88 – 5.30]
Dysrhythmia (n = 18)	11 (7.3)	3 (15)	1 (2.9)	3 (10)	0.185	0.38 [0.12 – 1.21]
Sepsis (n = 3)	3 (2)	0	0	0	0.791	-
Heart Failure (n = 2)	1 (0.7)	0	1 (2.9)	0	0.894	-
Cardiogenic Shock (n = 2)	1 (0.7)	0	0	1 (3.3)	0.371	0.22 [0.01 – 9.72]
Atelectasia (n = 16)	16 (10.7)	0	0	0	0.261	-
Reintubation (n = 3)	1 (0.7)	1 (5)	1 (2.9)	0	0.770	0.65 [0.07 – 6.11]
Renal Failure (n = 2)	1 (0.7)	0	0	1 (3.3)	0.894	0.22 [0.01 – 9.72]
Intra-Aortic Balloon Pump (n = 9)	8 (5.3)	0	0	1 (3.3)	0.924	1.75 [0.15 – 21.09]
Bleeding (n = 20)	12 (8)	2 (10)	2 (5.7)	4 (13.3)	0.551	0.57 [0.18 – 1.76]
Wound Infection (n = 9)	8 (5.3)	1 (5)	0	0	0.640	1.07 [0.13 – 9.04]
Mediastinitis (n = 8)	7 (4.7)	0	0	1 (3.3)	0.825	1.53 [0.12 –19.15]
Lung Infection (n = 4)	4 (2.7)	0	0	0	0.263	-
Tamponade (n = 3)	2 (1.3)	0	1 (2.9)	0	0.770	-
Myocardial Infarction (n = 12)	9 (6)	0	3 (8.6)	0	0.126	-
Pressure Ulcer (n = 7)	4 (2.7)	0	2 (5.7)	1 (3.3)	0.738	2.68 [0.25 – 28.48]
Pulmonary Embolism (n = 3)	3 (2)	0	0	0	0.791	-
Mortality (n = 4)	4 (2.7)	0	0	0	0.263	-

[a] G1: diabetes +/ metabolic syndrome +; G2: diabetes +/ metabolic syndrome -; G3: diabetes -/ metabolic syndrome +; G4: diabetes -/ metabolic syndrome -.
b Data are presented as mean ± SD or No. (%).
[c] P value for effect modification of diabetes × metabolic syndrome, according to two-way ANOVA models; no main effects were statistically significant.

Table 5. Effect Modification of Diabetes and Metabolic Syndrome on Late Complications

	Group [a,b]				P value	Common OR [CI95%]
	G1 (n = 150)	G2 (n= 20)	G3 (n = 35)	G4 (n = 30)		
Cardiogenic Shock (n = 1)	0	0	1 (2.9)	0	0.939	-
Readmission (n = 24)	16 (10.7)	2 (10)	6 (17.1)	0	*	*
Atelectasia (n = 1)	1 (0.7)	0	0	0	0.235	-
Renal Failure (n = 1)	1 (0.7)	0	0	0	0.235	-
Wound Infection (n = 4)	4 (2.7)	0	0	0	0.263	-
Lung Infection (n = 2)	2 (1.3)	0	0	0	0.560	-
Myocardial Infarction (n = 3)	2 (1.3)	0	1 (2.9)	0	0.770	-
Mediastinitis (n = 9)	8 (5.3)	1 (5)	0	0	0.640	1.07 [0.13 - 9.04]
Pulmonary Embolism (n = 8)	2 (1.3)	1 (5)	5 (14.3)	0	0.339	2.91 [0.45 - 18.92]
Mortality (n = 3)	3 (2)	0	0	0	0.791	-

[a] G1: diabetes +/ metabolic syndrome +; G2: diabetes +/ metabolic syndrome -; G3: diabetes -/ metabolic syndrome +; G4: diabetes -/ metabolic syndrome -;
*, Effect modification observed. No common OR. P value for the association between readmission and metabolic syndrome in patients with diabetes was 0.927 and in nondiabetic was 0.027 .
[b] Data are presented as No.(%).

Table 6. Associations Between Diabetes, Metabolic Syndrome, Mortality and Surgery Complications After Three Months of Follow-up [a]

	Diabetes Mellitus		P value	Metabolic Syndrome		P value
	Yes (n = 170)	No (n = 65)		Yes (n = 185)	No (n = 50)	
Cardiogenic Shock (n = 1)	0	1 (1.5)	0.277	1 (0.5)	0	0.787
Re - admission (n = 24)	18 (10.6)	6 (9.2)	0.759	22 (11.9)	2 (4)	0.102
Atelectasia (n = 1)	1 (0.6)	0	0.723	1 (0.5)	0	0.787
Renal Failure (n = 1)	1 (0.6)	0	0.723	1 (0.5)	0	0.787
Wound Infection (n = 4)	4 (2.4)	0	0.576	4 (2.2)	0	0.581
Lung Infection (n = 2)	2 (1.2)	0	0.423	2 (1.1)	0	0.619
Myocardial Infarction (n = 3)	2 (1.2)	1 (1.5)	0.623	3 (1.6)	0	0.486
Mediastinitis (n = 9)	9 (5.3)	0	0.051	8 (4.3)	1 (2)	0.447
Pulmonary Embolism (n = 8)	3 (1.8)	5 (7.7)	0.025	7 (3.8)	1 (2)	0.537
Mortality (n = 3)	3 (1.8)	0	0.563	3 (1.6)	0	0.486

[a] Data are presented as No. (%).

The effect modifications of diabetes and other complications were investigated. The results showed that readmission was associated with MetS in patients without diabetes (P = 0.027); but no association was observed in patients with diabetes (P = 0.927). All the patients who died had MetS, but the P value was not significant.

5. Discussion

The present study was the first prospective study in Iran, which indicated that MetS is a strong and independent risk factor for operative morbidity in CABG patients. Our study showed a high prevalence of MetS in patients with coronary artery disease scheduled for CABG.

The prevalence of MetS in the elderly Iranian population was reported to be 50.8% according to the ATP III (5). The prevalence of MetS in our patients was 77%, which is higher compared to other studies (22). It could be due to higher proportion of women and higher percentage of low HDL cholesterol (81.3%) in our study population. Low HDL cholesterol could be attributed to life-style modification, fatty diet, decreased physical activity, and increased prevalence of hypertriglyceridemia and obesity. MetS had a higher prevalence amongst our female patients, Consistent with previous study (22-24). This sex differentiation is due the higher prevalence of hyperlipidemia and obesity as well as lack of regular physical activity.

MetS is known to increase the risk of acute renal failure (25), stroke (12), wound infection (26), all–cause mortality (27, 28) and cardiovascular death (25). Some studies in the medical literature did not show any difference between MetS and non-MetS complications (27, 29). The major finding of the present study was the high incidence of perioperative morbidity amongst patients with MetS undergoing CABG. The most prevalent complications in

our study were bleeding, atelectasia, dysrhythmia, and myocardial infarction. The explanation for this difference may be due to the longer duration of the aforementioned studies.

According to our findings, diabetes and MetS can be considered as risk factors for a long ICU stay (> 5 days) and atelectasia. There was an increase in the incidence of myocardial infarction in our patients with MetS (12 vs. 0, P = 0.052), which is in line with the result of some previous studies (25, 27).

During our three-month follow-up, readmission [24 (10.2%)] and mediastinitis [9 (3.8%)] occurred more frequently than other complications; nevertheless, significant associations were observed between diabetes and pulmonary embolism (P = 0.025) and mediastinitis (P = 0.05), which is consistent with the findings of some other studies (30, 31). There was also an increased incidence of readmission amongst our nondiabetic patients with MetS. This finding suggests that metabolic abnormality in this syndrome is associated with a much greater impact on the outcome following CABG than the diabetes dose in line with some other studies (32).

There have been reports of higher rates of operative mortality after CABG in patients with MetS (22, 23, 25, 27). All of those who died in the present study had MetS, but there was no difference in mortality rate between the patients with MetS and those without it during the three-month follow-up, which was in line with some other previous studies (27, 29, 33). The difference between these studies and ours is presumably attributed to different definitions of MetS applied. The present study was conducted in accordance with the NCEP ATP III criteria, in which the waist circumference is measured for obesity, whereas other studies used BMI for the classification of individuals regarding obesity.

The short follow-up duration of the present study was its most significant limitation; studies with longer durations are required to shed further light on this issue. The current study demonstrated the high prevalence of MetS in patients scheduled for CABG in Iran. This is the first study in an Iranian population, which showed that identification of MetS before CABG can predict the surgery outcome. It is of great significance to improve risk stratification and management of patients with coronary artery disease. Our findings also suggested that prevention or modification of the metabolic component of this syndrome in patients candidate for CABG can confer shorter ICU admissions, lower frequency of atelectasia, and less likelihood of myocardial infarction and readmission.

In the 21th century, reduced physical activity and industrialized dietary habits are the causes of increased rate of obesity and MetS. Patients with MetS have more established coronary artery disease; therefore, they might benefit from early aggressive risk reduction. Our findings indicated that an acute modification of MetS components can prevent perioperative morbidities.

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Authors' Contributions

This study was conceived by Maryam Ardeshiri and Zahra Faritus and its methods developed by all the authors. Data was collected by Zahra Ojaghi Haghighi and Faranak Kargar, analyzed by Hooman Bakhshandeh. The manuscript was drafted by Hooman Bakhshandeh and Rokhsareh Aghili, critically revised by Maryam Ardeshiri and Zahra Faritus and approved for publication by all the authors.

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