

# Perioperative Cardiovascular Outcome in Patients with Coronary Artery Disease Undergoing Major Vascular Surgery: A Retrospective Cohort Study

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## ABSTRACT

**Background:** Major adverse cardiac events (MACE) are a major contributor to morbidity and mortality in patients undergoing major vascular surgeries. We aim to assess the incidence, risk factors, and outcome of MACE in patients with coronary artery disease (CAD) undergoing aortic surgeries.

**Methods:** In this retrospective observational study, we included patients with CAD who underwent elective major vascular surgery, namely, thoracoabdominal aortic aneurysm repairs and vascular bypass surgeries for aorto-occlusive disease, in our institute from January 2010 to December 2019. The association of preoperative risk factors including revised cardiac risk index factors, functional status of patients, severity of CAD, and its treatment status and technique of anesthesia with occurrence of MACE was analyzed.

**Results:** Medical records of 141 patients were studied. The incidence of perioperative MACE was 11.3% (16/141) and overall in-hospital mortality was 6.4% (9/141), all of them related to MACE; implicating a 56.2% mortality in patients who develop MACE. The odds of a patient who had undergone preoperative coronary revascularization to develop a MACE was higher than a nonrevascularized patient (odds ratio: 3.9; 95% confidence interval [CI], 1.34–11.34). There was found to be no benefit in the addition of epidural analgesia to general anesthesia in reducing perioperative MACE.

**Conclusions:** Major vascular surgeries in patients with CAD are a highly morbid procedure and a perioperative MACE places them at a significantly high risk of mortality. Early detection of CAD and preoperative medical optimization can play a major role in reducing the risk of MACE.

**Keywords:** Coronary artery disease, major vascular surgeries, perioperative MACE

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Major vascular diseases such as aneurysms and dissections have become common and pose for urgent, if not emergency repair. With the elderly population presenting for such surgeries the proportion of patients at risk of perioperative adverse cardiac events is increasing. Literature analysis shows an incidence of 1.4% to 3.9%

of perioperative cardiac events in patients undergoing noncardiac surgery.<sup>[1]</sup> The POISE (Perioperative Ischemic Evaluation) trial showed a 2.7% perioperative mortality after noncardiac surgery, half of which was attributed to a cardiovascular cause alone.<sup>[2]</sup>

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Although major adverse cardiac events (MACE) have not been authoritatively defined in the past, this has come to constitute a wide range of issues ranging from nonfatal myocardial infarction, hemodynamically significant arrhythmias, and pulmonary edema to cardiac arrest. Perioperative myocardial infarction (PMI) is a major critical event that has been repetitively shown to be an important predictor of long-term morbidity and mortality after noncardiac surgery.<sup>[3]</sup> Vascular surgeries in particular have been shown to contribute to a large proportion of perioperative cardiac events.<sup>[4,5]</sup> In addition to the surgical morbidity, the incidence of coronary artery disease (CAD) per se in these patients has been verified to be significantly high, as supported by the presence of common risk factors for CAD and aortic aneurysms.<sup>[6,7]</sup>

We retrospectively investigated the perioperative cardiovascular outcome in the form of PMI, perioperative arrhythmias, cardiac arrest, and death in patients with CAD who had undergone elective major vascular surgery. We analyzed the occurrence of perioperative MACE during two different anesthetic techniques (general anesthesia [GA] vs. combined GA with epidural anesthesia). We also assessed the incidence of cardiac complications in relation to the severity of CAD and the impact of coronary revascularization prior to surgery on the same. The secondary objectives of the study was to assess the perioperative outcomes in the form of duration of mechanical ventilation, need for tracheostomy, duration of intensive care unit (ICU) stay and hospital stay, incidence of acute kidney injury, stroke, and in-hospital mortality were also determined.

## METHODS

### Study design and patient population

The study was approved by the appropriate Institutional Review Board (IRB) (SCT/IEC/1599/December 2020), and the requirement for written informed consent was waived by the IRB as this was a retrospective observational cohort study conducted from our hospital medical record database. We examined medical records dated between January 2010 and December 2019 of patients diagnosed with CAD who had undergone major vascular surgery in our tertiary care center. Among them, patients who had undergone elective surgery for thoracoabdominal aortic aneurysms and aortoiliac occlusive disease were included for assessment. Patients who had undergone emergency vascular surgeries, ascending aortic aneurysm repairs, carotid endarterectomy, redo vascular surgeries, combined coronary artery bypass graft surgery (CABG) with vascular interventions, hybrid endovascular repairs, patients with

preoperative arrhythmias, and deficient medical records were excluded. This manuscript adheres to the applicable STROBE guidelines.

### Study observations

#### *Risk assessment*

The presence of other risk factors for MACE such as diabetes, cerebrovascular disease, chronic kidney disease, history of unstable angina, or heart failure were recorded and a revised cardiac risk index (RCRI) was calculated. Lee's RCRI system is the most widely used tool to assess the risk of perioperative MACE in patients undergoing noncardiac surgery and hence was chosen in our study to risk stratify the patients.<sup>[8]</sup> Preoperative echocardiogram and coronary angiogram details were retrieved and patients were grouped into single-, double-, or triple-vessel coronary lesions. Their medical records were perused for the information on preoperative medical or surgical optimization strategies performed in each patient. CAD was defined as the presence of an obstructive or nonobstructive coronary lesion on noninvasive functional imaging, computed tomographic coronary angiography, or invasive coronary angiography, or a history of acute coronary syndrome, or stable angina with similar diagnostic evidence.<sup>[9]</sup>

#### *Perioperative markers of MACE*

Incidence of MACE, namely, PMI, hemodynamically significant arrhythmias and cardiovascular death was recorded, along with the emergency interventions taken for the same. Intraoperative details regarding the technique of anesthesia, incidence of significant hypotension episodes ( $>20\%$  fall in mean arterial pressure from preoperative value), and the inotrope and vasopressor use were noted. PMI was diagnosed as detection of high-sensitivity cardiac troponin test concentrations above the 99<sup>th</sup> percentile of upper reference limit along with evidence of myocardial ischemia in the form of ST segment of Electrocardiographic (ECG) waveform, repeated episodes of hypoxia, hypotension, tachycardia, or imaging evidence of myocardial ischemia in the perioperative or postoperative period.<sup>[10]</sup> Hemodynamically relevant arrhythmias were defined as cardiac arrest, sustained ventricular tachycardia, atrial fibrillation with the need of treatment, and atrioventricular block III.<sup>[5]</sup> Cardiovascular death included death attributable to PMI, sudden cardiac arrest, acute heart failure, stroke, cardiovascular procedure, and pulmonary embolism.<sup>[11]</sup> Secondary outcome parameters such as duration of mechanical ventilation, need for tracheostomy, duration of ICU stay and hospital stay, the incidence of acute kidney injury and stroke, and in-hospital mortality were noted.

## Statistical analysis

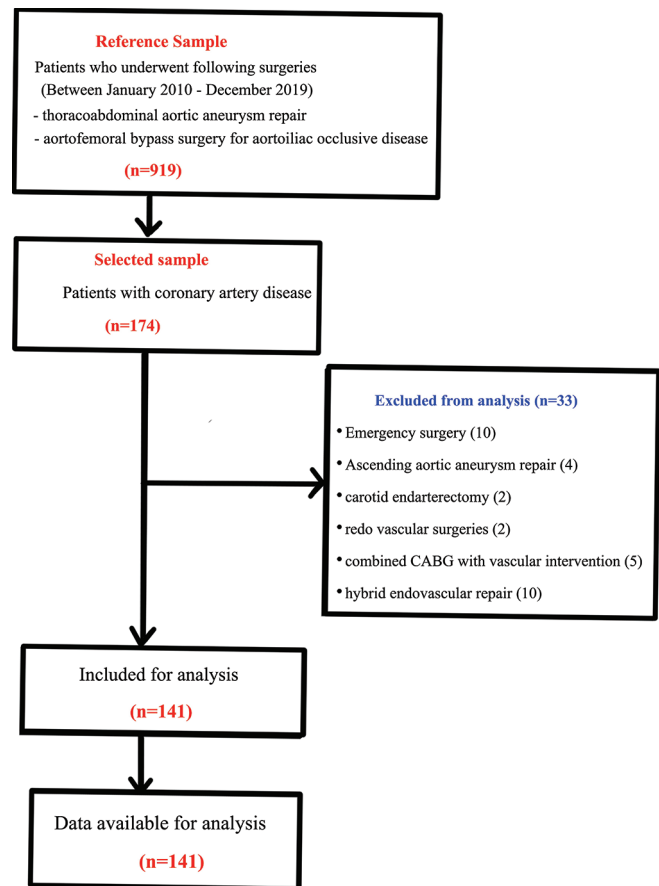
All statistical analyses were performed using SPSS version 21.0 for windows (IBM Software analyses, Chicago, IL 60606). Descriptive statistics were calculated and reported as percentages for categorical variables and means  $\pm$  SD for continuous data. Pearson's Chi-square test was used for the analysis of categorical variables and Student's *t*-test to compare means. A *P* value of  $<0.05$  was considered statistically significant. To study the association of MACE with multiple variables, the cohort was analyzed as two groups with and without the primary outcome. The association of MACE with coronary vascular disease severity was assessed with Pearson's Chi-square test for multivariate data. Further characterization of patients was done by analyzing them as a group of GA vs. GA plus epidural anesthesia group.

## RESULTS

A total of 141 patients with CAD who had undergone major vascular surgery in our hospital over 10 years from January 2010 to December 2019 were included in our study [Figure 1]. All the patients included in the analysis were 105 males and 36 females aged between 45 and 86 years with a mean age of  $63.2 \pm 8.1$  years.

The severity of CAD left ventricular ejection fraction, New York Heart Association (NYHA) classification of functional status, comorbidities, and RCRI risk factors of MACE are given in Table 1. The severity of CAD was almost equally distributed in our cohort. Most patients had normal left ventricular ejection fraction (75%) and belonged to NYHA functional class II (80%). About 81% of patients had only two RCRI risk factors for MACE. [Table 1]. All patients were on medical therapy with most of them receiving antiplatelets, statins, and  $\beta$ -blockers [Table 2]. Apart from medical therapy, 24 patients (17%) had received coronary revascularization therapy by the percutaneous coronary intervention (PCI) and 16 (11%) had undergone CABG [Table 2].

Sixteen patients developed a MACE in the perioperative period, amounting to an incidence of 11.3% [Table 2]. Five (3.5%) patients had PMI, out of which three patients developed myocardial infarction in the intraoperative period and the remaining two within 24 h of surgery. Although emergency PCI was done to revascularize the affected coronaries in two of these patients they succumbed in the postprocedure period. Another two patients were medically managed in the postoperative ICU who; however, developed multiorgan dysfunction following heart failure and died. Out of the above five patients, only



**Figure 1:** STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) flow diagram of the study design. CABG, coronary artery bypass grafting.

one patient recovered postoperatively after undergoing emergency PCI and initiation of dual antiplatelet therapy. Six patients (4.2%) developed arrhythmias ranging from supraventricular tachycardia to ventricular fibrillation. Four patients had irreversible hypotension after declamping of aorta that could not be revived leading to death in operation room. One patient had a sudden cardiac death on postoperative day 5 and the cause was not known.

Although the MACE was contributed by an 18% incidence in patients with three or more RCRI risk factors and 10% in those with two risk factors, there was no statistically significant difference between the two RCRI risk groups ( $P = 0.1913$ ) [Table 3]. In the entire study cohort, 40 patients (28%) had received preoperative coronary revascularization therapy and the remaining 101 (72%) patients were nonrevascularized and were on medical therapy. There was a significant difference in the incidence of MACE between the revascularized (22%) and nonrevascularized cohorts (7%) ( $P = 0.0086$ ) [Table 3] suggesting an association between preoperative revascularization to the occurrence of perioperative

**Table 1: Preoperative clinical data of study cohorts**

Comorbid illness	
Hypertension	101 (72%)
Diabetes Mellitus	33 (23%)
Chronic obstructive pulmonary disease	22 (16%)
Smoking	85 (60%)
Chronic kidney disease	9 (6%)
Dyslipidemia	38 (27%)
Prior myocardial infarction	42 (30%)
RCRI score	
0	0
1	0
2	114 (81%)
≥ 3	27 (19%)
Preoperative cardiac function status	
Severity of coronary artery disease	
Single-vessel disease	44 (31%)
Double-vessel disease	49 (35%)
Triple-vessel disease	48 (34%)
Left ventricular systolic function	
Normal (LVEF >50%)	107 (75%)
Mild dysfunction (LVEF 40%-50%)	24 (18%)
Moderate dysfunction (LVEF 30%-40%)	10 (7%)
Severe dysfunction (LVEF <30%)	0
NYHA class	
I	17 (12%)
II	113 (80%)
III	11 (8%)
IV	0

Values are expressed as numbers (proportion). LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RCRI, Revised Cardiac Risk Index

**Table 2: Preoperative cardiac medications, revascularization therapy, type of vascular disease, and incidence of MACE among the study cohorts**

Preoperative cardiac medications	
β-blockers	114 (81%)
Antiplatelets	138 (98%)
Statins	121 (86%)
Nitrates	25 (18%)
Antiarrhythmic drugs	4 (3%)
Preoperative revascularization therapy	
Percutaneous coronary intervention	24 (17%)
Coronary artery bypass grafting	16 (11%)
Type of vascular disease	
TAAA type II	5 (3%)
TAAA type III	10 (7%)
TAAA type IV	53 (38%)
TAAA type V	32 (23%)
Aortoiliac-occlusive disease	41 (29%)
Incidence of MACE	
Perioperative myocardial infarction	5 (3.6%)
Hemodynamically significant arrhythmias	6 (4%)
Intraoperative irreversible hypotension	4 (3%)
Sudden cardiac death	1 (0.7%)

Values are expressed as numbers (proportion). TAAA, thoracoabdominal aortic aneurysm.

MACE. The odds ratio for MACE was hence calculated and found to be 3.9 (95% confidence interval [CI], 1.34, 11.34) for revascularized patients. The incidence of MACE

among revascularized (9 patients) was distributed as seven PCIs (77%) and two CABGs (23%). There was no significant difference in the incidence of MACE between supra diaphragmatic (11%) and infra diaphragmatic (12%) types of surgery ( $P = 0.8510$ ) [Table 3].

Although the incidence of MACE was highest in patients with triple vessel disease, there was found to be no statistically significant association of MACE with the disease severity [Table 4]. In this cohort, 66 patients (47%) underwent surgery under GA alone, whereas 75 patients (53%) were given GA with epidural anesthesia [Table 5]. Nine patients (13.5%) who underwent surgery under GA developed MACE, whereas the incidence was 9.3% (7 patients) in those who received GA with epidural anesthesia [Table 5]. This was not found to be a clinically significant difference ( $P = 0.4215$ ). Also, 41% of patients in the GA group required inotrope to support significant hypotension episodes in the perioperative period, whereas it was 50.6% in the GA with the epidural group, a difference not clinically significant ( $P = 0.2461$ ). However, there was found to be a clinically significant difference in the use of noradrenaline between the two groups, GA with epidural group requiring it more often ( $P = 0.0391$ ).

The mean duration of postoperative mechanical ventilation was  $10.2 \pm 3.4$  h. ICU stay averaged at  $3.5 \pm 1.8$  days and hospital stay was  $13.2 \pm 2.4$  days. Eight patients developed Acute kidney Injury (AKI) (5.7%) and three (2.1%) had undergone tracheostomy in view of prolonged mechanical ventilation. The incidence of stroke was 0.8%, whereas the overall in-hospital mortality was 6.4%. This translates as MACE-related mortality of 56.2%.

## DISCUSSION

Early multicenter cohort studies reported in the past 2 decades have shown an incidence of MACE ranging from 1% to 7% in noncardiac surgeries comprising a large variety of surgeries and patients with widely different preoperative cardiac risks.<sup>[4,12-14]</sup> The incidence of 11.3% cardiac events that we report is, however, less than the 15.2% reported by Szgary *et al.*,<sup>[5]</sup> wherein the focus was on noncardiac surgeries done in high-risk patients similar to our cohort; they found a high incidence of MACE in vascular surgeries, second only to thoracic surgeries. Their markedly higher incidence could be due to the older age group of patients in their cohort, median age of 73 years, inclusion of emergency surgeries with inadequate preoperative optimization, and an improved screening method for MACE. Studies that focused on postoperative myocardial infarction in patients undergoing abdominal aortic surgeries

have reported an incidence of 3.1% to 5.2%, which is similar to the incidence of PMI in our study of 3.5%.<sup>[15-17]</sup>

In our study, 80.8% of the sample population was on preoperative  $\beta$ -blocker therapy, which could explain the high incidence of intraoperative hypotension (46.1%), as reasoned by the POISE trial that showed a significantly higher incidence of hypotension in their patient group that received extended-release metoprolol.<sup>[2]</sup> However, the incidence we report is three times that stated by the POISE study group. Although we assessed only patients with CAD undergoing major vascular surgery, their multicenter large-scale trial included only 43% of patients with CAD, and an overall 36% of patients undergoing major vascular surgery, the contribution to results by the specific cohort we focussed on was not detailed. The large hemodynamic fluctuations associated with aortic surgeries and the extensive free radical and anaerobic metabolite release that affect circulatory status after a period of low systemic perfusion during aortic clamping contribute to the significant hypotension in our group. However, the rate of PMI was comparable with their results.

Lee's RCRI risk scoring system has been validated over the years as a valuable tool to predict perioperative MACE in noncardiac surgery. The incidence of 18.5%

cardiac events among patients with three or more RCRI risk factors is drastically higher than the 11% predicted by Lee *et al.*,<sup>[8]</sup> but closer to the 15% risk predicted based on external validation studies done over 15 years and recommended by the Canadian cardiovascular society.<sup>[18]</sup> This could be explained by the improved sensitivity of diagnostic techniques that are in place now compared with 2 decades ago when RCRI was introduced and the increasingly morbid surgeries and risk group of patients they are subjected to. The reliability of RCRI is reflected by the 9.6% incidence of MACE in patients with two risk factors, which is comparable with the 10.1% predicted by the Canadian group. RCRI's predictive capability with regard to vascular surgeries has been questioned in the past and is not anymore considered the best method for the same, although its widespread use, ease of calculation, and popularity among clinicians have sustained it so far.<sup>[18]</sup> Vascular Quality Initiative (VQI) Cardiac Risk Index (CRI) as a risk prediction tool was designed specifically for vascular surgeries, although their specific focus on open abdominal aortic aneurysm repairs, as one of the indices, precluded the group of thoracoabdominal aortic aneurysm repairs that we studied.<sup>[19]</sup>

We found a prior history of coronary revascularization to be associated strongly with PMI (22.5%) in our population, echoing the findings by Bertges *et al.*,<sup>[19]</sup> who specifically examined PMI events in patients undergoing surgery for open abdominal aortic aneurysms. Smilowitz *et al.*,<sup>[20]</sup> also found a significant risk of PMI as well as MACE in patients who had a coronary stent compared with those who did not. One of the factors leading to this may be abstinence of antiplatelet therapy preoperatively in our patients due to the anticipated intraoperative excessive blood loss. Compounding factors like blood transfusion, surgical stress, and as discussed previously the extreme hemodynamic fluctuations associated with manipulation of the thoracic aorta worsen the coronary perfusion of an already compromised myocardium.

Although GA with epidural anesthesia has been the preferred anesthetic technique during the latter half

**Table 3: Comparison of MACE with preoperative risk factors among the study cohorts**

Risk factors	MACE (n=16)	No MACE (n=125)	P
<b>RCRI classification</b>			
RCRI - 2	11 (10%)	103 (90%)	0.1913
RCRI - $\geq$ 3	5 (18%)	22 (82%)	
<b>Preoperative coronary revascularization*</b>			
Revascularized	9 (22%)	31 (78%)	0.0086
Nonrevascularized	7 (7%)	94 (93%)	
<b>Type of surgery</b>			
Supra diaphragmatic	5 (11%)	42 (89%)	0.8510
Infra diaphragmatic	11 (12%)	83 (88%)	

Values are expressed as numbers (proportion).  $P < 0.05$  considered statistically significant MACE, major adverse cardiac events; RCRI, revised cardiac risk index; \*preoperative coronary revascularization in the form of percutaneous coronary intervention or coronary artery bypass graft surgery.

**Table 4: Incidence of perioperative MACE and emergency revascularization among different severity of coronary artery disease**

MACE	Severity of CAD (n=141)			P
	SVD (n=44)	DVD (n=49)	TVD (n=48)	
Perioperative myocardial infarction	0	1 (2%)	4 (8%)	0.1611
Hemodynamically significant arrhythmias	3 (7%)	0	3 (6%)	0.9122
Intraoperative irreversible hypotension	1 (2%)	2 (4%)	1 (2%)	0.8085
Sudden cardiac death	0	0	1 (2%)	-
Emergency revascularization	0	1 (2%)	1 (2%)	0.9882

Values are expressed as numbers (proportion).  $P < 0.05$  considered statistically significant CAD, coronary artery disease; DVD, double vessel disease; MACE, major adverse cardiac event; SVD, single-vessel disease; TVD, triple-vessel disease

**Table 5: Comparison of hypotension events, vasopressors use, MACE, and duration of surgery between GA group and GA with epidural group**

Variable	GA group (n=66)	GA with epidural group (n=75)	P
Clinically significant reversible hypotension	27 (41%)	38 (51%)	0.1517
Inotrope and vasopressors use	27 (41%)	38 (50.6%)	0.2461
Noradrenaline (%)	18 (27.5%)	33 (44%)	0.0391
Adrenaline (%)	3 (4.5%)	1 (1.3%)	0.2516
Noradrenaline + adrenaline (%)	6 (9%)	4 (5.3%)	0.3857
Overall MACE incidence	9 (14%)	7 (9%)	0.4215
Perioperative myocardial infarction	1 (1.5%)	4 (5%)	0.2212
Intraoperative irreversible hypotension	3 (4.5%)	1 (1.3%)	0.2516
Arrhythmias	5 (7.5%)	1 (1.3%)	0.0668
Sudden cardiac death	0	1 (1.3%)	
Duration of surgery (h)	6.4±1.9	5.95±1.48	0.1168

Values are expressed as means±standard deviation or number (proportion).  $P < 0.05$  considered statistically significant. GA, general anesthesia; MACE, major adverse cardiac event

of the decade as evidenced in our study population, no benefit or harm could be associated with it with regard to MACE occurrence, as supported by other studies on limb surgeries as well as abdominal aortic surgeries.<sup>[21-23]</sup> However, conflicting reports were shown by Cochrane-based studies that proved a significant advantage of postoperative epidural analgesia over opioid-based analgesia in reducing PMI, ICU stays, duration of mechanical ventilation, and pulmonary complications after abdominal aortic surgeries.<sup>[24,25]</sup> In light of this evidence, the 2014 American College of Cardiology/American Heart Association guidelines on perioperative management of noncardiac surgeries have suggested epidural analgesia over opioid-based analgesia as a class IIa recommendation to reduce postoperative MI; however, reiterating the lack of evidence regarding cardioprotective effects of epidural anesthesia as an adjuvant to GA.<sup>[26]</sup> The higher requirement of inotropes intraoperatively in patients who received GA with epidural anesthesia in our study could be explained by the dense sympathetic blockade resulting from thoracic epidural anesthesia in thoracoabdominal aortic surgeries, in addition to the hemodynamic fluctuations associated with the handling of the thoracic aorta. The significantly higher use of noradrenaline in the GA with epidural group points to a larger propensity of anesthesia practitioners to prophylactically initiate noradrenaline infusion anticipating hypotension in patients receiving epidural anesthesia.

The overall in-hospital mortality in our study was 6.4%, comparable with the 5%–10% reported in previous studies on elective thoracoabdominal surgeries,<sup>[27,28]</sup> despite our focus on high-cardiac-risk patients. The mean duration of ICU stay and hospital stay was also comparable with those previously reported.<sup>[27]</sup> The incidence of AKI was 5.6% in our population, which was less than that reported by Wynn *et al.*,<sup>[28]</sup> (7.6%) who used estimated glomerular filtration rate to diagnose AKI specifically in patients undergoing thoracoabdominal surgeries. Our study group

included patients undergoing infrarenal aortic surgeries, which have a lesser adverse effect on renal perfusion and thus contribute to the lower incidence of AKI. The 0.8% stroke incidence we report is also comparable with those reported in earlier studies.<sup>[29]</sup> Although the morbidity was comparable with previously reported data, MACE-related mortality was found to be substantially high at 56.2%. Early studies had shown a wider mortality risk of 16.4% to 30.4% in associating with PMI.<sup>[15]</sup> Recent evidence, however, stated a 37.4% incidence of 1-year mortality in patients who had PMI after undergoing high-risk vascular surgery.<sup>[30]</sup> Although excluding thoracoabdominal surgery from analysis, they had included carotid artery procedures, peripheral artery surgeries, and endovascular aortic aneurysm repair procedures, which are specifically known for their low risk of PMI. The elevated risk in our cohort can thus be associated with the focussed analysis of patients with CAD and the inclusion of more morbid surgeries involving the thoracic aorta.

We acknowledge that this being a retrospective study, there were limitations in available data, diagnostic tests, and modalities that could be used for evaluation. Our sample size was limited as the number of major aortic vascular surgeries done in patients with CAD is less due to the predicted high mortality and morbidity. Long-term functional outcomes at 1 year and 5 years and long-term mortality were not assessed. Being a single-center study and the study group requiring high surgical and anesthetic expertise, our results must be generalized only with caution.

## CONCLUSION

In conclusion, the incidence of MACE in patients with CAD undergoing major vascular surgery can be reduced with prior risk assessment and optimization before surgery. The addition of epidural anesthesia to general anesthesia did not have any significant effect on MACE events.

Patients with varied severity of coronary vascular lesion did not have any significant effect on the incidence of MACE. Perioperative mortality was high in patients who developed intraoperative MI and irreversible hypotension after declamping of aorta. There is the future scope for multicentric prognostic studies in this cohort of patients and assessment of functional outcomes with a specific focus on spinal cord injury, paraplegia, and long-term mortality.

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### Conflicts of interest

There are no conflicts of interest.

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