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ORIGINAL RESEARCH

Predictors of short- and long-term outcome after open cardiac surgery in a high-volume referral tertiary hospital: the role of surgical team caseload

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Abstract

Very few studies have investigated the role of surgeon and anesthesiologist caseloads and high-sensitive troponin I (hs-TnI) on short- and long-term outcomes in cardiac surgery. In this study we assessed the relationship between perioperative hs-TnI measurements with 1-year mortality and major cardiovascular events (MACE) at 30 days as a function of surgeon and anesthesiologist volume experience. This is a single center, prospective observational study in a tertiary high-volume hospital enrolling 1000 consecutive adult patients undergoing open cardiac surgery. All patients were managed according to a standardized protocol, as per routine practice. Exclusion criteria were age <18, no written consent, ongoing myocardial infarction, preoperative hs-TnI ≥ 300 ng/L, salvage cardiac surgery, isolated thoracic aortic surgery or implantation of a ventricular assist device. At the multivariable analysis, lowest hematocrit during cardiopulmonary bypass [Odd ratio (OR): 0.81; 95% confidence intervals (CI): 0.74–0.92], preoperative activated thromboplastin time (OR: 1.04; 95% CI: 1.01–1.08), expert anesthesiologist (OR: 22.8; 95% CI: 1.73–301.87), post-operative intra-aortic balloon pump (OR: 5.20: 95% CI: 1.62–16.44), post-operative venous-arterial-extracorporeal membrane oxygenator (OR: 83.93; 95% CI: 4.95–1436.55), transfusion (OR: 10.17; 95% CI: 2.41–42.94) and MACE (OR: 3.93; 95% CI: 1.28–12.18) were independently associated with 1-year mortality [Hosmer and Lemeshow chi-test = 4.82; $p = 0.77$; AUC of the model corrected for optimism: 0.92 (95% CI: 0.89–0.94)]. We found that surgeons and anesthesiologists were not independent predictors of MACE at 30 days. The hs-TnI, measured at several time points, was not effective in predicting 1-year mortality or MACE at 30 days. Anesthesiologist- and surgeon-related annual case volume did not affect MACE at 30 days, while 1-year mortality was independently associated with anesthesiologist providers with the highest caseload.

Keywords

Perioperative; Outcome; Mortality; MACE; Cardiac surgery; Anesthesiologist; Perioperative; Quality; Surgical volume

1. Introduction

A growing body of literature currently demonstrates that morbidity and mortality rates in high-volume centers are lower compared to those of medium- and low-volume surgical providers, mainly due to a more effective treatment of complications [1, 2]. In spite of this, the surgical and anesthesiologic team-related characteristics and their association with outcomes remains not fully understood, especially in the cardiac surgery arena. Indeed, disregarding the crucial members of the team leads to an incomplete vision of the perioperative surgical care, with potential impact on both medical and economic perspectives [3]. So far, only Papachristofi *et al.* [4] evaluated the impact of the anesthesiologist's and surgeon's monthly caseload volume on mortality after cardiac surgery. However, they limited their analysis at the in-hospital death. Thus, to our knowledge, no previous studies considered this aspect in patients undergoing open cardiac surgery.

In the last decade, conventional troponin (cTn) has evolved as an invaluable tool for both the diagnosis and prognosis of myocardial infarction [4]. The advent of High-sensitivity Tro-

ponin (hs-Tn), which has higher sensitivity and negative predictive value in detecting myocardial injury compared to cTn, has significantly enhanced the definition of non-ST elevation-acute coronary syndrome and its clinical management [5]. Since in the context of cardiac surgery the cTn release is multifactorial—cardiac manipulation, defibrillation, suboptimal myocardial protection [6]—and not exclusively associated with myocardial ischemia, the cTn release is a less reliable predictor of myocardial injury [7]. Therefore, the cTn in cardiac surgery should be considered as a cardiac-specific biomarker rather than a disease-specific biomarker. Recent studies conducted in cardiac surgery confirmed this hypothesis, corroborating the hs-Tn prognostic value in predicting short-, medium-, and long-term adverse outcomes [7]. Unfortunately, the diagnostic thresholds to predict early and late postoperative complications remain relatively neglected [8, 9].

For these reasons, we determine the predictors of 1-year mortality and the incidence of major cardiovascular events (MACE) at 30 days in patients undergoing open cardiac surgery, taking into account perioperative high-sensitivity Troponin I (hs-TnI) release and surgical team experience in a high-volume tertiary hospital.

2. Materials and methods

This is a single-center prospective observational study including consecutive patients undergoing open cardiac surgery at IRCCS San Raffaele Scientific Institute between January 2017 and April 2019. The study was supported by a grant (GR-2013-02356129) from the Italian Ministry of Health.

The study was designed according to the principles of the Declaration of Helsinki [10] and the present report follows the guidelines for observational studies based on the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines [11] (**Supplemental Table 1**). All patients gave written informed consent allowing for scientific data management as for Ethical committee approval (24/INT/2016). While a large number of procedures are classified as routine primary procedures, a conspicuous number of complex and redo cardiac surgery are equally performed annually. Exclusion criteria were patient younger than 18, no written consent, ongoing myocardial infarction, preoperative hs-TnI $\geq$300 ng/L, salvage cardiac surgery, isolated thoracic aortic surgery or implantation of a ventricular assist device.

All patients received intramuscular morphine 0.1 mg/kg and atropine 0.01 mg/kg 1 hour before surgery. In the operating theatre, the invasive blood pressure was obtained through cannulation of the radial artery. A right internal jugular 7-Fr central venous line and an 8.5-Fr percutaneous pulmonary artery sheath introducer were placed in the right internal jugular vein with a double stitch technique. General anesthesia was induced with fentanyl (10–20 μg/kg), propofol (2 mg/kg) and rocuronium 0.6 mg/kg. Anesthesia was maintained with propofol (2–4 mg/kg/h), sevoflurane or desflurane (end-tidal concentration $<$1 minimum alveolar concentration) and titrated to have a bispectral index (Medtronic, BIS^{TM}) between 45 and 55. Standard intraoperative monitoring included electrocardiography (leads II and V5) with ST-segment analysis, transesophageal echocardiography, invasive blood pressure, temperature, pulse oximetry, end-tidal carbon dioxide, urine output and central venous blood pressure. All patients received a loading dose of 1 g of tranexamic acid, immediately after the induction of general anesthesia, followed by a 400 mg/h infusion. Moderate hemodilution with mild hypothermia (32 °C–34 °C) were maintained during cardiopulmonary bypass. In order to achieve an activated coagulation time greater than 480 seconds before cannulation, a bolus of 300 U/kg of unfractionated heparin was administered. The pump flows were adjusted to have a cardiac index between 2.0 and 2.4 L/min/m^2 throughout surgery. Heparin reversal was performed with protamine at the end of the operation in 1:1 ratio. No aprotinin was administered. After surgery, all patients were moved to the cardiac intensive care unit. In order to dose the hs-TnI five blood samples were drawn at the following fixed time points: within 3 hours before surgery, 3–12 hours after surgery, and once a day from the first to the third postoperative day. Among these measurements, the highest hs-TnI value for each patient was considered to be the peak. All operations were performed by members of the perioperative care team, composed by six surgeons and twenty anesthesiologists, who were anonymized and given unique numerical identifiers. Case volume was calculated separately for each surgeon and anesthesiologist. In particular, the annual caseload was divided in percentiles. We considered "expert" an annual caseload higher than the 75th percentile, "junior" lower than the 25th percentile, and "intermediate" in between. According to this, surgeons were considered to be expert if they performed more than 269 cases per year, intermediate between 110 and 269, and junior below 110. Similarly, we deemed as expert an anesthesiologist with more than 101 operations per year, junior with less than 56, and intermediate between 56 and 101. All anesthesiologists worked with all surgeons without systematic "pairings".

The following validated criteria [12] were considered just before starting the weaning from mechanical ventilation: normal gas exchange, positive end-expiratory pressure lower than 10 cmH_2O, normothermia, electrolytes in the normal range, inotropes/vasopressors reduced or unchanged over previous hours, and more than 6 breaths/min with 10 mmHg of pressure support. When the following criteria were fulfilled, a patient was considered ready to be discharged from the intensive care unit: oxygen saturation $\geq$94% with a fraction of inspired oxygen $\leq$0.5, no inotropes/vasopressors administration, absence of clinically relevant arrhythmias, body temperature below 37 °C, chest tube drainage $<$50 mL/h, urine output $>$0.5 mL/kg/h. Criteria for hospital discharge were absence of chest drainage and external pacemaker, clean and dry incisions, normothermia, independent ambulation and feeding.

The primary outcome was 1-year mortality and the secondary occurrence of MACE at 30 days. The latter was a composite outcome including non-fatal myocardial infarction (new Q-wave $\geq$40 milliseconds or loss of R-wave in at least two continuous leads of the same vascular territory), cardiac arrest, stroke, pulmonary embolism, prolonged mechanical ventilation (mechanical ventilation for more than three days), major bleeding (chest drainage of 1000 mL at 12 hours and/or reoperation for bleeding); new episode of heart failure or atrial

TABLE 1. Baseline clinical characteristics.

	Population	Survivor at 1 year	Death at 1 year	*p*-value
	(N = 1000)	(N = 971)	(N = 29)	
Demographic data				
Age, years (IQR)	65 (55–72)	65 (55–72)	70 (65–75)	0.008
Female sex, n (%)	360 (37.2)	360 (37.1)	12 (41.4)	0.639
Body Surface Area, m^2 (IQR)	1.84 (1.71–1.96)	1.84 (1.70–1.97)	1.87 (1.63–1.95)	0.578
NYHA class				
————1, n (%)	2 (0.2)	2 (0.2)	0 (0.0)	0.001
————2, n (%)	577 (57.8)	563 (58)	14 (48.3)	
————3, n (%)	122 (12.2)	116 (12)	6 (4.9)	
————4, n (%)	11 (1.1)	7 (0.7)	4 (13.8)	
CCS score				
CCS score 0, n (%)	863 (86.3)	838 (86.3)	25 (86.2)	0.338
CCS score 1, n (%)	78 (7.8)	75 (7.7)	3 (10.3)	
CCS score 2, n (%)	44 (4.4)	44 (4.5)	0 (0.0)	
CCS score 3, n (%)	15 (1.5)	14 (1.4)	1 (3.4)	
Ejection fraction, % (IQR)	60 (55–65)	60 (55–66)	55 (45–61)	0.003
Comorbidities				
Prior myocardial infarction, n (%)	61 (6.1)	57 (5.9)	4 (13.8)	0.950
Prior Cardiac Arrest, n (%)	7 (0.7)	6 (0.6)	1(3.4)	0.187
Previous Stroke, n (%)	31 (3.1)	29 (3)	2(6.9)	0.226
Previous TIA, n (%)	28 (2.8)	26 (2.7)	2 (6.9)	0.193
Prior Deep Vein Thrombosis, n (%)	3 (0.3)	3 (0.3)	0 (0.0)	0.915
Prior Pulmonary embolism, n (%)	2 (0.2)	2 (0.2)	0 (0.0)	0.943
Peripheral venous disease, n (%)	27 (2.7)	24 (2.5)	3 (10.3)	0.400
Hypertension, n (%)	442 (44.2)	428 (44.1)	14 (48.3)	0.655
Prior Pulmonary hypertension, n (%)	28 (2.8)	24 (2.5)	4 (13.8)	0.007
Prior Atrial fibrillation, n (%)	201 (20.1)	189 (19.5)	12 (41.4)	0.008
COPD, n (%)	42 (4.2)	37 (3.8)	5 (17.2)	0.006
Diabetes, n (%)	110 (11)	104 (10.7)	6 (20.7)	0.121
End stage renal disease, n (%)	7 (0.7)	5 (0.5)	2 (6.9)	0.016
Dialysis, n (%)	2 (0.2)	2 (0.2)	0 (0.0)	0.943
Cancer, n (%)	12 (1.2)	10 (1)	2 (6.9)	0.045
Smoke, n (%)	527 (52.7)	513 (52.8)	14 (48.3)	0.629
Chronic Heart failure, n (%)	2 (0.2)	1 (0.1)	1 (3.4)	0.057
Aortic stenosis, n (%)	232 (23.2)	223 (23.0)	9 (31.0)	0.326
Redo, n (%)	115 (11.5)	107 (11.0)	8 (27.6)	0.013
Medications				
ACE inhibitors, n (%)	259 (26)	252 (26.1)	7 (24.1)	0.944
ARB, n (%)	70 (7.0)	66 (6.8)	4 (13.8)	0.141
Beta blockers, n (%)	540 (54.2)	523 (54.1)	17 (58.6)	0.632
Alpha Blockers, n (%)	2 (0.2)	2 (0.2)	0 (0.0)	0.943
Calcium channel blockers, n (%)	12 (1.2)	11 (1.1)	1 (3.4)	0.300
Dihydropyridine, n (%)	86 (8.6)	83 (8.6)	3 (10.3)	0.465
Potassium-sparing diuretic, n (%)	67 (6.7)	60 (6.2)	7 (24.1)	0.002
Digoxin, n (%)	48 (4.8)	41 (4.2)	7 (24.1)	0.001
Long lasting nitrate, n (%)	2 (0.2)	2 (0.2)	0 (0.0)	0.943
Statins, n (%)	322 (32.3)	305 (31.6)	17 (58.6)	0.003
Sulfonylureas, n (%)	4 (0.4)	4 (0.4)	0(0.0)	0.888
ASA, n (%)	52 (5.2)	50 (5.2)	2 (6.9)	0.660
Clopidogrel, n (%)	13 (1.3)	13 (1.3)	0 (0.0)	0.679
Ticagrelor, n (%)	8 (0.8)	8 (0.8)	0 (0.0)	0.789
Prasugrel, n (%)	1 (0.1)	1 (0.1)	0 (0.0)	0.971

TABLE 1. Continued.

	Population (N = 1000)	Survivor at 1 year (N = 971)	Death at 1 year (N = 29)	*p*-value
Glycoprotein iib/iiia inhibitors, n (%)	7 (0.7)	7 (0.7)	0 (0.0)	0.812
Warfarin, n (%)	22 (2.2)	21 (2.1)	1 (3.4)	0.482
Dabigatran, n (%)	3 (0.3)	3 (0.3)	0 (0.0)	0.915
Apixaban, n (%)	6 (0.6)	6 (0.6)	0 (0.0)	0.838
Other new oral anticoagulant, n (%)	1 (0.1)	1 (0.1)	0 (0.0)	0.971
Rivaroxaban, n (%)	4 (0.4)	4 (0.4)	0 (0.0)	0.889
Surgeon's experience				0.744
Expert, n (%)	628 (62.7)	610 (62.8)	18 (62.1)	
Intermediate, n (%)	231 (23.1)	223 (22.9)	8 (27.6)	
Junior, n (%)	142 (14.2)	139 (14.3)	3 (10.3)	
Anesthesiologist's experience				0.141
Expert, n (%)	443 (44.3)	434 (44.7)	9 (31.0)	
Intermediate, n (%)	358 (35.8)	348 (35.8)	10 (34.5)	
Junior, n (%)	200 (20)	190 (19.5)	10 (34.5)	
Laboratory tests				
Hemoglobin, mg/dl (IQR)	13.9 (12.8–14.9)	13.9 (11.7–15.0)	12.4 (11.0–13.8)	0.001
White Blood Cell, 10^9/L (IQR)	6.60 (5.55–7.70)	6.6 (5.5–7.7)	6.4 (5.6–7.7)	0.915
Platelets, 10^9/L (IQR)	207 (176– 243)	207 (176–244)	199 (156–236)	0.262
aPTT, s (IQR)	29 (28–31)	29 (28–31)	32 (29–47)	0.009
INR, n (IQR)	1.00 (1.00–1.10)	1.00 (1.00–1.10)	1.10 (1.05–1.20)	0.001
Glucose, mg/dL (IQR)	94 (86–105)	94 (86–105)	101 (88–130)	0.340
Creatinine, mg/dL (IQR)	0.94 (0.81–1.09)	0.94 (0.81–1.08)	1.07 (0.92–1.29)	0.001

IQR, interquartile ranges; NYHA, New York Heart Association; CCS, Canadian Cardiovascular Society; TIA, transient ischemic attack; COPD, Chronic obstructive pulmonary disease; OSAS, Obstructive Sleep Apnea Syndrome; ACE, Angiotensin converting enzyme; ARB, Angiotensin II Receptor Blockers; PPI, proton pump inhibitor; ASA, acetylsalicylic acid; aPTT, activated partial thromboplastin time; INR, international normalized ratio.

fibrillation, pneumonia (new or increased radiographic infiltrate with a positive quantitative culture of bronchoalveolar lavage), and sepsis.

3. Statistical analysis

Data were stored electronically and analyzed by the use of STATA software version 16 (College Station, Texas 77845 USA) and R version 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria). $p < 0.05$ was considered statistically significant. Kolmogorov–Smirnov test was used to test the normal distribution of the continuous variables. No imputation for missing data was done. Continuous variables were presented as median and interquartile ranges (IQR) while categorical variables as numbers and proportions. Differences between continuous variables were tested with Mann-Whitney test and the categorical variables with the χ-square test or Fisher exact test, when required.

The primary outcome for the analysis were MACE at 30 days and survival at 1 year after surgery. The candidate independent variables were selected if showed a $p \leq 0.05$ at the univariate analysis. All continues variables were tested for co-linearity. Multicollinearity was managed using only the variable with the best predictive value in a set of variables with a correlation coefficient lower than –0.9 or greater than 0.9 in the regression analysis. Then, a multivariable logistic regression analysis was run to assess the association between preoperative, intraoperative and postoperative variables with a p value ≤ 0.05 at the univariate analysis along with anesthesiologist/surgeon case volume and the primary outcome.

A multivariable penalized regression analysis was run to reduce overfitting while performing simultaneously variable selection. Thus, we used the GLM-path package [13] to fit adaptive least absolute shrinkage and selection operator (LASSO) penalized logistic regression models [14] to the data. The response variables were MACE at 30 days or 1-year mortality and the predictors preoperative, intraoperative and postoperative variables significant at the invariable screening forcing surgeon's and anesthesiologist's experience into the model. The tuning variable was selected on modified Akaike's Information Criterion [15, 16]. Selected models' prediction performance was then assessed for calibration and discrimination. Model calibration was evaluated with the Hosmer and Lemeshow test for goodness of fit and a $p > 0.05$ considered a good fit of the model, as it indicates that there is no significant difference between the predicted and observed outcomes.

A bootstrapping technique (200 bootstraps) was used to build unbiased, conservative estimates of the classification accuracy of the multiple prediction models identified by GLM-path. In order to obtain the final model and model optimism

TABLE 2. Operating theatre.

	Population (N = 1000)	Survivor at 1 year (N = 971)	Death at 1 year (N = 29)	*p*-value
Preoperative Inotropes/vasopressors, n (%)	3 (0.3)	2 (0.2)	1 (3.4)	0.085
Preoperative IAPB, n (%)	5 (0.5)	5 (0.5)	0 (0.0)	0.563
Urgency rating				0.105
Elective, n (%)	996 (99.6)	968 (99.7)	28 (96.6)	
Urgent, n (%)	2 (0.2)	2 (0.2)	0 (0.0)	
Emergent, n (%)	2 (0.2)	1 (0.1)	1 (3.4)	
Endocarditis, n (%)	15 (1.5)	15 (1.5)	0 (0.0)	0.641
CAD, n (%)	4 (0.4)	3 (0.3)	1 (3.4)	0.111
AMI, n (%)	4 (0.4)	3 (0.3)	1 (3.4)	0.111
Dissection, n (%)	2 (0.2)	1 (0.1)	1 (0.1)	0.105
Cardiogenic shock, n (%)	4 (0.4)	3 (0.3)	1 (0.1)	0.111
Pulmonary Edema, n (%)	4 (0.4)	3 (0.3)	1 (0.1)	0.111
On pump surgery, n (%)	983 (98.3)	954 (98.2)	29 (100)	0.604
Aortic cross clamp, n (%)	968 (96.8)	941 (96.9)	27 (93.1)	0.495
Cardioplegia type				0.654
None, n (%)	32 (3.2)	30 (3.1)	2 (6.9)	
Buckberg, n (%)	7 (0.7)	7 (0.7)	0 (0.0)	
Custudiol, n (%)	961 (96.1)	934 (97.2)	27 (2.8)	
Surgical Approach				
Sternotomy, n (%)	956 (95.6)	928 (95.6)	28 (96.6)	0.632
Minimal Invasive, n (%)	44 (4.4)	43 (4.4)	1 (3.4)	
Cardioplegia delivery				0.731
None, n (%)	32 (3.2)	30 (3.1)	2 (6.9)	
Anterograde, n (%)	893 (89.3)	871 (89.4)	25 (86.2)	
Retrograde, n (%)	5 (0.5)	5 (0.5)	0 (0.0)	
Combined, n (%)	70 (7.0)	68 (7.0)	2 (6.9)	
Aortic valve surgery, n (%)	339 (33.9)	328 (33.8)	11 (37.9)	0.645
Mitral valve surgery, n (%)	481 (48.1)	470 (48.4)	11 (37.9)	0.263
Tricuspid valve surgery, n (%)	112 (1.12)	103 (10.6)	9 (31)	0.003
Pulmonary valve surgery, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	1.000
Coronary bypass grafting, n (%)	186 (18.6)	175 (18)	11 (37.9)	0.130
Graft number				
1, n (%)	70 (37.6)	63 (36)	7 (63.6)	0.251
2, n (%)	64 (34.4)	61 (34.9)	3 (27.3)	
3, n (%)	48 (25.8)	47 (26.9)	1 (9.1)	
4, n (%)	4 (2.2)	4 (2.3)	0 (0.0)	
Ascending Aorta surgery, n (%)	137 (13.7)	134 (13.8)	3 (10.3)	0.422
Bentall, n (%)	27 (2.7)	25 (2.6)	2 (6.9)	0.183
Ascending Aorta Enlargement, n (%)	6 (0.6)	6 (0.6)	0 (0.0)	0.838
Aortic Arch Surgery, n (%)	9 (0.9)	8 (0.8)	1 (3.4)	0.234
DHA, n (%)	18 (1.8)	16 (1.6)	2 (6.9)	0.930
Ascending Aorta replacement, n (%)	97 (9.7)	97 (9.7)	0 (0.0)	0.051
Left ventricle aneurysmectomy, n (%)	4 (0.4)	4 (0.4)	0 (0.0)	0.889
Septal defect closure, n (%)	22 (2.2)	21 (2.1)	1 (3.4)	0.480

TABLE 2. Continued.

	Population	Survivor at 1 year	Death at 1 year	*p*-value
	(N = 1000)	(N = 971)	(N = 29)	
Septal defect type				0.864
Atrial, n (%)	21 (2.1)	20 (2.1)	1 (3.4)	
Ventricular, n (%)	1 (0.1)	1 (0.1)	0 (0.0)	
Atrial Fibrillation Ablation, n (%)	56 (5.6)	56 (5.6)	0 (0.0)	0.402
CPB time, min (IQR)	83 (66–112)	82 (66–112)	112 (83.5–168)	0.023
Aortic cross clamp time, min (IQR)	158 (146–249)	62 (49–186)	91 (47–96)	0.200
Lowest temperature CPB, °C (IQR)	30 (28–31)	29 (18–30)	27 (23–32)	0.232
Lowest Ht CPB, % (IQR)	23 (20–24)	25 (22–28)	22 (19–24)	0.001
Lowest glucose surgery, mg/dL (IQR)	96 (89–135)	128 (89–168)	95 (88–102)	0.277

IQR, interquartile ranges; IABP, intra-aortic balloon pump; AMI, acute myocardial infarction; DHA, Deep Hypothermic Arrest; RBC, Red blood cell; CPB, Cardiopulmonary bypass; Ht, hematocrit.

TABLE 3. Postoperative course.

	Population	Survivor at 1 year	Death at 1 year	*p*-value
	(N = 1000)	(N = 971)	(N = 29)	
Inotropes/Vasopressors >4 h, n (%)	724 (72.5)	701 (72.1)	23 (81.1)	0.225
Mechanical circulatory support, n (%)	116 (11.6)	85 (8.8)	14 (48.3)	0.001
IABP, n (%)	99 (9.9)	64 (6.6)	13 (46.4)	
ECMO, n (%)	6 (0.6)	3 (0.3)	3 (10.3)	
Other, n (%)	11(1.1)	10 (1.0)	1 (3.4)	
ICU stay, days (IQR)	1 (1–2)	2 (1–3)	6.5 (3–18)	0.001
Orotracheal Intubation time, hours (IQR)	12 (10–17)	16 (12–21)	68.5 (23–165)	0.001
Reintubation, n (%)	13 (1.3)	7 (0.7)	6 (21.0)	0.001
Chest drainage, ml (IQR)	400 (300–540)	562 (387–891)	685 (472–1125)	0.002
Creatinine peak, mg/dL (IQR)	0.79 (0.65–0.96)	0.79 (0.64–0.94)	1.02 (0.81–1.50)	0.001
Troponin preoperative, ng/L (IQR)	7 (4–15)	9 (5–20)	17.5 (9.5–26.8)	0.001
Troponin 3–12 hours post-surgery, ng/L (IQR)	3624 (2117–2363)	4330 (2260–7804)	3715 (2658–18046)	0.329
Troponin at day 1, ng/L (IQR)	4126 (2363–6907)	4794 (2735–8669)	7085 (2055–24167)	0.007
Troponin at day 2, ng/L (IQR)	2104 (1207–3717)	2502 (1332–4881)	4172 (1341–25627)	0.006
Troponin at day 3, ng/L (IQR)	1201 (696–2032)	1336 (784–2606)	2526 (557–12403)	0.016
Troponin Peak, ng/L (IQR)	4711 (2744–7817)	5606 (3290–8696)	9053 (2658–29520)	0.011
Reoperation, n (%)	4 (0.4)	3 (0.3)	1 (3.4)	0.111
Hospital stay, days (IQR)	5 (4–7)	5 (4–7)	11 (6–39)	0.001
Transfusion, n (%)	328 (32.8)	302 (31.1)	26 (89.7)	0.001
MACE, n (%)	369 (36.9)	347 (35.7)	22 (75.9)	0.001

IQR, Interquartile range; IABP, Intra-aortic balloon pump; MACE, major cardiovascular event.

corrected performance, the selection of predictors was applied to each bootstrap sample and the final model performance was compared to original data for each bootstrap sample. Finally, bootstrap corrected area under the curve was obtained by subtracting the optimism from the original area under the curve.

The sample size calculation was based on 1-year mortality. Since the incident rate of the primary outcome reported in the literature was around 3% [17] with a sample size of 1000 we expected to have a precision of a 95% confidence interval (CI) ranging between 2.0–4.3%. Taking into account these considerations, the probability to avoid the Type II error was above 90% with an alpha set at 0.05 (College Station, Texas 77845 USA).

TABLE 4. Multivariable logistic regression model for 1-year mortality.

Variable	Odd ratio	Adjusted odd ratio	95% CI	*p* value
Lowest Ht during CPB	0.81	0.87	0.74–0.92	0.014
aPTT	1.04	1.03	1.01–1.08	0.0026
Anesthesiologist's experience				
Intermediate	6.95	1.93	0.60–80.6	0.118
Expert	22.8	7.92	1.73–301.87	0.017
Mechanical circulatory support				
IABP	5.20	2.97	1.62–16.44	0.005
VA-ECMO	83.93	33.11	4.95–1436.55	0.002
Other	1.93	0	0.15–24.77	0.280
Need of transfusion	10.17	2.91	2.41–42.94	0.001
MACE	3.93	2.41	1.28–12.18	0.016

CI, confidence intervals; Ht, hematocrit; CPB, cardiopulmonary bypass; aPTT, activated thromboplastin time; MCS, mechanical circulatory support; IABP, intra-aortic balloon pump; VA-ECMO; venous-arterial extracorporeal membrane oxygenator; MACE, major cardiovascular event; Adjusted OR, OR corrected for overoptimism after internal validation.

4. Results

Overall, 1052 patients were considered eligible during the study period. Among these, 21 declined to participate, 5 had ongoing myocardial infarction and/or preoperative hs-TnI ≥300 ng/L, 16 underwent left ventricular assist device implantation, 8 patients required salvage cardiac surgery, 2 were younger than 18 years old. Thus, the overall population consisted of 1000 open cardiac surgery procedures performed by 6 surgeons (median annual case volume 178) and 20 anesthesiologists (median annual case volume = 86). The overall in-hospital mortality was 2% (20 patients).

The results of the univariate predictors of 1-year mortality are depicted in Tables 1,2,3. Age ($p = 0.008$), New York Heart Association class ($p = 0.001$), ejection fraction ($p = 0.003$), history of atrial fibrillation ($p = 0.008$), chronic pulmonary disease ($p = 0.006$), cancer (0.045), prior pulmonary hypertension ($p = 0.007$), end-stage renal disease ($p = 0.016$), and Redo cardiac surgery ($p = 0.013$) were associated with 1-year mortality. Patients who died at 1 year were more often on potassium-sparing diuretics ($p = 0.002$), digoxin ($p = 0.001$) and statins ($p = 0.003$). Among the lab tests, only a low level of hemoglobin ($p = 0.001$), a long preoperative activated thromboplastin time ($p = 0.009$) and international normalized ratio ($p = 0.001$), and high creatinine value ($p = 0.001$) were significantly associated with 1-year mortality. Intraoperative variables associated to 1-year mortality were tricuspid valve surgery (31% vs 10.6%; $p = 0.003$), long cardiopulmonary bypass time (112 minutes vs 82 minutes; $p = 0.023$) and low hematocrit nadir on pump (22% vs 25%; $p = 0.001$). Postoperatively, serum peak creatinine ($p = 0.001$), use of mechanical circulatory support ($p = 0.001$), length of stay in the intensive care unit ($p = 0.001$), duration of mechanical ventilation ($p = 0.001$), as well as chest drainage volume ($p = 0.002$) were associated with 1-year mortality together with reintubation ($p = 0.01$), need of transfusion ($p = 0.001$), length of hospital stay and MACE ($p = 0.001$). Interestingly, in this univariate analysis, hs-TnI levels in patients who died are statically higher ($p < 0.05$) compared to those who survived at each time point, with the exception of those measured at 3–12 hours post-surgery. A multivariable analysis to identify independent predictors of 1-year mortality found that hematocrit nadir during cardiopulmonary bypass (OR: 0.81; 95% CI: 0.74–0.92), activated thromboplastin time (OR: 1.04; 95% CI: 1.01–1.08), expert anesthesiologist (OR: 22.8; 95% CI: 1.73–301.87), postoperative intra-aortic balloon pump (IABP) (OR: 5.20; 95% CI: 1.62–16.44), postoperative venous-arterial-extracorporeal membrane oxygenator (VA-ECMO) (OR: 83.93; 95% CI: 4.95–1436.55), need of transfusion (OR: 10.17; 95% CI: 2.41–42.94) and MACE (OR: 3.93; 95% CI: 1.28–12.18) were independently associated with 1-year mortality after controlling for several preoperative, intraoperative and postoperative variables. The final model was highly significant (Hosmer and Lemeshow chi-test = 4.82; $p = 0.77$) and well calibrated (**Supplemental Fig. 1**). After bootstrapping the mean slope shrinkage was 0.389. This adjusted the ORs as summarized in Table 4. The AUC of the model corrected for the optimism decreased from 0.96 (95% CI: 0.93–0.98) to 0.92 (95% CI: 0.89–0.94).

We repeated the univariate (**Supplemental Tables 2,3,4**) and the multivariable analysis to identify independent predictors of MACE at 30 days and we found that age (OR: 1.04; 95% CI: 1.02–1.05), reoperation (OR: 2.95; 95% CI: 1.66–5.33), and postoperative need of IABP (OR: 1.81; 95% CI: 1.18–2.93) were independently associated with MACE after adjusting for confounders. This model showed good discrimination and calibration as detected by a non-significant Hosmer-Lemeshow goodness of fit test ($p = 0.393$) and the calibration curve of the predicted and observed probabilities (**Supplemental Fig. 2**). The mean slope shrinkage factor after bootstrapping was 0.638 and led to adjusted ORs for all the predictors as reported in the **Supplemental Table 5**. The AUC corrected for optimism was 0.67 (95% CI: 0.63–0.71) from 0.72 (95% CI: 0.70–0.74).

5. Discussion

In a tertiary high-volume hospital for cardiac surgery, after controlling for several important co-variates, surgeon annual caseload had no effect on MACE at 30 days and 1-year mortality, while a greater anesthesiologist annual case volume increased mortality at 1 year with no effect on MACE at 30 days. In addition, hs-TnI showed no prognostic role on these outcomes.

The results of the present investigation are unique, since they address the association between surgeon and anesthesiologist caseload and unfavorable clinical outcomes with a long follow-up after cardiac surgery for the first time. Wilson *et al*. [18], for instance, observed that anesthesia provider's volume had no effect on the occurrence of major adverse events in patients undergoing major spine surgery, and only surgeon's annual case volume played a role in decreasing hospital length of stay. Memtsoudis *et al*. [3] found that the anesthesiologist experience did not affect the outcome, while a surgeon annual case volume >50 was associated with reduced complications and prolonged length of stay after joint arthroplasty surgery. Notably, the anesthesiologists did not affect the perioperative outcome, as reported by these publications. Thus, while there is a strong association between procedure volume and surgery outcomes in the context of cardiac surgery, especially for coronary bypass grafting, the relative contribution of surgeons and anesthesiologists is unknown. In fact, the team experience may be more important than the hospital volume itself. Consequently, a surgeon or anesthesiologist with a low caseload, although in a high-volume hospital, may perform worse than an expert surgeon or anesthesiologist who works in a medium-volume hospital [19]. Surprisingly, in the present study focusing on providers' skills we showed an inverse correlation between higher anesthesiologist caseload and 1-year mortality. This is somewhat counterintuitive and never reported previously. A possible explanation is that expert anesthesiologists usually manage more complex surgical cases, whereas younger anesthesiologists are assigned to easier procedures and are often supervised. As matter of fact, it is reasonable that the anesthesiologist's expertise may affect only 1-year mortality and not MACE. In fact, an expert anesthesiologist prevents and manages short-term complications better than a junior one, with little effect on patients' "natural history". Sicker patients suffer *per se* a worse outcome than a healthy population, regardless of the anesthesiologists' experience. In addition, surgeons' and anesthesiologists' performance, although complementary and synergic in the operating theatre, remains ontologically different. The surgical act is basically a "one man show", while the practice of anesthesia requires an integrated process involving several caregivers during the transitions between intraoperative and postoperative care. In other words, anesthesiologists work in a team and the association with 1-year mortality could be better interpreted as a marker of complex procedures. Our results confirmed that the anesthesiologist's caseload does not affect in-hospital mortality [4, 20].

The absence of any correlations between the hs-TnI dosage at several time-points and MACE at 30 days and 1-year mortality in patients with high complexity cardiac case-mix is another important finding. The lack of prognostic power of hs-TnI for impending postoperative complications may be due to several factors. The myocardial injury in cardiac surgery is essentially universal, decreasing hs-TnI value for the risk prediction after cardiac surgery. It is very well known that a more complicated perioperative course is associated with high levels of hs-TnI. Thus, it is reasonable that the association between hs-TnI and outcomes has been masked by the presence of other statistically strong independent variables which are epiphenomena of adverse events. For instance, predictors of MACE at 30 days were reoperation, advanced age and use of mechanical circulatory support. We know from the literature that all these factors are associated with higher release of hs-TnI compared to cases of uneventful hospital stay. The absence of correlations with mortality reported in our study is in line with Morone's trial in patients undergoing isolate coronary artery bypass grafting [21]. Therefore, the hs-TnI in patients undergoing cardiac surgery should be used to rule out worse outcomes rather than to predict adverse events.

The role of age and reoperation in increasing the odds of MACE at 30 days is well known in cardiac surgery. In fact, older age identifies patients with reduced cardiovascular reserve and a worse outcome, while reoperation relates to a population with a more complicated periprocedural course. Similarly the IABP is implanted as first line therapy in patients with cardiogenic shock after cardiac surgery [22].

Notably, excess 1-year mortality was higher in patients receiving postoperative IABP or VA-ECMO compared to the ones who did not, and proportional to the degree of hemodynamic support. As a consequence, mortality in patients on IABP was more than ten times lower compared to VA-ECMO, the former being implanted in patients with a less profound degree of postcardiotomy shock [23]. Nevertheless, our results confirmed that the implantation of any mechanical circulatory support detects both the sub-group of patients undergoing complex and prolonged procedures [24] and routine surgery complicated with unexpected technical difficulties (i.e., iatrogenic injury to a vital structure during surgery) [25].

The independent association between transfusion and 1-year mortality is confirmed in the present study. However, the excess mortality in transfused patients may be the expression of a more complex perioperative experience rather than a direct casual effect of the transfusion itself [26]. In fact, the administration of allogenic blood products aims at treating an underlying disease. The relevance of anemia on long-term outcome is somewhat confirmed by the fact that a lower hematocrit nadir during cardiopulmonary bypass leads to an increase in long-term mortality. The association between anemia, hemodilution and outcome has been already documented in the anesthesia literature [27].

The finding that baseline prolonged activated partial thromboplastin time remains related to the 1-year mortality after adjusting for several confounders may be the clinical manifestation of the use of heparin administration rather than the presence of a pending coagulopathy. As a matter of fact, heparin can be used as bridging therapy in patients with preoperative chronic fibrillation and/or Redo patients in whom the systemic anticoagulation is stopped before surgery. Both conditions are linked to a worse outcome by definition [28, 29].

As expected, the occurrence of major cardiovascular events at 30 days is significantly related to the risk of long-term mortality after recovery from surgery. Although intuitive, the long-term mortality of patients who recover sufficiently from MACE to be discharged from the hospital has not been adequately investigated after cardiac surgery. This result is not elusive and may have profound public health implications. In fact, the knowledge of the current burden of cardiovascular events following cardiovascular surgery allows clinicians to increase the surveillance on whom is at high risk of complications and the administrators to better allocate the resources required to address the problem.

The present investigation has strengths and limitations. This investigation is a single cardiac surgery center study, thus subjected to intrinsic bias due to the influence of specific procedures and a unique patient population. However, the inclusion of a relatively large number of patients along with a high number of preoperative, intraoperative, and postoperative risk factors included into the analysis may have balanced this limitation ensuring reliable single-center results. The effect of the echocardiographic skills of the individual anesthesiologists on outcome was not assessable in the present investigation due to the routine use of the transesophageal echocardiography, as recommended by several authors [30]. Nevertheless, we cannot exclude that the ability in imagining interpretation may have affected study results.

6. Conclusions

In conclusion, in a high-volume tertiary hospital, MACE at 30 days is predicted by advanced age, postoperative IABP insertion, and reoperation. Anesthesiologist- and surgeon-related annual case volumes do not affect this short-term outcome. On the contrary, 1-year mortality is independently and inversely associated with the anesthesiologist provider caseload, in addition to the relatively well-known risk factors confirmed in this study. This result, even if counterintuitive, depends on the hospital organization in which a more expert anesthesiologist takes care of more complex patients. Finally, the hs-TnI is not effective in predicting both MACE at 30 days and 1-year survival when important preoperative, intraoperative and postoperative variables are considered. Further studies are required to assess the strength and validity of the volume outcomes between providers in high-volume referral hospitals.

AUTHOR CONTRIBUTIONS

FM had full access to all the data in the study, take responsibility for the integrity of the data and the accuracy of the data analysis, did the drafting of the article. EF participated in conduct, reporting, interpretation of data and redaction of the manuscript. GB, GV and ML contributed to the study concept and design. GD, CN, CG did the acquisition of data. RL, CB and GS did the analysis and interpretation. EN, EC, MP participated in planning, conduct, reporting, acquisition of data, critical revision of the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study received approval by an independent Ethics Committee (Ethics Committee, San Raffaele Scientific Institute-IRCCS, Milan on 3rd of March). All study patients signed informed consent. All methods were carried out in accordance with relevant guidelines and regulations (Declaration of Helsinki).

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CONFLICT OF INTEREST

The authors declare no conflict of interest. Fabrizio Monaco is serving as one of the Editorial Board members of this journal. We declare that Fabrizio Monaco had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to JQ.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.signavitae.com/mre-signavitae/article/153735563841521254 4/attachment/Supplementary%20material.pdf.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. All data generated or analyzed during this study are included in this published article.

CONSENT FOR PUBLICATION

The manuscript does not contain any individual person's data in any form.

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