Observational Study

Medicine®

OPEN

Myocardial injury after noncardiac surgery—incidence and predictors from a prospective observational cohort study at an Indian tertiary care centre

Rubin George, MD[a], Vidya P. Menon, MD, FACP[a,*], Fabia Edathadathil, MSc[b], Sabarish Balachandran, MD[c], Merlin Moni, MD[a], Dipu Sathyapalan, MD[a], Preetha Prasanna, GNM[d], Gokuldas S, MD[e], Jerry Paul, MD, FCCM[f], Chandrababu K.K., D Ortho, MS Ortho[g], Lakshmi Kumar, MD, FCCM[h], Ashok Pillai, MD, DNB (NS)[i]

Abstract

Asymptomatic myocardial injury following noncardiac surgery (MINS) is an independent predictor of 30-day mortality and may go unrecognized based on standard diagnostic definition for myocardial infarction (MI). Given lack of published research on MINS in India, our study aims to determine incidence of MINS in patients undergoing noncardiac surgery at our tertiary care hospital, and evaluate the clinical characteristics including 30-day outcome.

The prospective observational study included patients >65 years or >45 years with either hypertension (HTN), diabetes mellitus (DM), coronary artery disease (CAD), cerebrovascular accident (CVA), or peripheral arterial disease undergoing noncardiac surgery. MINS was peak troponin level of ≥0.03 ng/dL at 12-hour or 24-hour postoperative. All patients were followed for 30 days postoperatively. Predictors of MINS and mortality were analyzed using multivariate logistic regression. Patients categorized based on peak troponin cut-off values determined by receiver operating characteristic curve were analyzed by Kaplan–Meir test to compare the survival of patients between the groups.

Among 1075 patients screened during 34-month period, the incidence of MINS was 17.5% (188/1075). Patients with DM, CAD, or who underwent peripheral nerve block anaesthesia were 1.5 ($P < .01$), 2 ($P < .001$), and 12 ($P < .001$) times, respectively, more likely to develop MINS than others. Patients with heart rates ≥96 bpm before induction of anesthesia were significantly associated with MINS ($P = .005$) and mortality ($P = .02$). The 30-day mortality in MINS cohort was 11.7% (22/188, 95% CI 7.5%–17.2%) vs 2.5% (23/887, 95% CI 1.7%–3.9%) in patients without MINS ($P < .001$). ECG changes ($P = .002$), peak troponin values >1 ng/mL ($P = .01$) were significantly associated with mortality. A peak troponin cut-off of >0.152 ng/mL predicted mortality among MINS patients at 72% sensitivity and 58% specificity. Lack of antithrombotic therapy following MINS was independent predictor of mortality ($P < .001$), with decreased mortality in patients who took post-op ASA (Aspirin) or Clopidogrel. Mortality among MINS patients with post-op ASA intake is 6.7% vs 12.1% among MINS patients without post-op ASA intake. Mortality among MINS patients with post-op Clopidogrel intake is 10.5% vs 11.8% among MINS patients without post-op Clopidogrel intake.

A higher (17.5%, 95% CI 15–19%) incidence of MINS was observed in our patient cohort with significant association with 30-day mortality. Serial postoperative monitoring of troponin following noncardiac surgery as standard of care, would identify "at risk" patients translating to improved outcomes.

Abbreviations: ACC = American College of Cardiology, AHA = American Heart Association, ASA = acetyl salicylic acid (Aspirin), CAD = coronary artery disease, CRF = case report form, CVA = cerebrovscular accident, DM = diabetes mellitus, ECG = electrocardiogram, HR = hazard ratio, hs TnI = high sensitive troponin-I, HTN = hypertension, MI = myocardial infarction, MINS = myocardial injury after noncardiac surgery, NPV = negative predictive value, POISE = PeriOperative ISchemia Evaluation, PPV = positive predictive value, VISION = Vascular Events In Noncardiac Surgery Patients Cohort Evaluation.

Keywords: myocardial injury after noncardiac surgery, perioperative care, troponin

Editor: Satyabrata Pany.

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

[a] Department of General Medicine, [b] Department of Allied Health Sciences, [c] Department of Emergency Medicine, [d] Department of Medical Administration, Amrita Institute of Medical Sciences, [e] Department of Anaesthesiology and Critical Care Medicine, [f] Anaesthesiology and Critical Care Medicine, Composite Tissue Allotransplantation, [g] Department of Centre for Orthopaedics, [h] Anaesthesiology and Critical Care Medicine, [i] Department of Neurosurgery, Amrita Institute of Medical Sciences, Amrita Vishwa Vidyapeetham, Kochi, Kerala, India—682041.

[*] Correspondence: Vidya P. Menon, Department of General Medicine, Amrita Institute of Medical Sciences, Ponekkara, AIMS Post, Kochi, India—682041 (e-mails: vidyapmenon@gmail.com, vidyamenon@aims.amrita.edu).

Medicine (2018) 97:19(e0402)

Received: 11 October 2017 / Received in final form: 30 December 2017 / Accepted: 15 March 2018

http://dx.doi.org/10.1097/MD.0000000000010402

1. Introduction

Of the 200 million patients undergoing noncardiac surgery per year globally, one million adults are estimated to die within 30 days postsurgery.[1] Cardiovascular events are the major cause for perioperative complications leading to morbidity and mortality after noncardiac surgeries.[2] Acute MI (myocardial infarction) accounts for 5.7% of morbidity following noncardiac surgeries. The standard diagnostic definition of MI requires the presence of myocardial necrosis as evidenced by elevated cardiac biomarkers and supportive electrocardiographic evidence. Patients who do not fulfill the clinical criteria for MI might still sustain a myocardial injury during postoperative period without exhibiting ischemic symptoms or hallmark ECG changes.[3,4] With advances in surgical techniques and anesthesia, elderly population with cardiovascular comorbidities undergoing noncardiac surgery continues to rise, thereby increasing the incidence of perioperative myocardial injury. Myocardial injury after noncardiac surgery (MINS) is a relatively new clinical concept, defined as "prognostically relevant myocardial injury due to ischemia that occurs during or within 30 days after noncardiac surgery."[5] In comparison with MI, the diagnostic definition of MINS allows us to capture prognostically relevant myocardial injuries occurring during the perioperative period. MINS patients generally have elevations in cardiac biomarkers (mainly troponin) without symptoms or electrocardiographic evidence of myocardial injury.[6] Ischemic symptoms are rarely observed and transient ECG changes tend to be overlooked for patients who are under analgesics or mechanical ventilation during perioperative period.[7] Patients with predisposing comorbidities are especially "at-risk" of adverse cardiac events following surgery.

Mortality due to MI following noncardiac surgery, in patients with and without ischemic symptoms was reported to be similar by the POISE (PeriOperative ISchemia Evaluation) trial.[2] The study determined the proportion of patients who had elevated levels of cardiac markers comparable to patients with symptomatic or asymptomatic MI but were not MI by definition, thereby establishing need for monitoring of cardiac biomarkers post-surgery. Most troponin elevations start within 24 to 48 hours after surgery and are attributed to postoperative stress.[8]

The VISION (Vascular Events In Noncardiac Surgery Patients Cohort Evaluation) study was an international prospective cohort study designed to assess major vascular events in patients who had undergone noncardiac surgery.[1] The study estimated a worldwide prevalence of MINS at 8% and reported its significant association with 30-day mortality. The study established that relatively high and previously indeterminate troponin ranges to be independent predictors of 30-day mortality irrespective of their ischemic nature. As predictors of mortality, the adjusted hazard ratios for troponin ranges of 0.03 to 0.29 and $>$ 0.3 ng/mL were estimated to be 5 (95% CI 3.7–6.7) and 10.4 (95% CI, 6.2–1.6), respectively. The diagnostic threshold for MINS determined by the VISION study was at peak troponin T level of $\geq$0.03 ng/mL. Presence of Coronary artery disease, heart failure, renal impairment evidenced by creatinine greater than 2mgs/dL, history of cerebrovascular stroke and diabetes mellitus have been identified as high risk indices for increased perioperative cardiac morbidity.[9]

Current standard of care in India do not require monitoring troponin in patients following noncardiac surgery. Conceding the knowledge gap in MINS from India, we sought to prospectively study the incidence, predictive factors, and association of MINS with 30-day mortality in a cohort of patients undergoing noncardiac surgery at our institution.

2. Materials and methods

2.1. Study design and eligibility criteria

2.1.1. Study design. A prospective observational study of patients undergoing noncardiac surgery at Amrita Institute of Medical Sciences, Kochi, India, based on previously published methodology, was done.[1] Ethical clearance was obtained from Institutional Ethics Committee prior to the study.

A sample size of 1104 was estimated for the study based on the prevalence rate of 8% reported by Botto et al,[1] using nMaster with a 95% confidence and 20% allowable error. The study period during which the perioperative troponin screening was performed was from July 2015 to August 2016. The procedural flow of the study is depicted in Figure 1.

2.1.2. Patients. The study cohort consisted of patients undergoing elective noncardiac surgery who required general, spinal or peripheral nerve block anesthesia and postoperative inpatient stay of more than 24 hours.

2.1.3. Inclusion criteria. Adults above the age of 45 years with one or more of the following comorbidities diabetes mellitus, systemic hypertension, coronary artery disease, cerebral vascular accident, peripheral vascular occlusive disease, and all adults aged above 65 years with or without co-morbidities were included in the study.

2.1.4. Exclusion criteria. Patients with sepsis, cardiac drug toxicity, pulmonary embolism, or chronic renal failure were excluded from the study. Pregnant women were also excluded from the study.

A process for screening of patients fulfilling the inclusion criteria with troponin I 12 and 24 hours following surgery was established in cooperation with the anesthesia and respective surgical departments to detect MINS. Following sensitization

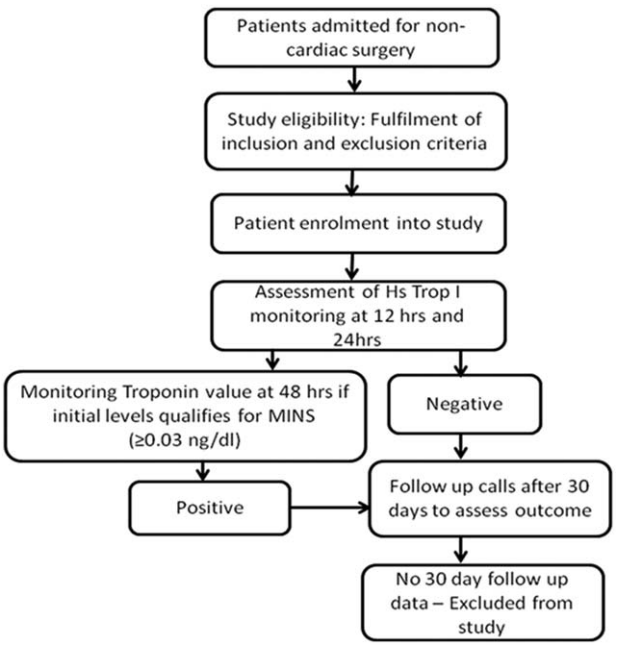

Figure 1. Procedural flow chart of the study.

about MINS screening, anesthetists and surgeons identified patients meeting the study criteria. Patients thus identified at preoperative anesthesia clinics, surgical wards, and surgical intensive care units were selected and screened. Informed consent was obtained prior to study enrollment.

2.1.5. Procedure. Troponin I or hs Troponin I are cardiac biomarkers exclusively used to detect myocardial injury. Troponin values were estimated at our hospital using ARCHITECT stat High Sensitive Troponin-I (hs TnI) assay (Abbott). Troponin I values were estimated at 12 and 24 hours after surgery for the study cohort along with the corresponding ECGs. These patients were reviewed on a daily basis to assess for symptoms of myocardial ischemia. The threshold values of Troponin I for MINS as determined by the Public Health Research Initiative (Canada) using Architect 2000i (Abbott) were followed in the study. If serial troponin values at 12 and 24 hours were elevated, then a 48-hour troponin value was estimated. All positive troponin values were reported to the primary physician or surgeon and the study team.

A peak troponin level of $\geq$ 0.03 ng/dL after surgery was considered as MINS. The research team collected basic demographic data and clinical information relevant to the procedure and perioperative complications. (Appendix 1—CRF; http://links.lww.com/MD/C238). Data on medications including antithrombotic agents and statins taken by the patient before and after MINS were also collected. All patients with positive troponin following surgery were advised cardiology consultation.

2.2. Outcomes

All patients enrolled into the study were followed-up at 30 days postsurgery for evaluating their outcome. Any history of hospitalization or adverse event during this period was recorded. For patients who expired, an attempt was made to determine if the cause of death was cardiac or noncardiac by retrieving data from hospital information system, medical records, or through telephone calls. Patients with missing or unavailable follow-up data were excluded from the final data analysis.

2.3. Statistical analysis

Descriptive statistics were used to summarize the prevalence rate of MINS and baseline characteristics of the study cohort. Multivariate logistic regression analysis was used to identify the predictors of MINS within the entire study cohort and predictors of mortality among the patients diagnosed with MINS. The predictive value of peak troponin levels for mortality within the MINS cohort was analyzed using the area under the receiver operating characteristic curve and an optimum threshold value was determined. Kaplan–Meier plot was used to evaluate the survival of patients in each group. A log-rank test was run to determine if there were differences in the survival distribution for the 2 types of patient groups created based on the chosen peak troponin cut off values. SPSS version 20 (IBM) was used for all statistical analysis.

3. Results

3.1. Baseline characteristics of study cohort

Among the 1107 patients enrolled into the study, 32 were lost to follow-up and 1075 patients were followed till 30 days after surgery. The study cohort exhibited a male preponderance (676, 63%) with 67% (723) patients between 60 and 79 years (Table 1). Hypertension (N = 652, 61%) and diabetes mellitus (N = 506, 47%) were the most common co-morbidities. Around 29% (312) of patients underwent abdominal surgery, 23% (251) head and neck surgery, and 22% (241) neurosurgery. A total of 88% (946) of the surgeries were performed under general anesthesia, 10% (104) under spinal anesthesia, and 2% (25) under peripheral nerve blocks.

Table 1

Baseline characteristics and prevalence of MINS.

Characteristics	N (%)	Status of MINS—N (%) MINS (N = 188, 17%)	Negative (N = 887, 83%)	P
Age				
45–59	286 (27)	38 (13)	248 (87)	Ref
60–79	723 (67)	135 (19)	588 (81)	.042
80 and above	66 (6)	15 (23)	51 (77)	.056
Gender				
Females	399 (37)	68 (17)	331 (83)	.4
Males	676 (63)	120 (18)	556 (82)	
Co-morbidities				
Hypertension	652 (61)	124 (19)	528 (81)	.26
Diabetes	506 (47)	108 (21)	398 (79)	.001
Dyslipidemia	230 (21)	39 (17)	191 (83)	.44
CAD	160 (15)	46 (29)	114 (74)	<.001
CVA	62 (5)	24 (39)	38 (61)	<.001
Heart rate				
96 bpm and above	40 (4)	14 (35)	26 (65)	<.005
Less than 96 bpm	1023 (95)	171 (17)	852 (83)	
ND	12 (1)	3 (25)	9 (75)	
Anesthesia				
GA	946 (88)	159 (17)	787 (83)	.53
Peripheral nerve blocks	25 (2)	14 (56)	11 (44)	<.001
SA	104 (10)	15 (14)	89 (86)	Ref
Departments				
Gastrosurgery	312 (29)	66 (21)	246 (79)	.04
Head and neck surgery	251 (23)	32 (13)	219 (87)	.02
Neurosurgery	241 (22.4)	42 (17)	199 (83)	.97
Orthopedics	140 (13)	26 (19)	114 (81)	.71
General Surgery	36 (3)	6 (17)	30 (83)	.89
Gynecology	27 (2)	0	27 (100)	.01
Plastic Reconstructive Surgery	28 (2)	6 (21)	22 (79)	.57
Others	7 (0.7)	4 (57)	3 (43)	.04
Urology	33 (3)	6 (18)	27 (82)	Ref
30-day mortality				
Alive	1030 (96)	166 (16)	864 (84)	<.001
Expired	45 (4)	22 (49)	23 (51)	
Length of stay, days				
7 days and less	342 (32)	44 (13)	298 (87)	<.001
Above 7 days	553 (51)	125 (23)	428 (77)	
ND	180 (17)	19 (10)	161 (89)	
ECG changes				
ST segment changes	14 (1.3)	13 (93)	1 (7)	<.001
Sinus tachycardia	16 (1.5)	1 (6)	15 (94)	
T wave changes	74 (7)	47 (64)	27 (37)	
No changes	971 (90)	127 (13)	844 (87)	

CAD = coronary artery disease, CVA = cerebrovscular accident, ECG = electrocardiogram, GA = general anesthesia, MINS = myocardial injury after noncardiac surgery.

3.2. Prevalence of MINS and its predictors

Myocardial injury after noncardiac surgery was diagnosed in 188 patients (17.5%; 95% CI 15%–19%). MINS was more pronounced in older patients as demonstrated by the increasing

Table 2

Optimized medical therapy.

Drugs	N (%)	MINS	Others	*P* value
Preop				
Preop beta blockers	269 (25)	51 (19)	218 (81)	.068
Preop clopidogrel	50 (4.7)	15 (30)	35 (70)	.025*
Preop statins	145 (13.4)	43 (29)	102 (71)	.001*
Preop ASA	129 (12)	21 (16)	108 (84)	<.001*
Postop				
Postop ASA	91 (8.5)	15 (17)	76 (83)	.4
Postop Clopidogrel	77 (7.1)	19 (24)	58 (76)	.07
Postop statins	239 (22.2)	58 (25)	181 (75)	.001*

ASA = acetyl salicylic acid (Aspirin).
* Denotes $P < 0.05$.

incidence rates of 13%, 19%, and 23% among the age groups 45 to 59 years, 60to 79 years, and above 80 years, respectively. Around 21% (108, 95% CI 18%–25%) of diabetic patients, 29% (46, 95% CI 22%–36%) of patients with coronary artery disease, and 39% (24, 95% CI 27%–51%) of individuals with history of CVA had an increased incidence of MINS as compared to the rest of the cohort. MINS was found to be significantly associated with patients who had diabetes mellitus ($P = .001$, OR 1.66, 95% CI 1.21–2.28), coronary artery disease ($P < .001$, OR 2.2, 95% CI 1.49–3.23) or history of stroke ($P < .001$, OR 3.27, 95% CI 1.91–5.6). Patients undergoing surgery under peripheral nerve block anesthesia (56%) had a significantly higher association with MINS (OR 7.55, 95% CI 2.8–19.7) compared to patients receiving spinal anesthesia (14%).

The incidence of MINS among our cohort of noncardiac surgeries was 13% in patients who underwent head and neck surgery ($P = .02$, OR 0.65, 95% CI 0.43–0.97). Incidence of MINS was significant among patients undergoing gastrointestinal surgery (21%, $P = .05$, OR 1.41, 95% CI 1.01–1.97). Patients who did not develop MINS postoperatively had inpatient stay < 7 days compared to those who developed MINS (23%, $P < .05$, OR 1.98, 95% CI 1.36–2.88). Around 67% of patients who developed MINS did not have any changes in serial ECG analysis. Patients with T-wave inversion (25%) and ST segment changes (7%) had a higher incidence of MINS ($P < .001$, OR 65.8, 95% CI 8.5–506.3). Patients with heart rates ≥96 bpm[10] before induction of anesthesia were significantly associated with MINS ($P = .005$).

The use of antithrombotic agents and statins as part of optimized medical therapy postoperatively was reviewed for 185 MINS positive patients for whom the data were available. Only 31 (16%) patients received antithrombotic agents postoperatively, with 15 (8%) receiving Aspirin and 19 (10%) receiving clopidogrel. Around 58 (31%) were started on statins following MINS positivity (Table 2).

A multivariate logistic regression analysis performed on all the significant variables obtained during univariate analysis to identify the predictors of MINS revealed that patients with diabetes, coronary artery disease or who received peripheral nerve block anesthesia were 1.5 ($P < .01$, 95% CI 1.10–2.15), 2.1 ($P < .001$, 95% CI 1.45–3.28), 12 ($P < .001$, 95% CI 4.21–34.3) times, respectively, more likely to develop MINS than individuals in the other groups (Table 3).

3.3. 30-day outcome

Around 11.7% (22/188) of patients diagnosed with MINS expired compared to 2.5% (23/887) of patients who did not have MINS ($P < .001$, HR 4.96, 95% CI 2.71–9.14).

Table 3

Predictors of MINS by multivariable logistic regression.

Variables	*P* value	OR	95% CI for OR	
			Lower bound	Upper bound
Diabetes	.01	1.545	1.108	2.153
CAD	<.001	2.184	1.451	3.288
Peripheral nerve block anesthesia	<.001	12.039	4.216	34.377

CAD = coronary artery disease.

Deaths due to primary cardiac events (1.3%, 14/1075) were significantly associated with the incidence of MINS in the whole cohort ($P < .001$, OR 18.31, 95% CI 5.06–66.31), with 6% of deaths among patients diagnosed with MINS compared to 0.3% among patients without MINS. A primary cardiac cause of death accounted for 50% (11) of the total mortality among patients diagnosed with MINS, while only 8.6% (2/23) among patients without MINS died of cardiac causes. The main noncardiac cause of death in the MINS cohort was sepsis (32%).

3.4. Predictors of 30-day mortality

Age was significantly associated with mortality within the entire study cohort. Patients belonging to the 45 to 59 year age group had a lower mortality (1.7%), while those 80 years and above had a mortality rate of 9% ($P < .05$). There was no association observed between age, gender, co-morbidities, type of surgery, and type of anesthesia with mortality within the MINS cohort. Interestingly, age was significantly associated with mortality in patients without MINS, ($P < .05$) reflecting the general characteristic of the whole cohort. Patients belonging to the 60 to 79 year age groups had a mortality of 13.3% in the MINS cohort vs 2.7% among patients who did not have MINS. No significant association was observed between gender, type of surgery, and type of anesthesia with mortality among patients without MINS.

Patients with MINS and serial ECG changes had a significant association with mortality (Table 4). Among the expired patients with MINS, 33% had ST segment changes ($P < .05$, OR 7.37, 95% CI 2.02–26.8) and 19% had T wave changes ($P < .05$, OR 3.49, 95% CI 1.26–9.68) compared to patients with no ECG changes (6%). Patients with heart rates ≥96 bpm[10] before induction of anesthesia were significantly associated with mortality ($P = .02$).

Patients within the peak troponin range of 0.03 to 0.09 ng/mL had a mortality rate of 5% (95% CI 1.3%–12%), when compared to the other troponin ranges. Additionally, patients in the peak troponin range of 1 ng/mL and above were 6.8 times more likely to die (26%) compared to those in the troponin range of 0.03 to 0.09 ($P < .05$, OR 6.8, 95% CI 1.75–27.1). A ROC curve was plotted to determine the ideal threshold value of peak troponin for predicting mortality among patients diagnosed with MINS (Fig. 2). A peak troponin value of 0.152 ng/mL and above was found to be significantly associated with mortality with a sensitivity of 72% and specificity of 58% (PPV = 18.4, NPV = 94.1% Youden's index = 0.305). The survival distributions as per Kaplan–Meier analysis were found to be significantly different between the patient groups with peak troponin above 0.15 and below 0.15 (log-rank test: $P = .008$) (Fig. 3). The 30-day survival rate was 81.6% for patients with peak troponin ≥ 0.15 ng/mL and 94.1% for patients with peak troponin < 0.15 ng/mL.

Among 984 patients who did not receive aspirin postoperatively, 30-day mortality was significantly ($P < .001$) associated with MINS (12.1%, 21/173) compared to patients without

Table 4

Predictors of mortality among patients diagnosed with MINS within the study cohort.

Variables	Outcome		*P* value	OR (95% CI)
	Alive (N = 166, 88.3%)	Expired (N = 22, 11.7%)		
Age group				
45–59	35 (92)	3 (8)	.879	1.2 (0.11–12.5)
60–79	117 (87)	18 (13)	.472	2.1 (0.26–17.3)
80 and above	14 (93)	1 (7)	Ref	Ref
Gender				
Female	384 (96)	15 (4)	.35	1.19 (0.63–2.24)
Male	646 (96)	30 (4)		
Co-morbidities				
Hypertension	112 (66)	12 (10)	.16	1.73 (0.7–4.25)
Diabetes	97 (90)	11 (10)	.29	1.41 (0.58–3.43)
Dyslipidemia	38 (97)	1 (3)	.03	6.23 (0.81–47.87)
CAD	41 (89)	5 (11)	.53	1.12 (0.39–3.21)
CVA	23 (96)	1 (4)	.1	3.38 (0.43–26.34)
Surgery				
Amputation	1 (50)	1 (50)	.272	7 (0.21–226.0)
Gastrosurgery—laparoscopy	6 (86)	1 (14)	.91	1.16 (0.05–22.9)
Gastrosurgery—open	48 (84)	9 (16)	.81	1.31 (0.14–12.0)
Head and neck and oncology	36 (97)	1 (3)	.26	0.19 (0.011–3.49)
Neurosurgery—brain	24 (92)	2 (8)	.67	0.58 (0.04–7.42)
Neurosurgery—spine	15 (94)	1 (6)	.6	0.46 (0.02–8.59)
Orthopedic —Implant/Nail	9 (82)	2 (18)	.73	1.55 (0.11–20.8)
Orthopedic— Replacement	11 (85)	2 (15)	.85	1.27 (0.09–16.8)
Orthopedic Arthroscopy	0	2	–	–
Urology	5 (83)	1 (17)	.82	1.4 (0.07–28.1)
Vascular	2 (67)	1 (33)	.44	3.5 (0.14–84.6)
Wound Debridement	7 (88)	1 (12)	Ref	Ref
Heart rate				
96 bpm and above	35 (88)	5 (12)	.02	3.6 (1.34–9.7)
Less than 96 bpm	984 (96)	39 (4)		0.28 (0.1–0.75)
ND	11 (92)	1 (8)		–
Anesthesia				
GA	143 (90)	16 (10)	.24	0.44 (0.11–1.75)
Peripheral nerve blocks	11 (79)	3 (21)	.92	1.09 (0.18–6.58)
SA	12 (80)	3 (20)	Ref	Ref
ECG changes				
ST segment changes	10 (66)	5 (33)	.002	7.37 (2.02–26.8)
T wave changes	38 (81)	9 (19)	.016	3.49 (1.26–9.68)
No changes	118 (94)	8 (6)	Ref	Ref
Peak Troponin ranges				
0.03–0.09	78 (95)	4 (5)	Ref	Ref
0.10–0.49	58 (84)	11 (16)	.032	3.69 (1.12–12.2)
0.50–0.99	13 (93)	1 (7)	.72	1.5 (0.15–14.4)
1 and above	17 (74)	6 (26)	.006	6.8 (1.75–27.1)

CAD = coronary artery disease, CVA = cerebrovscular accident, ECG = electrocardiogram, GA = general anesthesia.

MINS (2.7%, 22/811). In patients who received postoperative aspirin, the mortality reduced to 6.7% (1/15) in MINS patients (Table 5). Similarly among 998 patients who did not receive Clopidogrel postoperatively, 30-day mortality was significantly ($P < .01$) associated with MINS (12.1%, 21/173) compared to patients without MINS (2.7%, 22/811). Mortality was significantly associated with MINS irrespective of receiving statins postoperatively. A significant association was not observed between antithrombotics and outcome in the MINS cohort.

4. Discussion

The 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery[11] has stated the usefulness of postoperative screening for MI, with serial troponin levels in high-risk individuals without symptoms or signs of myocardial ischemia as uncertain (Class IIb).[12] Lack of a defined management strategy for these patients has been of concern. Recent evidence, led by the VISION study[1] showed a strong association between peak troponin levels after surgery and 30-day mortality. An implementation of serial postoperative troponin evaluations in high-risk patients undergoing noncardiac surgery was done to understand the burden of "at risk" population in our setting. Prospective evaluation estimated the prevalence of MINS in our tertiary care hospital at 17.5% (188/1075). Around 11.7% (22/188) of patients who were diagnosed with MINS expired within 30 days compared to 2.5% (23/887) of patients who did not have MINS ($P < .001$). The mortality in our MINS cohort was higher than the 9.8% mortality reported in the VISION study. The incidence of MINS in our cohort was significantly higher than the incidence of 8% reported by the VISION study.[2] We believe that the

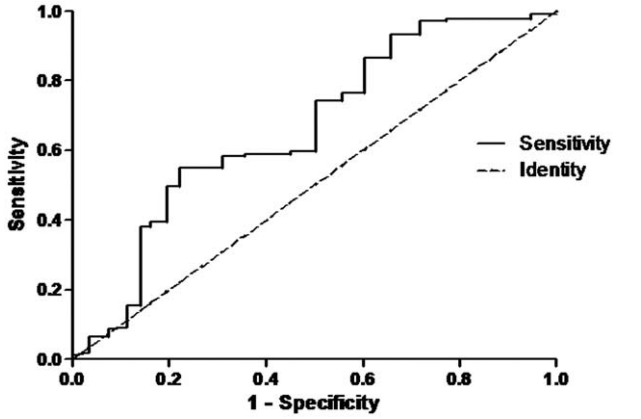

Figure 2. Receiving operating characteristic curve of peak Troponin values for predicting outcome among patients diagnosed with MINS. MINS = myocardial injury after noncardiac surgery.

increased inherent cardiovascular risk in our South Indian population could have contributed to the higher incidence of MINS. Considering the fact that all of the events were asymptomatic, the number of individuals who develop MINS is definitely alarming.

With patients from all adult age groups undergoing surgery, our results were similar to the VISION trial,[2] which revealed individuals older than 75 years had a significant association with MINS. Diabetes, coronary artery disease, and cerebrovascular accidents are fast gaining the status of potential epidemics in India. Since our study reveals significant association with these noncommunicable diseases, an increase in the prevalence of MINS can be expected to parallel any rise in the incidence of these individual co-morbidities in coming years. In our cohort, the patients with high perioperative risk underwent surgery with peripheral nerve block anesthesia as compared to general or spinal anesthesia. This has contributed to higher incidence of MINS and associated mortality. The high negative predictive value of the peak troponin level cut-off of 0.152 ng/mL can be translated to screen patients with MINS who would not require close follow up within 30 days postsurgery.

Use of the standard criteria for MI alone in our cohort would have missed the diagnosis of prognostically relevant MI in 67% of our patients. We wish to highlight the importance of potential under diagnosis of this condition, as it silently emerges into a major postoperative entity. Our clinical research team overcame significant skepticism from surgeons and anesthesiologists to implement this risk based screening protocol for MINS. Based on our results, we believe we have sufficient evidence at present to standardize this protocol and integrate it into routine care.

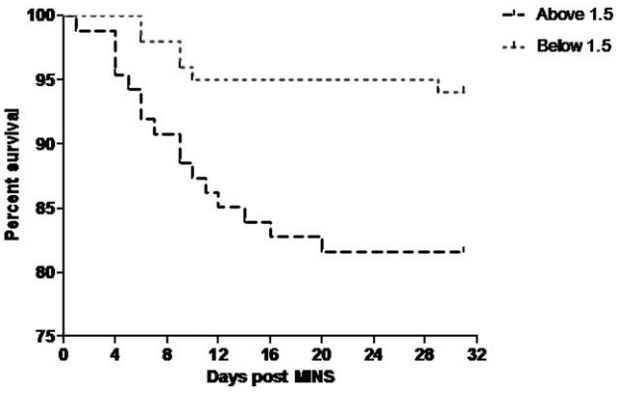

Figure 3. Kaplan–Meier survival distributions for the two groups with peak Troponin values above 0.15 ng/mL and below 0.15 ng/mL.

Table 5

Optimized medical therapy and mortality.

Optimized medical therapy	Alive	Expired	*P* value
Received postoperative ASA			
MINS	14 (93)	1 (7)	.34
Negative	75 (99)	1 (1)	
Did not receive postoperative ASA			
MINS	152 (88)	21 (12)	<.001*
Negative	789 (97)	22 (3)	
Received postoperative Clopidogrel			
MINS	17 (90)	2 (10.5)	.058
Negative	58 (100)	0	
Did not receive postoperative Clopidogrel			
MINS	149 (88)	20 (11.8)	<.001*
Negative	806 (97)	23 (2.8)	
Received postoperative statins			
MINS	55 (95)	3 (5)	.045*
Negative	180 (99)	1 (0.6)	
Did not receive postoperative statins			
MINS	111 (85)	19 (14.6)	<.001*
Negative	684 (97)	22 (3)	

ASA = acetyl salicylic acid (Aspirin), MINS = myocardial injury after noncardiac surgery.
* Denotes $P < 0.05$.

We did not observe any significant association of MINS and 30-day mortality and type of surgery, with almost similar percentage of patients undergoing gastrointestinal, neuro- and orthopedic surgery in our cohort. This is similar to previously published data suggesting correlation with MINS and outcome in only patients undergoing major vascular surgery.[6]

The comparatively higher mortality in MINS patients in our study due to a cardiac cause and the significant association noted with lack of antithrombotic medications after MINS is of concern. At present there is no standard of care for management of MINS patients. Our observation of increased incidence and mortality in patients who did not have antithrombotics is distressing. Better awareness about MINS among the surgeons and education with respect to prescription of antithrombotic medications in this patient group could improve outcomes till definitive treatment options are available.

Our study strengths include the prospective nature and wide and diverse array of surgeries done in our tertiary care hospital allowing us to screen the "at risk" patients for MINS. Another factor was the establishment of screening troponin in the high-risk population after surgery as standard process, with active participation from the anesthesia and respective surgical departments. As compared to the VISION trial, we used Troponin I instead of Troponin T, which is shown to be less influenced by renal dysfunction, hence revealing a more accurate value.[13,14]

Our study has several limitations. The study cohort included Southern Indian population; hence generalizing the observations to the Indian population at large would require broader and more widespread study to determine the true prevalence of MINS. Issues associated with physician reservations to recruit patients coupled with lack of patient consent have led to the inclusion of a random subset of screened patients, which could have potentially biased our observations. Our hospital being a tertiary care referral centre, for the state, we see high risk complex medical

cases contributing to a potential bias in the study cohort. Furthermore, Troponin I was only measured on the first 2 days' postsurgery and hence MI occurring after 48 hours could have been missed. A third Troponin I measurement is only taken when any one of the two initial tests within 48 hours turns positive, possibly omitting any MINS positivity occurring within a window of following 24 hours.

Given the asymptomatic nature of MINS, awareness with a high index of suspicion and screening "at risk" patients will improve outcomes following noncardiac surgery. Our state being a capital for diabetes and harboring CAD at younger ages, we have a higher incidence of MINS and associated mortality compared to developed countries. Screening patients to diagnose MINS based on elevated Troponin I levels should be standard of care that could be incorporated into routine clinical practice. Due to the scarcity of published data in the Indian population, the role of MINS in influencing the outcomes of patients undergoing noncardiac surgery all over India is unknown. The results of our study emphasize the need of further research studies on MINS and identifying the various clinical variables associated with its incidence and related mortality.

5. Conclusion

We report a prospective study demonstrating a higher prevalence of MINS in our region (17.5%) when compared to the worldwide incidence of 8%, with significant association with 30-day mortality. In clinical practice, elevated troponin in the perioperative period has prognostic utility and can prepare surgical teams for adverse events so that they can be recognized, evaluated, and treated in a timely manner. We have demonstrated the feasibility of implementing a risk based screening protocol for MINS following noncardiac surgery. A greater importance must be assigned to MINS and its treatment as it has significant association with postoperative morbidity and mortality. The time interval between troponin elevation and death potentially allows physicians to modify prognosis by initiating medical treatment of myocardial ischemia. The results of our study emphasize the need of further research studies on MINS identifying the various clinical variables risk factors and ideal treatment options.

Acknowledgments

The authors would like to acknowledge the critical review and valuable feedback provided by Dr Manuraj, Clinical Professor, General Pediatrics, Amrita Institute of Medical Sciences. We would like to acknowledge the MANAGE (Management of Myocardial Injury After Noncardiac Surgery Trial) group for their knowledge base. Authors would also like to acknowledge Rekha M Jayaprasad, Clinical Research Co-ordinator, Medical Administration, Amrita Institute of Medical Sciences for facilitating and coordinating the clinical data collection process of the study. The study has not been funded directly by any resources.

Author contributions

Conceptualization: Vidya P Menon, Sabarish Balachandran, Dipu Sathyapalan, Ashok Pillai.
Data curation: Rubin George, Vidya P Menon, Fabia Edathadathil, Dipu Sathyapalan, Preetha Prasanna.
Formal analysis: Rubin George, Vidya P Menon, Fabia Edathadathil, Sabarish Balachandran, Merlin Moni, Ashok Pillai.
Funding acquisition: Vidya P Menon, Ashok Pillai.
Investigation: Rubin George, Vidya P Menon, Sabarish Balachandran, Merlin Moni, Dipu Sathyapalan, Preetha Prasanna, Jerry Paul, ChandraBabu K K, Lakshmi Kumar, Ashok Pillai.
Methodology: Rubin George, Vidya P Menon, Fabia Edathadathil, Sabarish Balachandran, Merlin Moni, Dipu Sathyapalan, Preetha Prasanna, Gokuldas S, Jerry Paul, ChandraBabu K K, Lakshmi Kumar, Ashok Pillai.
Project administration: Rubin George, Vidya P Menon, Merlin Moni, Preetha Prasanna, Gokuldas S, Jerry Paul, ChandraBabu K K, Lakshmi Kumar, Ashok Pillai.
Resources: Rubin George, Vidya P Menon, Preetha Prasanna, Gokuldas S, Jerry Paul, ChandraBabu K K, Lakshmi Kumar, Ashok Pillai.
Software: Vidya P Menon, Fabia Edathadathil.
Supervision: Vidya P Menon, Merlin Moni, Gokuldas S, ChandraBabu K K, Lakshmi Kumar, Ashok Pillai.
Validation: Vidya P Menon, Fabia Edathadathil, Ashok Pillai.
Visualization: Vidya P Menon, Fabia Edathadathil.
Writing – original draft: Rubin George, Vidya P Menon, Fabia Edathadathil, Sabarish Balachandran, Dipu Sathyapalan, Ashok Pillai.
Writing – review & editing: Rubin George, Vidya P Menon, Fabia Edathadathil, Merlin Moni, Dipu Sathyapalan, Ashok Pillai.

References

[1] Botto F, Alonso-Coello P, Chan MTV, et al. Myocardial injury after noncardiac surgery. Anesthesiology 2014;120:564–78.
[2] Devereaux PJ. Characteristics and short-term prognosis of perioperative myocardial infarction in patients undergoing noncardiac surgery. Ann Intern Med 2011;154:523.
[3] Paniagua Iglesias P, Díaz Ruano S, Álvarez-García J. Myocardial injury after noncardiac surgery. Rev Española Cardiol (English Ed) 2014; 67:794–6.
[4] Ali ZA, Callaghan CJ, Ali AA, et al. Perioperative myocardial injury after elective open abdominal aortic aneurysm repair predicts outcome. Eur J Vasc Endovasc Surg 2008;35:413–9.
[5] Khan J, Alonso-Coello P, Devereaux PJ. Myocardial injury after noncardiac surgery. Curr Opin Cardiol 2014;29:307–11.
[6] van Waes JAR, Nathoe HM, de Graaff JC, et al. Myocardial injury after noncardiac surgery and its association with short-term mortality. Circulation 2013;127:2264–71.
[7] Landesberg G, Beattie WS, Mosseri M, et al. Perioperative myocardial infarction. Circulation 2009;119:2936–44.
[8] Dawood MM, Gutpa DK, Southern J, et al. Pathology of fatal perioperative myocardial infarction: implications regarding pathophysiology and prevention. Int J Cardiol 1996;57:37–44.
[9] Eagle KA, Berger PB, Calkins H, et al. ACC/AHA guideline update for perioperative cardiovascular evaluation for noncardiac surgery—executive summary. J Am Coll Cardiol 2002;39:542–53.
[10] Abbott TEF, Ackland GL, Archbold RA, et al. Preoperative heart rate and myocardial injury after non-cardiac surgery: results of a predefined secondary analysis of the VISION study. Br J Anaesth 2016;117:172–81.
[11] Fleisher LA, Fleischmann KE, Auerbach AD, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;130:e278–333.
[12] Roos M, Brodbeck J, Sarkozy A, et al. A Critical analysis of the scientific evidence behind international guidelines related to cardiac arrhythmias. Circ Arrhythmia Electrophysiol 2011;4:202–10.
[13] Tanidi A. Troponin elevation in conditions other than acute coronary syndromes. Vasc Health Risk Manag 2011;7:597–603.
[14] Buiten MS, de Bie MK, Rotmans JI, et al. Serum cardiac Troponin-I is superior to Troponin-T as a marker for left ventricular dysfunction in clinically stable patients with end-stage renal disease. PLoS One 2015;10: e0134245.