

**Cardiovascular Outcome in View of the Revised
Cardiac Risk Index and Geriatric Sensitive Cardiac
Risk Index in oldest-old Following Spinal Anesthesia**

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List of abbreviations

AF	Atrial fibrillation
ASA	American Society of Anaesthesiologists
AUC	Area under the curve
CA	Cardiac arrest
CI	Confidence interval
GSCRI	Geriatric sensitive cardiac risk index
HF	Heart failure
ICU	Intensive care unit
IDDM	Insulin dependent diabetes mellitus
IMC	Intermediate care
LOS	Length of hospital stay
MACE	Major adverse cardiac event
MI	Myocardial infarction
OR	Odds ratio
PACU	Post anesthesia care unit
RCRI	Revised Cardiac Risk Index
SA	Spinal anesthesia

1. English summary

1.1 Introduction

The proportion of "oldest-old people", those aged 80 or above (Encyclopedia.com), is rapidly increasing. By 2050, it is expected to triple, reaching 459 million people worldwide (United Nations, 2022) and 10 million in Germany, accounting for 13 % of the German population (Eisenmenger, 2006).

Meanwhile, the prevalence and severity of cardiovascular diseases increase significantly with age (Nanayakkara et al., 2018); the number of geriatric patients who need to be submitted to non-cardiac surgeries is increasing (Jeong et al., 2017). These high-risk elderly cardiac patients pose a significant challenge to anesthesiologists and surgeons.

Cardiovascular complications following non-cardiac surgery have been linked to a hospital mortality rate of 65% in cases of cardiac arrest (CA) and 25 % in cases of myocardial infarction (MI), according to studies conducted by Devereaux et al. (2005) and Sprung et al. (2003), as well as Chow et al. (2012). The latter reported greater susceptibility to these complications in older patients.

Therefore, accurate preoperative cardiac risk stratification is crucial for geriatric patients undergoing surgeries to determine the feasibility of surgery and develop individualized postoperative management plans to minimize perioperative complications.

The revised cardiac risk index (RCRI) (Lee et al., 1999) and the geriatric sensitive cardiac risk index (GSCRI) (Alrezk et al., 2017) are two of several risk indices available to assess the risk of postoperative major adverse cardiac event (MACE) after non-cardiac surgery. GSCRI was specifically designed for patients aged 65 years and older.

Spinal anesthesia (SA) is widely used in geriatric patients, particularly those classified as American Society of Anaesthesiologists (ASA) class III (Messina et al., 2013). According to several studies, it is a safe and effective anesthetic method for elderly patients undergoing hip surgeries (Matsuo et al., 2018) as well as lumbar spine

surgeries (Lessing et al., 2017). The use of SA has also been proven to improve postoperative outcomes (Jw et al., 1993). Although SA seems to be the preferred technique in geriatric

patients, it is not risk-free as it is associated with significant hemodynamic changes, as described in detail in previous studies (Lairez et al., 2015; Rooke et al., 1997).

Neither the RCRI nor the GSCRI take into account the type of anesthesia or the age factor of oldest-old patients, who may be at a higher risk of postoperative cardiac complications. This study hypothesized that the interaction between cardiovascular aging-induced hemodynamic changes (Lakatta et al., 1999 ; Priebe et al., 2000) and the hemodynamic changes associated with SA may differently impact the cardiovascular outcome and, as a result, affect the accuracy of the aforementioned indices in predicting the risk of postoperative MACE.

The main objective of this study was to evaluate the ability of RCRI and GSCRI to predict postoperative in-hospital MACE in patients aged 80 years and older who underwent surgeries under SA and to identify other potential risk factors for postoperative in-hospital MACE in this setting. The secondary objective was to investigate the association between the two risk indices and perioperative changes in blood pressure and heart rate, vasopressor requirements, need for postoperative intensive care unit (ICU) admission, and length of hospital stay (LOS).

1.2 Patients and methods

Design: Single-center retrospective observational cross-sectional cohort study.

The study involved a review of the electronic medical records of all patients aged 80 years or older who underwent surgery under SA at Klinikum Dortmund between January 2016 and September 2019. Patients were excluded from the study if they had undergone long operations that required additional general anesthesia, had more than one surgery during their hospital stay, or if their medical records contained incomplete data.

The study collected data on various potential preoperative cardiovascular risk factors, including all risk factors relevant to both indices. Additionally, intraoperative blood

pressure and heart rate values were recorded, along with any required use of vasopressors. In the post-anesthesia care unit (PACU), data was collected on initial, minimal, and final readings of blood pressure and heart rate. Postoperatively, the study recorded in-hospital MACE, defined as MI, CA, and heart failure (HF). The study also gathered data on in-hospital mortality, the need for postoperative ICU admission, and LOS.

MACE risk estimation using the RCRI and the GSCRI:

The RCRI assigns 1 point to each of six variables, including ischemic heart disease, heart failure, stroke or transient ischemic attack, insulin-dependent diabetes, serum creatinine level ≥ 2 mg/L, and high-risk surgery, with a maximum score of 6. Patients were categorized into 4 predicted risk classes (I, II, III, and IV) depending on the number of preoperative risk factors according to the RCRI. GSCRI, on the other hand, uses seven predictors, including history of stroke, ASA class, surgery type, functional status, serum creatinine level, history of heart failure, and diabetes, to estimate the risk of MACE. The predicted risk percentage for each patient was calculated (Qx MD), and the patients were stratified into 5 predicted risk classes (A, B, C, D, and E), with cut-off values similar to those of the RCRI as shown in table 1.

Tab. 1: The revised cardiac risk index (RCRI) and the geriatric sensitive cardiac risk index (GSCRI) risk classes with their corresponding expected risk percentages. N.: number. Fayed et al (2023)

RCRI	Class	I	II	III	IV	
	N. of predictors	0	1	2	≥ 3	
	Risk %	0.4	0.9	6.6	11	
GSCRI	Class	A	B	C	D	E
	Risk %	≤ 0.4	$>0.4 - \leq 0.9$	$>0.9 - \leq 6.6$	$>6.6 - \leq 11$	>11

Statistical analysis

Descriptive statistics:

The statistical analysis was conducted using R version 4.1.1. The numeric variables were presented as median and interquartile ranges. The Wilcoxon rank-sum test was employed for non-parametric data, while Fischer's exact test and chi-square test were

used for categorical data. Categorical variables were presented as counts and percentages. The level of statistical significance was set at 0.05.

External validation of the RCRI and GSCRI:

1- Discrimination (C statistics) evaluates the ability of the risk index to distinguish patients who experienced MACE from those who did not through the estimation of the area under the curve (AUC). An AUC below 0.7 is considered poor discrimination.

2- Calibration evaluates whether the predicted risks using the indices were comparable to the observed risks. The calibration plots visually compared the observed and predicted risks, while the Chi-square Goodness of Fit test assessed whether the observed and predicted risk values were significantly different.

3-Clinical utility (net benefit and decision curve analysis) evaluates the clinical usefulness of the risk prediction models.

The models were updated by adding more predictors identified through the regression analysis in order to improve their fit for the external validation cohort.

Four models have been studied: the univariate (original) models of the RCRI and the GSCRI and the multivariate models (after introducing other risk factors identified through the regression analysis).

Because a predictive model is typically expected to perform better in the original derivation sample than in new but similar samples, a bootstrap analysis was used to evaluate the multivariable models' performance in the external validation cohort. It was performed through 100- times resampling, and calibration curves that relate the predicted probability to the observed number of events were produced.

The study's secondary outcome was assessed by performing Spearman's correlation.

This study was written following the World Medical Association Declaration of Helsinki. (World Medical Association, 2013)

1.3 Results

In this study, 1042 electronic medical records were screened, and 836 patients were included, as depicted in Figure 1. From a surgical perspective, 7.2% of the surgeries

were categorized as high-risk procedures and 54.1% of the patients underwent non-elective surgeries. Interestingly, the majority of patients (65.3%) and a significant portion of those experiencing in-hospital MACE (82.5%) underwent trauma surgery.

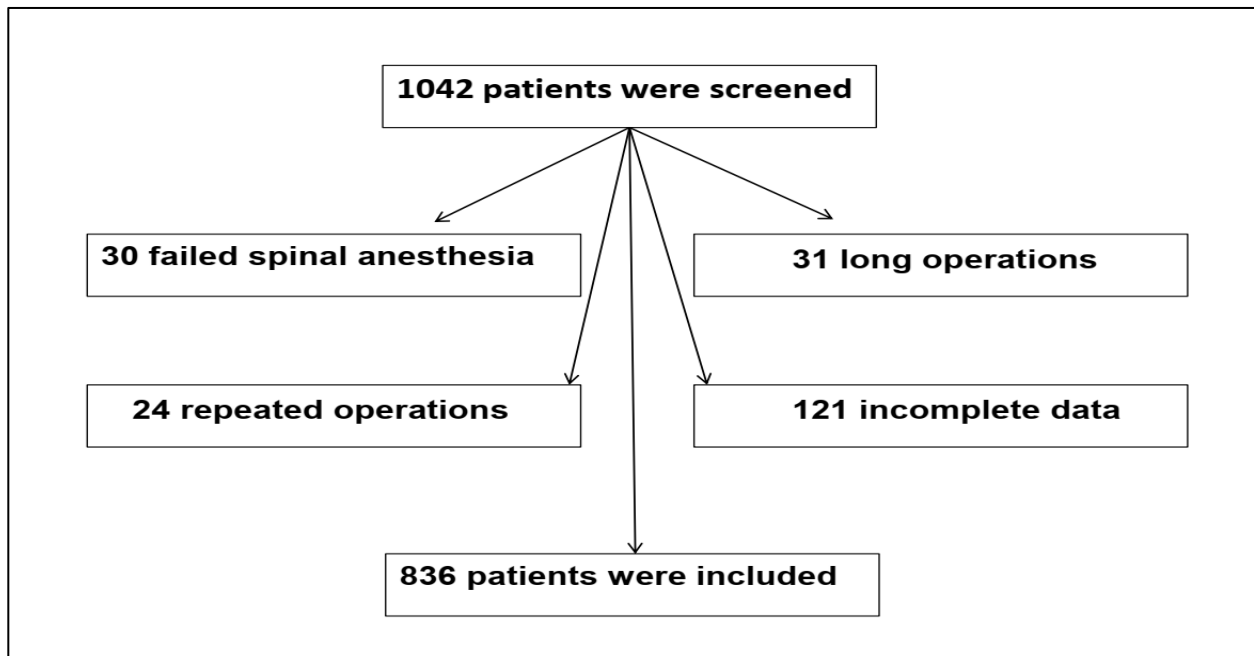


Fig. 1: Study flowchart. Fayed et al (2023)

The prevalence of preoperative coronary artery disease, cerebrovascular events, and heart failure did not exhibit statistically significant differences when comparing patients with and without in-hospital MACE. Conversely, several factors not included in the design of both indices, such as aortic stenosis, pre-existing atrial fibrillation, and pulmonary hypertension, demonstrated a notably high prevalence among patients experiencing in-hospital MACE, as illustrated in Table 2. Patients with in-hospital MACE had significantly lower blood pressure and a higher heart rate than those without in-hospital MACE, as shown in table 3. Intraoperative data analysis revealed significant differences between patients who experienced MACE and those who did not. Notably, individuals with MACE had prolonged surgery duration, increased requirements for blood and fluid transfusions, higher reliance on vasopressor support and more frequent need for invasive monitoring. These findings are summarized in Table 4. Postoperative outcomes, as presented in table 5, highlight that out of 836 patients, 63 (7.5%) encountered at least one MACE, resulting in a total of 81 events. The mortality rate among those who experienced MACE stood

at 60.3% (38 out of 63 cases). Additionally, the incidence of postoperative acute kidney injury, pulmonary artery embolism, and ICU admissions was significantly higher among patients who suffered-MACE.

Tab. 2: Patients' preoperative characteristics and relevant clinical data across MACE status. MACE: major adverse cardiac events; N: number of the patients; ASA: American Society of Anaesthesiology risk class; PD: partial dependent; TD: total

Parameter	Overall N (%) 836 (100)	No MACE N (%) 773 (100)	MACE N (%) 63 (100)	p-value
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dependent; TI: total independent; RCRI: revised cardiac risk index; GSCRI: geriatric sensitive cardiac risk index; NIDDM: non-insulin dependent diabetes mellitus; IDDM: insulin dependent diabetes mellitus; ACEI: angiotensin-converting enzyme inhibitor; PAOD: peripheral arterial occlusive disease; COPD: chronic obstructive pulmonary disease; P value: indicates significance when comparing patients with and without postoperative MACE; ¹ Median (IQR). Fayed et al (2023)

Sex	Male	398 (47.6)	371 (48.0)	27 (42.9)	0.432
	Female	438 (52.4)	402 (52.0)	36 (57.1)	
¹ Age (years)		85 (82, 89)	85 (82,89)	87 (80,91)	0.0001
ASA	1	6 (0.7)	6 (0.8)	0 (0.0)	0.0001
	2	119 (14.2)	117 (15.1)	2 (3.2)	
	3	499 (59.7)	473 (61.2)	26 (41.3)	
	4	212 (25.4)	177 (22.9)	35 (55.6)	
Functional status	PD	610 (73.0)	564 (73.0)	46 (73.0)	0.0001
	TD	110 (13.2)	93 (12.0)	17 (27.0)	
	TI	116 (13.9)	116 (15.0)	0 (0.0)	
Type of surgery	General	4 (0.5)	4 (0.5)	0 (0.0)	0.0001
	Gynecological	3 (0.4)	3 (0.4)	0 (0.0)	
	Orthopedic	16 (1.9)	16 (2.1)	0 (0.0)	
	Trauma	546 (65.3)	494 (63.9)	52 (82.5)	
	Urological	195 (23.3)	192 (24.8)	3 (4.8)	
	Vascular	72 (8.6)	66 (8.5)	6 (9.5)	
RCRI Class	1	381 (45.6)	364 (47.1)	17 (27.0)	0.002
	2	244 (29.2)	226 (29.2)	18 (28.6)	
	3	131 (15.7)	114 (14.7)	17 (27.0)	
	4	80 (9.6)	69 (8.9)	11 (17.5)	
Parameter		Overall N (%) 836 (100)	No MACE N (%) 773 (100)	MACE N (%) 63 (100)	p-value
GSCRI Class	A	116 (13.9)	116 (15)	0 (0)	0.0001
	B	280 (33.5)	263 (34)	17 (27)	
	C	325 (38.9)	296 (38.3)	29 (46)	
	D	45 (5.4)	35 (4.5)	10 (15.9)	
	E	70 (8.4)	63 (8.2)	7 (11.1)	
¹ Preoperative creatinine		1.03 (0.83,1.34)	1.02 (0.82,1.31)	1.35 (0.99,2.0)	<0.001
¹ Postoperative creatinine		1.03 (0.75,1.51)	0.99 (0.75,1.42)	1.66 (1.08,2.76)	<0.001

¹ Preoperative Hemoglobin		12.3 (10.9,13.4)	12.3 (10.9,13.0)	11.9 (10.1,13.1)	0.051
¹ Postoperative Hemoglobin		10.1 (9.3,11.2)	10.2 (9.4,11.2)	9.7 (8.7,10.7)	0.052
Aortic stenosis		46 (5.5)	37 (4.8)	9 (14.3)	0.007
Other valve disease		59 (7.1)	54 (6.9)	5 (7.9)	0.1
Atrial fibrillation		232 (27.8)	197 (25.5)	35 (55.6)	0.0001
Heart failure		186 (22.2)	168 (21.7)	18 (28.6)	0.2
Myocardial infarction		83 (9.9)	79 (10.2)	4 (6.3)	0.323
Coronary artery disease		217 (26.0)	195 (25.2)	22 (34.9)	0.05
Arterial hypertension		591 (70.7)	544 (70.4)	47 (74.6)	0.478
Pulmonary hypertension		16 (1.9)	11 (1.4)	5 (7.9)	0.005
Diabetes mellitus	No	613 (73)	571 (74)	42 (66)	0.021
	Yes	223 (26.7)	202 (26.1)	21 (33.3)	
	NIDDM	126 (15)	120 (15.5)	6 (9.5)	
	IDDM	97 (11.6)	82 (10.6)	15 (22)	
Renal impairment		162 (19.4)	139 (18.0)	23 (36.5)	0.0001
PAOD		85 (10.1)	80 (10.3)	5 (7.9)	0.27
Cerebrovascular events		123 (14.7)	115 (14.9)	8 (12.7)	0.639
Pace maker		68 (8.1)	61 (7.9)	7 (11.1)	0.369
Beta Blocker		379 (45.3)	347 (44.9)	32 (50.8)	0.365
ACEI		380 (45.5)	355 (45.9)	25 (39.7)	0.339
COPD		125 (15.0)	114 (14.8)	11 (17.5)	0.567

Tab. 3: The intraoperative and immediate postoperative blood pressure and heart rate changes across MACE status. PACU: post- anesthesia care unit; MP: measured parameter; BL: baseline values; Low: lowest value; End; end value; S: systolic blood pressure; D: diastolic blood pressure; HR: heart rate; MACE: major adverse cardiac events; P: indicates significant value when comparing patients with and without postoperative MACE. Data are expressed as the median (IQR). Fayed et al (2023)

	Intraoperative								PACU		
Group	MP	BL	5m.	10m.	15m.	20m.	Low	End	BL	Low	End
Overall	S	170 (150, 180)	150(130, 160)	140(120, 150)	130(115, 150)	130(110, 140)	110 (90, 130)	130 (115, 145)	125 (110, 140)	110(10, 130)	130(120, 140)
	D	90 (80,100)	76 (70,85)	70 (60,80)	70 (60,75)	65 (60,75)	60 (50, 70)	70 (60, 80)	60 (60, 80)	60 (50, 60)	65 (60, 75)
	HR	80 (70, 90)	76 (68,86)	75 (65,85)	73 (63,83)	70 (60,80)	65 (59, 75)	70 (61, 82)	65 (60, 80)	60 (55, 70)	68 (60, 80)
No MACE	S	170(150, 180)	150(130, 160)	140(120, 150)	130(117, 150)	130(110, 140)	110(100, 130)	130(115, 150)	130(110, 140)	110(100, 130)	130(120, 140)
	D	90 (80,100)	80 (70,90)	70 (60,80)	70 (60,80)	65 (60,75)	60 (50, 70)	70 (60, 80)	60 (60, 80)	60 (50,60)	65 (60, 75)
	HR	80 (70, 90)	76 (67,86)	75 (65,84)	72 (63,82)	70 (60,80)	64 (59, 75)	70 (61, 81)	65 (60, 80)	60 (55,70)	67 (60, 80)
MACE	S	150(130, 170)	130(110, 141)	120(110, 136)	110(100, 134)	110(100, 125)	100 (90,110)	120(100, 131)	120(100, 140)	100(90, 120)	115(100, 129)
	D	80 (68, 90)	70 (60,80)	60 (60,70)	60 (55,70)	60 (55,66)	50 (40, 60)	60 (60,70)	60 (50,68)	50 (40,60)	60 (55, 64)
	HR	82 (74,100)	84 (70,95)	80 (70,93)	80 (66,92)	78 (64,91)	70 (60,85)	80 (63,90)	72 (60,89)	67 (55,80)	72 (64, 90)
P S.		0.0001	0.001	0.0001	0.0001	0.0001	0.0001	0.0001	0.024	0.001	0.0001
P D.		0.0001	0.001	0.0001	0.0001	0.0001	0.0001	0.0001	0.001	0.0001	0.0001
P HR		0.008	0.007	0.004	0.004	0.003	0.007	0.004	0.139	0.011	0.01

Tab. 4: Intraoperative data across MACE status. Patients with MACE had a statistically significant longer duration of surgery, required more transfusion and vasopressor support, and should have been invasively monitored more frequently compared to those without MACE. N: number of the patients; MACE: major adverse cardiac events; B.T.: blood transfusion; D.S.: duration of surgery; VP: vasopressor; Norad.: noradrenaline; I.M.: invasive monitoring; P: indicates significance when comparing patients with and without MACE. ¹ Data are expressed as the median (IQR). Fayed et al (2023)

Parameter N (%)	B.T. N (%)	¹ Fluids (L)	¹ D.S. (min.)	VP N (%)	Norad. N (%)	Akrinor N (%)	Atropin N (%)	I. M N (%)
Overall 836(100)	196 (23.4)	0.5(0.5 ,1.0)	80 (55, 105)	260 (31.1)	82 (9.8)	231 (27.6)	18 (2.2)	133 (15.9)
No MACE 773 (100)	172 (22.2)	0.5(0.5 ,1.0)	80 (55, 105)	221 (28.6)	57 (7.4)	202 (26.1)	16 (2.1)	111 (14.4)
MACE 63(100)	24 (38.0)	1.0(0.5 , 1.0)	90 (70, 120)	39 (61.9)	25 (39.7)	29 (46.0)	2 (3.2)	22 (34.9)
P	0.015	0.003	0.007	0.0001	0.0001	0.0001	0.561	0.0001

Tab. 5: Postoperative in-hospital outcome distributed across MACE status. Patients with MACE had statistically significantly higher incidences of postoperative pulmonary embolism (PE), acute kidney injury (AKI), and ICU/IMC admission, while the length of hospital stay (LOS) and the incidence of postoperative cerebrovascular events (CVE) were insignificant. MACE: major adverse cardiac event; HF: heart failure; MI: myocardial infarction; CA: cardiac arrest; ICU: intensive care unit; IMC: intermediate care; N: number of patients; P value: indicates significance when comparing patients with and without postoperative MACE. ¹ Median (IQR). Fayed et al (2023)

Parameter	HF N %	MI N %	CA N %	CVE N %	PE N %	AKI N %	Death N %	ICU N %	IMC N %	¹ LOS
Overall N: 836	41 4.9	10 1.2	30 3.58	7 0.8	3 0.4	17 2.0	39 4.7	57 6.8	94 11.2	8(4, 12)
No MACE N: 773	0 0.0	0 0.0	0 0.0	6 0.8	0 0.0	6 0.8	1 0.1	24 3.1	81 10.5	8(5, 12)
MACE N: 63	41 65.0	10 15.9	30 47.6	1 1.6	3 4.8	11 17.5	38 60.3	33 52.4	13 20.6	8(4, 14)
P	<0.0001			0.497	0.0001			0.014	0.6	

The regression analysis highlighted statistically significant associations between certain factors and poor postoperative cardiovascular outcomes. Specifically: undergoing trauma surgery, increased age, and presence of AF. However, associations between adverse postoperative cardiovascular outcomes and preoperative coronary artery disease, cerebrovascular events, and HF did not reach statistical significance (Table 6).

Tab. 6: Regression analysis of the potential cardiovascular-related risk factors. Increasing age, atrial fibrillation, trauma surgery, aortic stenosis, pulmonary hypertension, preoperative renal failure, and insulin-dependent diabetes mellitus were statistically significantly associated with poor postoperative cardiovascular outcome, while the association between cerebrovascular events, coronary artery disease, and heart failure did not reach statistical significance. OR: odds ratio; C.I: confidence interval; ACEI: Angiotensin converting enzyme inhibitor. Fayed et al (2023)

Parameters	OR	95 % C.I	P value
Coronary artery disease	1.67	0.05 – 0.09	0.06
Myocardial infarction	0.754	0.29 – 1.93	0.54
Heart failure	1.40	0.79 – 2.49	0.25
Cerebrovascular events	0.81	0.37 – 1.75	0.59
Peripheral vascular disease	1.07	0.47 – 2.44	0.85
Renal failure	2.75	1.60 – 4.72	0.0004
Insulin dependent diabetes mellitus	2.54	1.36 – 4.73	0.005
Aortic stenosis	3.250	1.49 – 7.07	0.007
Other valve diseases	1.10	0.42 – 2.86	0.83
Pulmonary hypertension	5.86	1.97 – 17.4	0.005
Arterial hypertension	1.15	0.65 – 2.06	0.61
Beta blocker treatment	1.31	0.78 – 2.18	0.29
ACEI treatment	0.80	0.48 – 1.35	0.41
Atrial fibrillation	3.77	2.24 – 6.35	<0.0001
Pace maker	1.43	0.62 – 3.27	0.41
Trauma surgery	2.03	1.10 – 3.74	0.02
Haemoglobin < 10gm /dl	0.80	0.48 – 1.35	0.42
Age	1.09	1.03 – 1.14	0.0007

External validation: The ability of both indices to discriminate between different outcomes was limited as revealed through the C-statistics. For RCRI, the AUC was 0.69 (with a 95% CI of 0.70 to 0.83), while for GSCRI, it was 0.68 (with a 95% CI of 0.83 to

0.93), as demonstrated in figure 2. Regarding calibration, The Chi-square goodness-of-fit test showed that the RCRI underestimated the MACE risk in all classes, while the GSCRI underestimated the risk in the B, C, and D classes and overestimated the risk in class E (table 7). The calibration plots also confirmed this miscalibration (figure 3).

Tab. 7: Calibration of both indices. The Chi-square Goodness-of-Fit test showed that RCRI underestimated the MACE risk in all classes while GSCRI underestimated the risk in the B, C, and D classes and overestimated the risk in class E. MACE: major adverse cardiac events; RCRI: revised cardiac risk index; GSCRI: geriatric sensitive cardiac risk index; N: number of patients. Fayed et al (2023)

Index	Risk class	N	Expected MACE % Median (IQR)	Observed MACE N (%)	P Value
RCRI	I	381	0.4 (0.4,0.4)	17 (4.5)	0.0001
	II	244	0.9 (0.9,0.9)	18 (7.4)	
	III	131	6.6 (6.6,6.6)	17 (13)	
	IV	80	11 (11,11)	11 (13.8)	
GSCRI	A	116	0.3 (0.2,0.3)	0 (0.0)	0.00001
	B	280	0.9 (0.9,0.9)	17 (6.1)	
	C	325	1.9 (1.5,3)	29 (8.9)	
	D	45	8.3 (7.2,10.1)	10 (22.2)	
	E	69	18.3 (13.1,28.6)	7 (10.1)	

Update of the models: The regression analysis revealed that for each additional year beyond 80, the odds of MACE increased by 9%. Additionally, patients with AF had a 3.77-fold increased likelihood of experiencing MACE, while those undergoing trauma surgery were 2.03 times more likely to encounter such events. Upon incorporating these risk factors into the models, there was a noticeable enhancement in their discriminative ability. The AUC improved to 0.798 (95% CI: 0.73, 0.85) for the multivariable RCRI and to 0.777 (95% CI: 0.702, 0.83) for the multivariable GSCRI, as depicted in Figure 2. Furthermore, calibration curves of the multivariate RCRI and GSCRI, supported by a bootstrap analysis, indicated significant improvements in predictive accuracy of the multivariable GSCRI as demonstrated through minimal disparities between expected and observed outcomes up to a 40% risk threshold. Conversely, the multivariable RCRI exhibited discrepancies, particularly underestimating risk within a 10-20% risk index range and overestimating risk beyond a 20% incidence. Notably, alignment between expected and observed outcomes was only achieved when the risk was below 10%, as illustrated in figure 4.

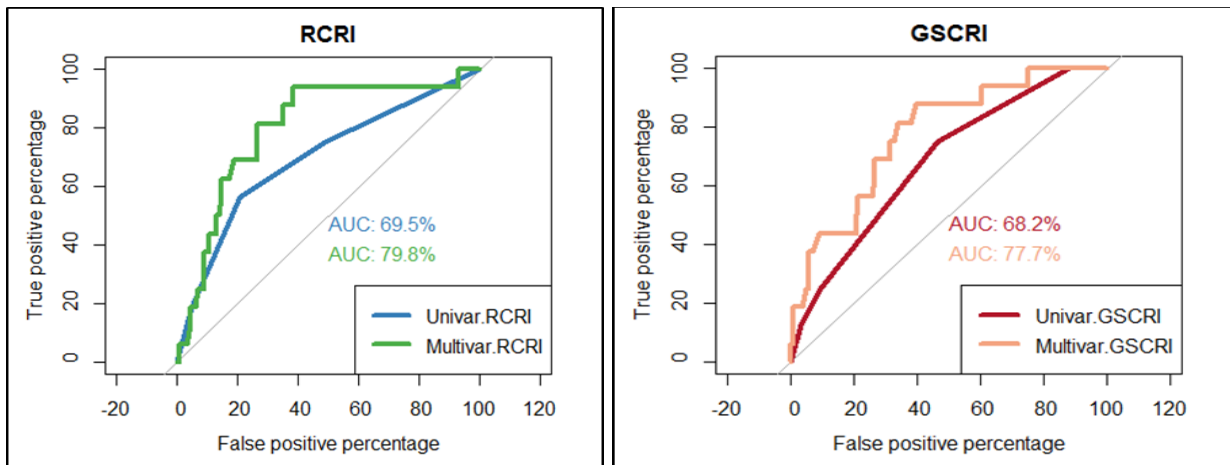


Fig. 2: C statistics of the univariate and multivariate RCRI and GSCRI. The area under the receiver operating characteristic curve (AUC) for the univariate indices indicated a limited discriminative ability. This has improved in multivariate indices (after the introduction of age, atrial fibrillation (AF), and trauma surgery as risk factors). RCRI: revised cardiac risk index; GSCRI: geriatric sensitive cardiac risk index. Fayed et al (2023)

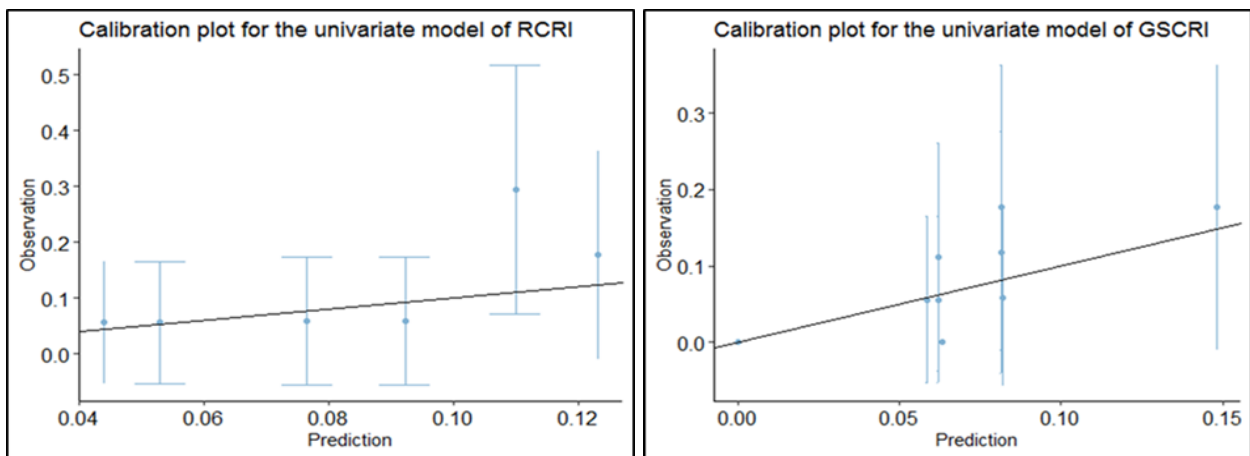


Fig. 3: Calibration plots for the RCRI and GSCRI univariate models. The ideal calibration plot is represented by a straight line starting from 0 and dividing the graphs into two similar halves. The purpose of a calibration plot is to demonstrate how much the observed probabilities (y-axis) are identical to the predicted probabilities (x-axis). The black line in the two graphs is the best fitting line through the first 10 observation probabilities and their corresponding prediction probabilities. The greater the similarity of this line to the ideal line, the better the model is. The points on the calibration plots represent the first 10 observation probabilities from the dataset, and the line around each point is the confidence interval level. Regarding the GSCRI plot, the slope of the line is higher than that of the RCRI, which gives the impression that the GSCRI is more accurate than the RCRI model. RCRI: revised cardiac risk index; GSCRI: geriatric sensitive cardiac risk index. Fayed et al (2023)

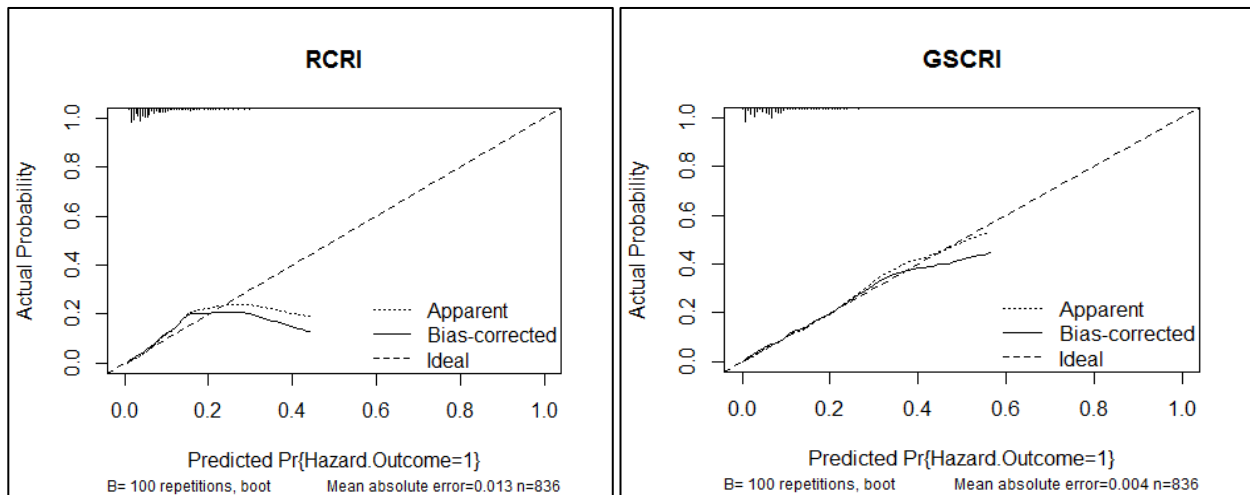


Fig. 4: Calibration curve of the multivariate (after the introduction of age, trauma surgery, and atrial fibrillation) RCRI and GSCRI with bootstrap resampling validation for predicting the risk MACE in the training set. The dashed line indicated the ideal model in which the predicted and actual probabilities were perfectly identical; the dotted line indicated actual performance with apparent accuracy; and the solid line presented a bootstrap-corrected estimate of the calibration curve. Fayed et al (2023)

In the decision curve analysis, the multivariable GSCRI demonstrated superior clinical utility, particularly at an expected risk of 10% or higher, whereas, the multivariable RCRI exhibited slightly better clinical utility overall, as depicted in Figure 5.

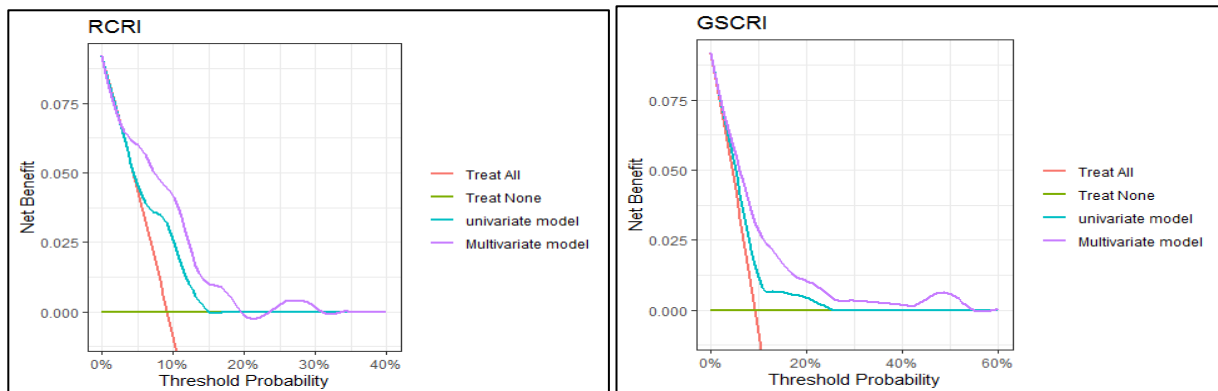


Fig. 5: Decision curve analysis. The curve with the highest value of net benefit at a particular risk threshold has the highest clinical utility. Patients must have at least a 10 % chance of having the hazard outcome to be checked by the index. The orange and green lines assume that all patients are treated as high-risk or low-risk, respectively. RCRI; revised cardiac risk index; GSCRI: geriatric sensitive cardiac risk index. The multivariate model of RCRI has a slightly better net benefit than the univariate model, while the multivariate GSCRI shows a superior net benefit compared to the univariate model. Multiplying the value of the net benefit by 1000 gives the number of net true positives per 1000 patients. Fayed et al (2023)

Both indices demonstrated statistically significant evidence of negligible correlations with blood pressure and heart rate changes, vasopressors need, ICU admission, and LOS (correlation coefficients < 0.3 in all cases), as shown in table 8. There was no reported data on post-SA complications, including convulsions, total spinal block, epidural hematoma, or postoperative neurological defects.

Tab. 8: Correlation of clinically relevant perioperative parameters and both indices. There is statistically significant evidence of negligible correlations between indices and perioperative blood pressure and heart rate changes, vasopressor requirements, postoperative IMC/ICU admission, and length of hospital stay. The correlation coefficients are less than 0.3 in all cases. RCRI: revised cardiac risk index; GSCRI: geriatric sensitive cardiac risk index; 0: at baseline; Low: lowest value; End: values at the end of the operation; PACU: post-anesthesia care unit. Fayed et al (2023)

Parameters	Correlation Coefficient (Sig. (2 tailed))	
	RCRI	GSCRI
Systolic blood pressure 0	-0.092 (0.008)	-0.063 (0.068)
Diastolic blood pressure 0	-0.067 (0.053)	-0.022 (0.519)
Intraoperative systolic blood pressure Low	-0.096 (0.005)	-0.124 (0.000)
Intraoperative diastolic blood pressure Low	-0.117 (0.001)	-0.149 (0.000)
Systolic blood pressure End	-0.105 (0.002)	-0.105 (0.002)
Diastolic blood pressure End	-0.085 (0.014)	-0.101 (0.003)
Heart rate 0	-0.017 (0.622)	0.016 (0.647)
Intraoperative heart rate Low	-0.059 (0.089)	-0.012 (0.735)
Vasopressor need	0.059 (0.089)	0.097 (0.005)
PACU systolic blood pressure Low	-0.083 (0.032)	-0.085 (0.028)
PACU diastolic blood pressure Low	-0.142 (0.000)	-0.148 (0.000)
Postoperative IMC admission	0.168 (0.000)	0.206 (0.000)
Postoperative ICU admission	0.140 (0.000)	0.109 (0.002)
Length of hospital stay	0.170 (0.000)	0.144 (0.000)

1.4 Discussion

1.4.1 Key-Findings

This study investigated the effectiveness of both the RCRI and GSCRI in assessing the risk of postoperative in-hospital MACE among the oldest-old patients undergoing surgery under SA. Additionally, it explored the correlation between these indices and

postoperative ICU admission rates and postoperative LOS. The study found that both indices had limited ability to estimate the risk of postoperative MACE and showed poor correlation with ICU admission and LOS. However, when additional risk factors such as increasing age, AF, and trauma surgery were incorporated into the indices, the performance of GSCRI improved while RCRI remained limited in predictive ability and clinical utility.

1.4.2 Choice of RCRI and GSCRI

The selection of RCRI and GSCRI was based on recommendations from the European Society of Cardiology/European Society of Anesthesiology guidelines (Kristensen et al., 2014), which suggest using two risk scales for preoperative estimation of postoperative MACE.

1.4.3 Performance of the indices in derivation studies

In the derivation studies of RCRI and GSCRI, both indices demonstrated good discriminative ability for detecting postoperative MACE, with an AUC of 0.76 for both. However, when RCRI was applied to the GSCRI dataset, the AUC dropped to 0.63 (13 % reduction). A subgroup analysis based on age in the GSCRI derivation study also showed lower discriminative ability in patients over 85 years of age, which aligns with the findings of this study.

1.4.4 Causes of poor performance of both indices

The suboptimal performance of both indices when externally validated in our patients can be attributed to several differences between the current study and the original validating studies.

1.4.4.1 Surgery as a risk factor

Differences in the urgency and types of surgeries could contribute to the poor performance of both indices. The original validating study of RCRI (Lee et al., 1999) included only elective surgeries, while GSCRI (Alrezk et al., 2017) excluded emergency surgeries. In contrast, our study encompassed both elective and non-elective surgeries,

including trauma surgery and emergency vascular surgeries. Numerous studies have demonstrated that urgent and emergency surgeries increase the incidence of MACE, supporting our findings (Kumar et al., 2001; Mullen et al., 2017; Puelacher et al., 2018). Trauma surgery, in particular, poses additional risks due to its non-elective nature and association with systemic inflammation, leading to worse cardiovascular outcomes (Amar et al., 2007; Goris et al., 1985; Nuytinck et al., 1988).

1.4.4.2 Atrial fibrillation as a risk factor

Atrial fibrillation as a predictive risk factor was not considered in the design of both indices, yet it was significantly prevalent in patients with MACE in our study. Many previous studies have extensively studied its association with perioperative morbidity and worse outcomes (Aggarwal et al., 2013; Hollenberg et al., 2000; Wang et al., 2016).

1.4.4.3 Increasing age as a risk Factor

The mean age in the RCRI and GSCRI cohorts (66 and 74 years, respectively) was lower than the mean age in the current study (85.9 years). In agreement with our results, previous studies have consistently demonstrated age as a risk factor for postoperative MACE (Banco et al., 2021; Hansen et al., 2016; Liu et al., 2020).

1.4.4.4 Cardiovascular risk factors for both indices

In this study, we explored the cardiovascular risk factors associated with MACE according to both indices. Interestingly, the prevalence of prior cerebrovascular events, coronary artery disease, and HF, did not show a statistically significant difference when comparing patients with and without postoperative in-hospital MACE. Moreover, the association between these risk factors and postoperative MACE did not reach statistical significance in the regression analysis. The non-predictive value of cerebrovascular events in this study may explain the overestimation of MACE incidence in risk class E, according to the GSCRI. Revising the data for risk class E showed that out of a total of 69 patients, 91.3 % (63/69) had a prior history of cerebrovascular events, which is considered a risk factor in the GSCRI but not in our study. This observation aligns with another study by Liu et al. (2020), which found no independent association between

cerebrovascular events and perioperative cardiac complications in elderly patients with coronary artery disease undergoing non-cardiac operations.

The positive impact of recent advancements in coronary artery disease management on short-term mortality, cardiac death, and myocardial infarction (Ahmad et al., 2022; Chacko et al., 2020), and the nature of the surgeries in our study (trauma, vascular, and urological), which only required thoracic dermatome sensory level block (minimized the hypotensive effects of SA and subsequent coronary hypoperfusion), might explain the non-predictive value of coronary artery disease in this study.

Considering patients with HF, SA may be a favorable choice due to its minimal reduction in blood pressure, avoidance of tachycardia, and preservation of myocardial contractility. These factors likely contribute to the non-significant difference in the prevalence of HF between patients with and without postoperative MACE. However, the lack of data regarding the phenotype, duration, and severity of HF limits our ability to draw definitive conclusions.

In the current study, 5.5 % of the patients had aortic stenosis, with 11 diagnosed as severe cases, while 1.9 % had pulmonary hypertension. The decision to administer SA to patients with severe aortic stenosis might have been influenced by the urgency of the operations, which limited the possibility of comprehensive preoperative cardiac assessment, and the diagnosis of severe aortic stenosis likely occurred postoperatively.

1.4.4.5 Spinal anesthesia as a supposed factor

One notable difference between our study and the derivation studies of both indices is the restriction to SA in the current study. SA has been found to have no association with altered odds of adverse cardiovascular outcomes in high-risk patients undergoing non-cardiac surgery (Rodgers et al., 2000) or even has been associated with reduced incidence of postoperative MI, pulmonary embolism, and mortality (Leslie et al., 2016). The POISE trial (Leslie et al., 2013), however, reported an increased risk of adverse cardiovascular outcomes with neuraxial block. It's important to note that the trial included patients who had combined general anesthesia and thoracic epidural block within the category of "neuraxial block," which may have led to the higher odds of adverse

outcomes in the neuraxial group compared to patients who had only general anesthesia. However, SA as the sole anesthetic technique was not associated with a high incidence of MACE (OR: 0.89) or MI (OR: 0.74) when compared to general anesthesia in that trial.

The in-hospital postoperative MACE incidence in our study was 7.5 %. A study by Sazgary et al. (2020) reported a higher postoperative MACE incidence of 15.2 % in high-risk cardiac patients. What might elucidate the elevated occurrence of MACE observed in the compared study is the longer duration of study (30 days versus focusing solely on in-hospital outcomes), the variances in anaesthetic approaches (general and SA versus exclusively SA), and the screening to detect non-symptomatic MACE in the compared study versus our study which depended only on the clinical presentation. In another study focusing on patients aged over 80 with coronary artery disease, the occurrence of postoperative MACE was notably higher at 19.4% (Liu et al., 2020). Variances between their findings and ours arise from the longer study duration of 30 days and the utilization of both general and neuraxial anesthesia in the compared study. Conversely, Sabaté et al. (2011) documented a much lower MACE rate of 4.3%. This contrast could be attributed to factors like the younger average age (67 years compared to our study's 85.9 years), lower percentage of high-risk surgeries (5.2% versus our study's 7.17%) and non elective surgery (7.1% versus our study's 54.1%) and better ASA scores (55.4% ASA II versus our study's 85.1% ASA III and IV). Moreover, the absence of trauma surgeries in the Sabaté et al. study might contribute to this disparity.

1.4.5 Secondary Outcome: The study also examined secondary outcomes such as postoperative ICU admission, LOS, blood pressure and heart rate changes, and vasopressor requirements. It found no significant correlation between the indices and these outcomes, which was expected given that both indices underestimated the likelihood of postoperative MACE, which is typically associated with ICU admission, prolonged LOS, and hemodynamic instability requiring vasopressor treatment.

1.4.6 Study limitations

This study is limited by retrospective, single-center design, smaller number of events than the recommended 100 MACE events, and the short-term (in-hospital) outcome.

1.5 Summary

In Germany, the proportion of oldest-old people is expected to reach 10 million by 2050 accounting for 13 % of the population. The prevalence and severity of cardiovascular diseases increase significantly with advancing age which explains the role of cardiovascular complications as the most important cause of postoperative morbidity and mortality after non-cardiac surgery in geriatric patients. Spinal anaesthesia is preferred for its potential to mitigate perioperative complications in geriatric patients. Therefore accurate preoperative cardiac risk stratification is crucial in this setting for tailored perioperative care. RCRI and GSCRI were designed to predict postoperative MACE. To date, no study has validated both risk indices in the oldest old patients undergoing surgery under spinal anaesthesia. This study aimed to evaluate the predictive accuracy of RCRI and GSCRI in assessing the incidence of postoperative MACE in patients aged 80 and above undergoing surgery under spinal anaesthesia. Additionally, it aimed to explore additional risk factors. The secondary outcome was to correlate both indices with ICU admission and length of hospital stay.

A retrospective, single centre study. Data from 836 patients were analyzed, categorizing them into risk classes based on RCRI and GSCRI. The predictive performance of the indices was tested in terms of the occurrence of postoperative in hospital MACE defined as myocardial infarction, cardiac arrest, or heart failure through discrimination, calibration and clinical utility. Furthermore, we have investigated the correlation of both indices with perioperative blood pressure and heart rate changes, vasopressor requirement, postoperative ICU admission and length of hospital stay using the appropriate statistical methods.

The study included 836 patients of whom 52.4 % were female. The occurrence rate of MACE stood at 7.5 %. The prevalence of preoperative coronary artery disease, cerebrovascular events, and heart failure was not significantly different when comparing patients with and without MACE, furthermore these factors did not reach a statistical significance in the regression analysis. 82.5% of the patients with postoperative MACE were submitted to trauma surgery and 55.6% had pre-existing atrial fibrillation. Both indices had limited discriminative ability (AUC for RCRI and GSCRI were 0.69 and 0.68

respectively) and underestimated the predicted risk according to the calibration plots. Upon regression analysis, it was observed that the likelihood of MACE rose by 9% with each passing year beyond the age of 80. Additionally, patients undergoing trauma surgery had a 2.03 times higher risk of encountering MACE, while those with atrial fibrillation faced a 3.77 times higher risk. Incorporating these factors into both indices through multivariable models significantly improved their ability to discern risks, with the AUC reaching 0.798 for RCRI and 0.777 for GSCRI. Bootstrap analysis revealed an enhancement in predictive capability for the multivariate GSCRI model, while the multivariate RCRI was still of limited predictive value. Decision curve analysis highlighted the superior clinical utility of the multivariate GSCRI over the multivariate RCRI. However, both indices showed weak correlations with postoperative intensive care unit admission and length of hospital stay.

Both the RCRI and GSCRI exhibited limited predictive capability for postoperative in-hospital MACE and displayed poor correlations with perioperative changes in blood pressure and heart rate, as well as ICU admission and length of stay in oldest-old patients undergoing surgery under spinal anaesthesia. Enhancements made to both indices, incorporating age, atrial fibrillation, and trauma surgery, notably improved the predictive ability and clinical utility of the multivariable GSCRI, while the multivariate RCRI did not see similar improvements. These findings highlight the need for improved risk assessment tools tailored to the oldest-old undergoing surgery under spinal anaesthesia.

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2. Publication

External Validation of the Revised Cardiac Risk Index and the Geriatric-Sensitive Perioperative Cardiac Risk Index in Oldest Old Patients Following Surgery Under Spinal Anaesthesia; a Retrospective Cross-Sectional Cohort Study

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Background: The Revised Cardiac Risk Index (RCRI) and the Geriatric Sensitive Cardiac Risk Index (GSCRI) estimate the risk of postoperative major adverse cardiac events (MACE) regardless of the type of anesthesia and without specifying the oldest old patients. Since spinal anesthesia (SA) is a preferred technique in geriatrics, we aimed to test the external validity of these indices in patients ≥ 80 years old who underwent surgery under SA and tried to identify other potential risk factors for postoperative MACE.

Methods: The performance of both indices to estimate postoperative in-hospital MACE risk was tested through discrimination, calibration, and clinical utility. We also investigated the correlation between both indices and postoperative ICU admission and length of hospital stay (LOS).

Results: The MACE incidence was 7.5%. Both indices had limited discriminative (AUC for RCRI and GSCRI were 0.69 and 0.68, respectively) and predictive abilities. The regression analysis showed that patients with atrial fibrillation (AF) were 3.77 and those with trauma surgery were 2.03 times more likely to exhibit MACE, and the odds of MACE increased by 9% for each additional year above 80. Introducing these factors into both indices (multivariable models) increased the discriminative ability (AUC reached 0.798 and 0.777 for RCRI and GSCRI, respectively). Bootstrap analysis showed that the predictive ability of the multivariate GSCRI but not the multivariate RCRI improved. Decision curve analysis (DCA) showed that multivariate GSCRI had superior clinical utility when compared with multivariate RCRI. Both indices correlated poorly with postoperative ICU admission and LOS.

Conclusion: Both indices had limited predictive and discriminative ability to estimate postoperative in-hospital MACE risk and correlated poorly with postoperative ICU admission and LOS, following surgery under SA in the oldest-old patients. Updated versions by introducing age, AF, and trauma surgery improved the GSCRI performance but not the RCRI.

Keywords: geriatric, anesthetic techniques, subarachnoid, risk, major adverse cardiac event

Introduction

Worldwide, the proportion of people aged 80 years or older, defined as the “oldest-old persons”¹ is growing even faster than that of older people overall and is projected to triple, from 157 million in 2022 to 459 million in 2050.² In Germany, over 6 million people were at least 80 years old in 2020. This number is expected to reach 10 million in 2050, representing a share of 13%.³

Seventy-two% of Germans above the age of 65 suffer from cardiovascular diseases⁴ and the cardiovascular diseases per se are the leading cause of death in approximately 40% of the reported mortalities in Germany.⁵ Meanwhile, the

prevalence and severity of cardiovascular diseases increase significantly with age,⁶ currently with the recent advances in surgery and anesthetic practice, the number of geriatric patients who need to be submitted to non-cardiac surgery is increasing⁷ so that we are confronted each day with oldest-old high-risk cardiac patients who should undergo non-cardiac surgery. Cardiovascular complications are the most important causes of morbidity and mortality in the first 30 days after non-cardiac surgery. Postoperative cardiac arrest (CA) and myocardial infarction (MI) are associated with a hospital mortality rate of 65%^{8,9} and 25%^{10,11} respectively, with more susceptibility in older patients.¹²

In various aspects, SA seems to be a well-accepted anesthetic technique that is supposed to reduce perioperative complications in geriatric patients, particularly in those older than 90 years with hip fractures¹² and those with American Society of Anaesthesiologists class (ASA) III.¹³ It is also considered as a safe and successful anesthetic modality for elderly patients undergoing particular surgeries^{14–16} with some evidence of improved postoperative outcome scores including consciousness, respiration, circulation, laboratory tests, and blood loss.¹⁷ Thus, accurate preoperative cardiac risk stratification in this age group, and under this preferred anesthetic technique, is essential for perioperative individualized decision-making about surgical feasibility and postoperative management.

Risk indices have been developed to aid in preoperative cardiac risk assessment. The RCRI,¹⁸ which is widely used to estimate perioperative risk, was derived and validated in patients undergoing non-cardiac surgeries without identifying any age group, while the GSCRI¹⁹ was validated to estimate the probability of perioperative MI or CA in patients >65 years following non-cardiac surgery. Yet, both indices did not consider the type of anesthesia or specify the oldest-old patients in whom postoperative cardiac complications are more prevalent.

The hemodynamic changes of the cardiovascular aging^{20–22} and the SA associated hemodynamic effects in healthy²³ and cardiac²⁴ elderly patients were extensively investigated and described in details in previous studies.

Our hypothesis was that the interaction between the hemodynamic changes of aging and that of SA could affect the postoperative cardiovascular outcome and subsequently influence the ability of the previously mentioned indices to precisely estimate the risk of postoperative MACE.

Aim of the study: the primary outcome was to test the performance of the RCRI and the GSCRI (through their external validation) in terms of the occurrence of postoperative in-hospital MACE in patients ≥ 80 years old who were submitted to surgery under SA and try to identify other potential risk factors for postoperative in-hospital MACE in this setting. The secondary outcome was to correlate both indices with the perioperative blood pressure and heart rate changes, vasopressor requirements, postoperative ICU admission, and LOS.

Patients and Methods

Inclusion and Exclusion Criteria

This retrospective cross-sectional cohort study was performed at Klinikum Dortmund, a tertiary-care teaching hospital with over 33,000 operations per year. The study protocol was approved by Universitätsklinikum Bonn, Germany (29.12.2020) under the following serial number DV 571/2020. Ethical approval was waived and consent to participate is not required as being retrospective study. Patient data confidentiality was completely respected and the information was used only for research purposes. All methods were carried out in accordance with the relevant guidelines and regulations.

The electronic medical files of all patients ≥ 80 years who had undergone surgery under SA from January 2016 to September 2019 were revised.

Exclusion Criteria

Long operations that mandated additional general anesthesia, more than one operation during hospital admission, and files with incomplete data.

Collected Data

Potential preoperative cardiovascular risk factors, including all risk factors for both indices.

Intraoperative blood pressure and heart rate values and required vasopressors.

Post-anesthesia care unit: initial, minimal, and final readings of blood pressure and heart rate. Postoperative in-hospital MACE (defined as MI, CA, and heart failure (HF)), in-hospital mortality, the need for postoperative intermediate care (IMC)/ ICU admission, and LOS.

Risk Estimation Using the RCRI and the GSCRI

The RCRI risk score was calculated by 1-point assignment for each of the following variables: 1) history of ischemic heart disease 2) heart failure 3) stroke or transient ischemic attack 4) insulin-dependent diabetes mellitus 5) serum creatinine level ≥ 2 mg / L and 6) high-risk surgery (intra-thoracic, vascular and intra-peritoneal), for a maximum score of 6.

Patients were categorized into 4 risk classes (I, II, III, and IV) depending on the number of preoperative risk factors according to the RCRI. The GSCRI depends on the following predictors to estimate the risk of postoperative MACE: 1) history of stroke 2) ASA class 3) surgery type 4) functional status 5) serum creatinine level 6) history of HF 7) diabetes mellitus. The predicted risk percentage for each patient was calculated²⁵ and the patients were stratified into 5 risk classes (A, B, C, D, and E), with cut-off values similar to those of the RCRI. Table 1 demonstrates the RCRI and GSCRI risk classes and the corresponding expected postoperative MACE risk percentages according to the number of risk predictors.

Statistical Analysis

Descriptive Statistics

Statistical analysis was done using R version 4.1.1. Numeric variables were presented in the median and interquartile ranges, as they were not normally distributed. Wilcoxon rank-sum test was used for non-parametric data. Categorical variables were presented by count and %. Fischer's exact test and chi-square test were used for categorical data. Statistical significance is set at 0.05.

External Validation of the RCRI and the GSCRI

1. Discrimination: C-statistics, the area under the curve (AUC), was used to assess discrimination. This measure assesses whether patients who experience the outcome have a higher predicted risk than patients who do not. AUC of 0.60 means that 60% of all patients who had MACE were classified as high risk according to the indices, AUC < 0.7 is considered poor discrimination, while an AUC of 0.7–0.8 is usually considered good and 0.9 is excellent.
2. Calibration determines whether the absolute predicted risks are similar to the observed risks. Both calibration plots and the Chi-square Goodness-of-fit test were used to assess the risk predictive ability of both indices.
3. Clinical utility was evaluated using net benefit (NB) (which puts benefits and harms on the same scale and is conveniently expressed in the unit of true positives or true negatives) and decision curve analysis (DCA) (which considers the consequences of using risk prediction models and making decisions based on risk thresholds).

Model Update

This aims to adjust the model to better fit the external validation cohort by adding more predictors (according to the regression analysis). Because a prediction model is expected to perform better in the original derivation sample than in new but similar samples, a bootstrap analysis was performed.

Table 1 The Revised Cardiac Risk Index (RCRI) and the Geriatric Sensitive Cardiac Risk Index (GSCRI) Risk Classes with Their Corresponding Expected Risk Percentages

RCRI	Classes	I	II	III	IV	
	Number of predictors	0	1	2	≥ 3	
	Risk %	0.4	0.9	6.6	11	
GSCRI	Classes	A	B	C	D	E
	Risk %	≤ 0.4	$>0.4 - \leq 0.9$	$>0.9 - \leq 6.6$	$>6.6 - \leq 11$	>11

Statistical Procedures

The data set was divided into 2 parts to assess the model performance, 80% to train the model and 20% to test the model and assess the prediction ability of the model.

Four models have been created: the univariate models of the RCRI and the GSCRI and the multivariate models (by introducing age, trauma surgery, and AF).

Bootstrap Analysis

Resampling was performed 100 times and calibration curves that relate the predicted probability to the observed number of events were produced.

NB: the number of net true positives and negatives per 1000 patients was calculated by using this equation:

Net true positive/1000 patients = $1000 * (\text{true positive/number} - \text{false positive/number} * \text{risk threshold} / (1 - \text{risk threshold}))$

Net true negative/1000 patients = $1000 * (\text{true negative/number} - \text{false negative/number} * (1 - \text{risk threshold}) / \text{risk threshold})$

The study's secondary outcome was assessed by performing Spearman correlation.

This study was written following the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) Statement,²⁶ and the World Medical Association Declaration of Helsinki.²⁷

Results

The total number of candidates was 1042 patients and only 836 patients were included in the study, as shown in Figure 1.

The median age was 85 (82–89) years and 52.4% of subjects were female. From the surgical point of view, 54.1% of the patients underwent non-elective surgeries, 7.2% of all surgeries were high-risk, and the majority of the patients (65.3%) and most of those who had experienced in-hospital MACE (82.5%) underwent trauma surgery. The distribution of the patients across RCRI risk classes showed that most of the patients were classified as risk class I (45.6%). However, the majority of the patients and most of those who experienced in-hospital MACE were classified as risk class C according to the GSCRI. Some factors that were not considered in the design of both indices, such as pre-existing AF, pulmonary hypertension, and aortic stenosis, showed high statistically significant prevalence in patients with in-hospital MACE. Prevalence of preoperative cerebrovascular events, coronary artery disease, and HF was not statistically

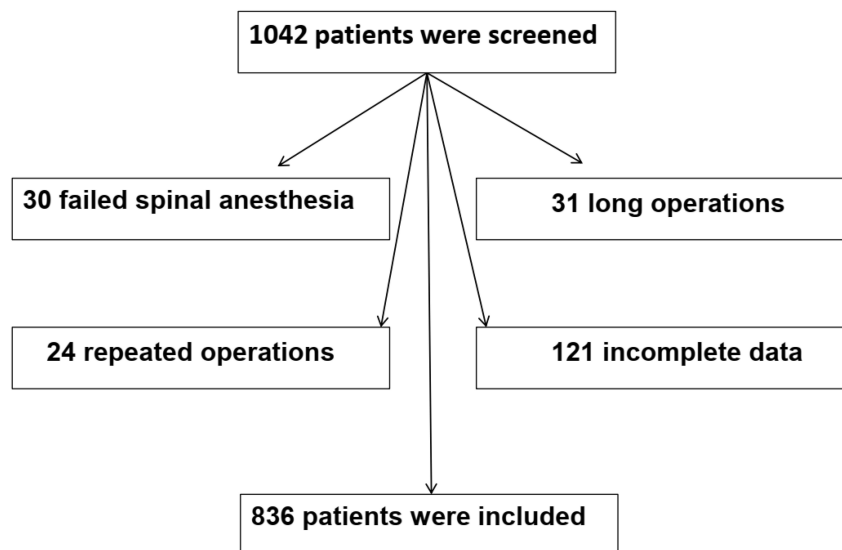


Figure 1 Study flowchart.

significantly different when comparing those with and without in-hospital MACE. The preoperative patient characteristics and cardiovascular-related risk factors distributed across MACE status are presented in Table 2.

Intraoperative and immediate postoperative systolic and diastolic blood pressure and heart rate changes showed that patients with in-hospital MACE had significantly lower blood pressure and higher heart rate than those without in-hospital MACE (Table 3).

Table 2 Patients' Preoperative Characteristics and Relevant Clinical Data Across MACE Status

Parameter		Overall N (%) 836 (100)	No MACE N (%) 773 (100)	MACE N (%) 63 (100)	p-value
Sex	Male	398 (47.6)	371 (48.0)	27 (42.9)	0.432
	Female	438 (52.4)	402 (52.0)	36 (57.1)	
Age (years) ^a		85 (82, 89)	85 (82, 89)	87 (80, 91)	0.0001
ASA	I	6 (0.7)	6 (0.8)	0 (0.0)	0.0001
	2	119 (14.2)	117 (15.1)	2 (3.2)	
	3	499 (59.7)	473 (61.2)	26 (41.3)	
	4	212 (25.4)	177 (22.9)	35 (55.6)	
Functional status	Partial dependent	610 (73.0)	564 (73.0)	46 (73.0)	0.0001
	Total dependent	110 (13.2)	93 (12.0)	17 (27.0)	
	Total independent	116 (13.9)	116 (15.0)	0 (0.0)	
Type of surgery	General	4 (0.5)	4 (0.5)	0 (0.0)	0.0001
	Gynecological	3 (0.4)	3 (0.4)	0 (0.0)	
	Orthopedic	16 (1.9)	16 (2.1)	0 (0.0)	
	Trauma	546 (65.3)	494 (63.9)	52 (82.5)	
	Urological	195 (23.3)	192 (24.8)	3 (4.8)	
	Vascular	72 (8.6)	66 (8.5)	6 (9.5)	
RCRI Class	I	381 (45.6)	364 (47.1)	17 (27.0)	0.002
	2	244 (29.2)	226 (29.2)	18 (28.6)	
	3	131 (15.7)	114 (14.7)	17 (27.0)	
	4	80 (9.6)	69 (8.9)	11 (17.5)	
GSCRI Classes	A	116 (13.9)	116 (15)	0 (0)	0.0001
	B	280 (33.5)	263 (34)	17 (27)	
	C	325 (38.9)	296 (38.3)	29 (46)	
	D	45 (5.4)	35 (4.5)	10 (15.9)	
	E	70 (8.4)	63 (8.2)	7 (11.1)	
Preoperative creatinine ^a		1.03 (0.83, 1.34)	1.02 (0.82, 1.31)	1.35 (0.99, 2.0)	<0.001
Postoperative creatinine ^a		1.03 (0.75, 1.51)	0.99 (0.75, 1.42)	1.66 (1.08, 2.76)	<0.001
Preoperative Hemoglobin ^a		12.3 (10.9, 13.4)	12.30 (10.9, 13.0)	11.9 (10.1, 13.1)	0.051
Postoperative Hemoglobin ^a		10.1 (9.3, 11.2)	10.2 (9.4, 11.2)	9.7 (8.7, 10.7)	0.052

(Continued)

Table 2 (Continued).

Parameter		Overall N (%) 836 (100)	No MACE N (%) 773 (100)	MACE N (%) 63 (100)	p-value
Aortic stenosis		46 (5.5)	37 (4.8)	9 (14.3)	0.007
Other valve disease		59 (7.1)	54 (6.9)	5 (7.9)	0.1
Atrial fibrillation		232 (27.8)	197 (25.5)	35 (55.6)	0.0001
Heart failure		186 (22.2)	168 (21.7)	18 (28.6)	0.2
Myocardial infarction		83 (9.9)	79 (10.2)	4 (6.3)	0.323
Coronary artery disease		217 (26.0)	195 (25.2)	22 (34.9)	0.05
Arterial hypertension		591 (70.7)	544 (70.4)	47 (74.6)	0.478
Pulmonary hypertension		16 (1.9)	11 (1.4)	5 (7.9)	0.005
Diabetes mellitus	No	613 (73)	571 (74)	42 (66)	0.021
	Yes	223 (26.7)	202 (26.1)	21 (33.3)	
	NIDDM	126 (15)	120 (15.5)	6 (9.5)	
	IDDM	97 (11.6)	82 (10.6)	15 (22)	
Renal impairment		162 (19.4)	139 (18.0)	23 (36.5)	0.0001
PAOD		85 (10.1)	80 (10.3)	5 (7.9)	0.27
Cerebrovascular events		123 (14.7)	115 (14.9)	8 (12.7)	0.639
Pace maker		68 (8.1)	61 (7.9)	7 (11.1)	0.369
Beta Blocker		379 (45.3)	347 (44.9)	32 (50.8)	0.365
ACEI		380 (45.5)	355 (45.9)	25 (39.7)	0.339
COPD		125 (15.0)	114 (14.8)	11 (17.5)	0.567

Notes: P value: indicates significance when comparing patients with and without postoperative MACE; *Median (IQR).

Abbreviations: MACE, major adverse cardiac events; N., patient number; ASA, American Society of Anaesthesiology risk class; RCRI, revised cardiac risk index, GSCRI, geriatric sensitive cardiac risk index, NIDDM, non-insulin dependent diabetes mellitus; IDDM, insulin dependent diabetes mellitus; ACEI, angiotensin- converting enzyme inhibitor; PAOD, peripheral arterial occlusive disease; COPD, chronic obstructive pulmonary disease.

Concerning other intraoperative data, patients who had experienced in-hospital MACE, had a statistically significant longer duration of surgery, required more blood and fluid transfusion, more vasopressor support, and should have been invasively monitored more frequently compared to those without in-hospital MACE as shown in [Table 4](#).

The postoperative outcome, including MACE, was presented in [Table 5](#). Sixty-three patients had at least one MACE (7.5%) with a total record of 81 major adverse cardiac events and a mortality rate of 60.3% (38/63). A statistically significantly higher incidence of pulmonary artery embolism, postoperative acute kidney injury, and ICU admissions also accompanied the occurrence of MACE.

The regression analysis demonstrated that increased age, AF, trauma surgery, aortic stenosis, pulmonary hypertension, renal failure, and insulin-dependent diabetes mellitus (IDDM) were statistically significantly associated with the poor postoperative cardiovascular outcome while the association between cerebrovascular events; coronary artery disease, and HF did not reach statistical significance ([Table 6](#)).

External Validation

Discrimination: the C-statistics showed that both indices had limited discriminative ability. The AUC for RCRI was 0.69 (95% CI: 0.70, 0.83) and for GSCRI was 0.68 (95% CI: 0.83, 0.93) ([Figure 2](#)).

Table 3 The Intraoperative and the Immediate Postoperative Blood Pressure and Heart Rate Changes Across MACE Status. Patients with in-Hospital MACE Had Statistically Significantly Lower Blood Pressure and Higher Heart Rate Compared to Those Without in-Hospital MACE

	Intraoperative								PACU		
Group	MP	BL	5m.	10m.	15m.	20m.	Low	End	BL	Low	End
Total	Sys	170 (150, 180)	150 (130, 160)	140 (120, 150)	130 (115, 150)	130 (110, 140)	110 (90, 130)	130 (115, 145)	125 (110, 140)	110 (100, 130)	130 (120, 140)
	Dias	90 (80, 100)	76 (70, 85)	70 (60, 80)	70 (60, 75)	65 (60, 75)	60 (50, 70)	70 (60, 80)	60 (60, 80)	60 (50, 60)	65 (60, 75)
	HR	80 (70, 90)	76 (68, 86)	75 (65, 85)	73 (63, 83)	70 (60, 80)	65 (59, 75)	70 (61, 82)	65 (60, 80)	60 (55, 70)	68 (60, 80)
No MACE	Sys	170 (150, 180)	150 (130, 160)	140 (120, 150)	130 (117, 150)	130 (110, 140)	110 (100, 130)	130 (115, 150)	130 (110, 140)	110 (100, 130)	130 (120, 140)
	Dias	90 (80, 100)	76.53 (12.6)	70 (60, 80)	70 (60, 80)	65 (60, 75)	60 (50, 70)	70 (60, 80)	60 (60, 80)	60 (50, 60)	65 (60, 75)
	HR	80 (70, 90)	76 (67, 86)	75 (65, 84)	72 (63, 82)	70 (60, 80)	64 (59, 75)	70 (61, 81)	65 (60, 80)	60 (55, 70)	67 (60, 80)
MACE	Sys	150 (130, 170)	130 (110, 141)	120 (110, 136)	110 (100, 134)	110 (100, 125)	100 (90, 110)	120 (100, 131)	120 (100, 140)	100 (90, 120)	115 (100, 129)
	Dias	80 (68, 90)	70 (60, 80)	60 (60, 70)	60 (55, 70)	60 (55, 66)	50 (40, 60)	60 (60, 70)	60 (50, 68)	50 (40, 60)	60 (55, 64)
	HR	82 (74, 100)	84 (70, 95)	80 (70, 93)	80 (66, 92)	78 (64, 91)	70 (60, 85)	80 (63, 90)	72 (60, 89)	67 (55, 80)	72 (64, 90)
P Sys		0.0001	0.001	0.0001	0.0001	0.0001	0.0001	0.0001	0.024	0.001	0.0001
P Dias		0.0001	0.001	0.0001	0.0001	0.0001	0.0001	0.0001	0.001	0.0001	0.0001
P HR		0.008	0.007	0.004	0.004	0.003	0.007	0.004	0.139	0.011	0.01

Notes: P: indicates significant value when comparing patients with and without postoperative MACE. Data are expressed as median (IQR).

Abbreviations: PACU, post anesthesia care unit; MP, measured parameter; BL, baseline values; low, lowest value; Sys, Systolic blood pressure; Dias, diastolic blood pressure; HR, heart rate; MACE, major adverse cardiac events.

Table 4 Intraoperative Blood and Fluid Transfused, Vasoactive Medications Required, Duration of Surgery and the Need for Preoperative Invasive Monitoring Distributed Across MACE Status. Patients with MACE Had a Statistically Significant Longer Duration of Surgery, Required More Transfusion and Vasopressor Support, and Should Have Been Invasively Monitored More Frequently Compared to Those Without MACE

Parameter	B.T. N. (%)	Fluids (mL) ^a	D.S. (min.) ^a	VP N. (%)	Norad. N. (%)	Alrinor N. (%)	Atropin N. (%)	I. M. N. (%)
Total 836 (100%)	196 (23.4)	500 (500, 1000)	80 (55, 105)	260 (31.1)	82 (9.8)	231 (27.6)	18 (2.2)	133 (15.9)
No MACE 773 (100%)	172 (22.2)	500 (500, 1000)	80 (55, 105)	221 (28.6)	57 (7.4)	202 (26.1)	16 (2.1)	111 (14.4)
MACE 63 (100%)	24 (38.0)	1000 (500, 1000)	90 (70, 120)	39 (61.9)	25 (39.7)	29 (46.0)	2 (3.2)	22 (34.9)
P	0.015	0.003	0.007	0.0001	0.0001	0.0001	0.561	0.0001

Notes: P: indicates significance when comparing patients with and without MACE. ^aData are expressed as median (IQR).

Abbreviations: MACE, major adverse cardiac events; B.T., blood transfusion; D.S., duration of surgery; VP, vasopressor; Norad., noradrenaline; I.M., invasive monitoring.

Table 5 Postoperative in-Hospital Outcome Distributed Across MACE Status. Patients with MACE Had Statistically Significantly Higher Incidences of Postoperative Pulmonary Embolism (PE), Acute Kidney Injury (AKI), and ICU/IMC Admission, While the Length of Hospital Stay (LOS) and the Incidence of Postoperative Cerebrovascular Events (CVE) Were Insignificant

Parameter	HF	MI	CA	CVE	PE	AKI	Death	ICU	IMC	LOS ^a
	N.(%)	N.(%)	N.(%)	N.(%)	N.(%)	N.(%)	N.(%)	N.(%)	N.(%)	
Total, N:836	41(4.9)	10(1.2)	30 (3.58)	7(0.8)	3(0.4)	17(2.0)	39(4.7)	57 (6.8)	94(11.2)	8 (4, 12)
No MACE, N:773	0(0.0)	0(0.0)	0(0.0)	6(0.8)	0 (0.0)	6 (0.8)	1(0.1)	24(3.1)	81(10.5)	8 (5, 12)
MACE, N:63	41(65.07)	10(15.9)	30(47.6)	1(1.6)	3(4.8)	11(17.5)	38(60.3)	33(52.4)	13(20.6)	8 (4, 14)
P	<0.0001			0.497	0.0001				0.014	0.6

Notes: P value: indicates significance when comparing patients with and without postoperative MACE. ^aMedian (IQR).

Abbreviations: MACE, major adverse cardiac event, HF, heart failure, MI, myocardial infarction, CA, cardiac arrest; ICU, intensive care unit; IMC, intermediate care; N, number of patients.

Regarding calibration, The Chi-square Goodness-of-Fit test showed that the RCRI underestimated the MACE risk in all risk classes while the GSCRI underestimated the risk in the B, C, and D classes and overestimated the risk in class E. (Table 7) The calibration plots (Figure 3) also confirmed this miscalibration.

Update of the Models

The regression analysis (Table 6) showed that patients with AF were 3.77 and those with trauma surgery were 2.03 times more likely to exhibit MACE, and the odds of MACE increased by 9% for each additional year above 80. Introducing these risk factors into the models improved their discriminative ability as the AUC reached 0.798 (95% CI: 0.73, 0.85) for the multivariable RCRI and 0.777 (95% CI: 0.702, 0.83) for the multivariable GSCRI (Figure 2).

Calibration curves of the multivariate (after introducing age, trauma surgery, and atrial fibrillation) RCRI and GSCRI with a bootstrap resampling validation indicated that the predictive ability of the multivariable GSCRI has improved as there are few differences between the ideal and the apparent lines up to 40% risk. The multivariable RCRI underestimates the risk between a risk index of 10–20% and overestimates the risk when the incidence is >20% and matches only when the risk is lower than 10% as evidenced by the huge difference between the ideal and the apparent lines (Figure 4).

The multivariable RCRI showed a slightly better clinical utility, while the multivariable GSCRI showed superior clinical utility at ≥10% expected risk, as shown by the DCA (Figure 5).

Table 6 Regression Analysis of the Potential Cardiovascular Related Risk Factors. Increasing Age, Atrial Fibrillation, Trauma Surgery, Aortic Stenosis, Pulmonary Hypertension, Preoperative Renal Failure, and Insulin- Dependent Diabetes Mellitus Were Statistically Significantly Associated with Poor Postoperative Cardiovascular Outcome While the Association Between Cerebrovascular Events, Coronary Artery Disease, and Heart Failure Did Not Reach Statistical Significance

Parameters	OR	95% C.I.	P value
Coronary artery disease	1.67	0.05–0.09	0.06
Myocardial infarction	0.754	0.29–1.93	0.54
Heart failure	1.40	0.79–2.49	0.25
Cerebrovascular events	0.81	0.37–1.75	0.59
Peripheral vascular disease	1.07	0.47–2.44	0.85
Renal failure	2.75	1.60–4.72	0.0004
Insulin-dependent diabetes mellitus	2.54	1.36–4.73	0.005
Aortic stenosis	3.250	1.49–7.07	0.007
Other valve diseases	1.10	0.42–2.86	0.83
Pulmonary hypertension	5.86	1.97–17.4	0.005
Arterial hypertension	1.15	0.65–2.06	0.61
Beta blocker treatment	1.31	0.78–2.18	0.29
Angiotensin converting enzyme inhibitor treatment	0.80	0.48–1.35	0.41
Atrial fibrillation	3.77	2.24–6.35	<0.0001
Pace maker	1.43	0.62–3.27	0.41
Trauma surgery	2.03	1.10–3.74	0.02
Haemoglobin < 10 gm /dl	0.80	0.48–1.35	0.42
Age	1.09	1.03–1.14	0.0007

Abbreviations: OR, Odds Ratio; C.I., confidence interval.

Secondary Outcome

Correlations of both indices with blood pressure and heart rate changes, vasopressors need, ICU admission, and LOS are shown in Table 8. Our results showed statistically significant evidence of negligible correlations between both indices and the previously mentioned clinical parameters, with correlation coefficients of less than 0.3 in all cases.

There was no reported data on post-SA complications, including convulsions, total spinal block, epidural hematoma, or postoperative neurological defects.

Discussion

This retrospective study reported a limited ability of RCRI and GSCRI to predict postoperative in-hospital MACE and a poor correlation of both indices with postoperative ICU admission and LOS following surgery under SA in the oldest-old patients. Implementing other potential risk factors such as increasing age, AF, and trauma surgery into both indices has improved the performance of the GSCRI, while RCRI was still of limited predictive ability and clinical utility.

We selected these two indices, in particular, following the European Society of Cardiology/European Society of Anesthesiology (ESC/ESA) guidelines,²⁸ which have recommended using two risk scales for preoperative estimation of postoperative MACE: the Surgery Risk Calculator of the American College of Surgeons-National Surgical Quality

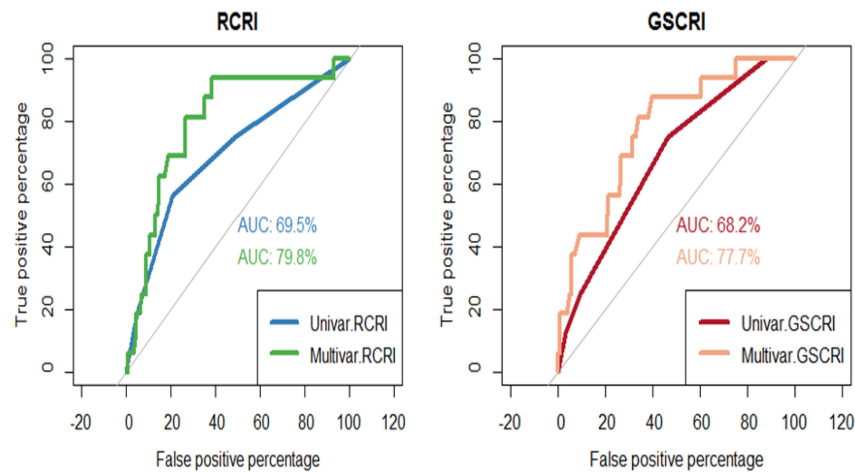


Figure 2 C statistics of the univariate and multivariate revised cardiac risk index (RCRI) and geriatric sensitive cardiac risk index (GSCRI). The area under the receiver operating characteristic curve (AUC) for the univariate indices indicated a limited discriminative ability. This has improved in multivariate indices (after introduction of age, atrial fibrillation, and trauma surgery as risk factors).

Abbreviations: RCRI, revised cardiac risk index; GSCRI, geriatric sensitive cardiac risk index.

Improvement Program (NSQIP) and the Revised Cardiac Risk Index. Of the NSQIP scales, we have selected the GSCRI as being specific for geriatric patients.

In the RCRI and GSCRI derivation studies, the two indices showed good discriminative ability when applied to detect postoperative MACE with an AUC of 0.76 for both. Whereas applying the RCRI to the same GSCRI dataset yielded an AUC of 0.63 (13% reduction, $P < 0.001$).¹⁹

A careful revision of the GSCRI derivation cohort according to age subgroups as shown in the published supplemental material of Alrezk et al study¹⁹ showed a lower discriminative ability of both indices when applied to estimate postoperative MACE in the patients > 85 years, with an AUC of 0.55 and 0.66 for the RCRI and the GSCRI results, respectively, which comes in agreement with our results. The poor discriminative ability of RCRI was also previously reported when externally validated to detect postoperative MACE risk following vascular²⁹ and renal transplant³⁰ surgeries.

Table 7 Calibration of Both Indices. The Chi-Square Goodness-of-Fit Test Showed That RCRI Underestimated the MACE Risk in All Classes While GSCRI Underestimated the Risk in the B, C, and D Classes and Overestimated the Risk in Class E

Index	Risk Class	N.	Expected MACE% Median (IQR)	Observed MACE N (%)	P value
RCRI	I	381	0.4 (0.4, 0.4)	17 (4.5%)	0.0001
	II	244	0.9 (0.9, 0.9)	18 (7.4%)	
	III	131	6.6 (6.6, 6.6)	17 (13%)	
	IV	80	11 (11, 11)	11 (13.8%)	
GSCRI	A	116	0.3 (0.2, 0.3)	0 (0.0%)	0.00001
	B	280	0.9 (0.9, 0.9)	17 (6.1%)	
	C	325	1.9 (1.5, 3)	29 (8.9%)	
	D	45	8.3 (7.2, 10.1)	10 (22.2%)	
	E	69	18.3 (13.1, 28.6)	7 (10.1%)	

Abbreviations: MACE, major adverse cardiac events; RCRI, revised cardiac risk index; GSCRI, geriatric sensitive cardiac risk index; N, number of patients.

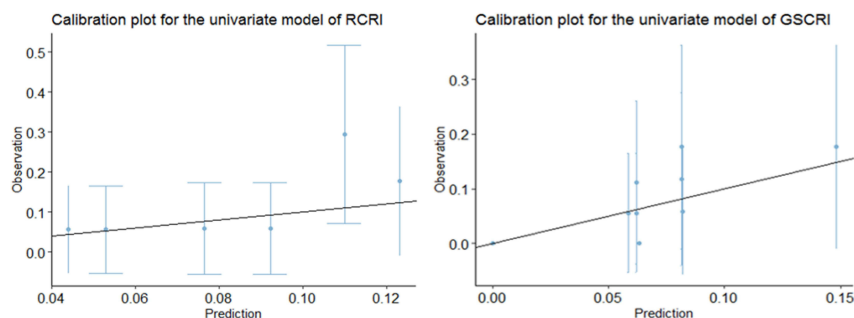


Figure 3 Calibration plots for the revised cardiac risk index (RCRI) and geriatric sensitive cardiac risk index (GSCRI) univariate models. The purpose of calibration plots is to demonstrate how much the observed probabilities (y-axis) are identical to the predicted probability (x-axis). The ideal calibration plot is represented by a straight line starting from 0 and dividing the graphs into 2 similar halves. The black line in the 2 graphs is the best fitting line through the first 10 observation probabilities and their corresponding prediction probabilities. The more the similarity of this line to the ideal line, the better the model is. The slope of the geriatric sensitive cardiac risk index (GSCRI) plot is higher than that of the revised cardiac risk index (RCRI), which gives an impression that the GSCRI is more accurate than the RCRI model.

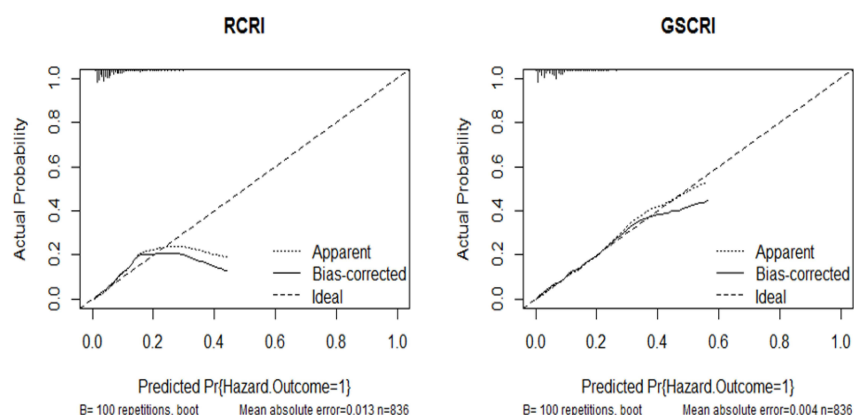


Figure 4 Calibration curve of the multivariate (after the introduction of age, trauma surgery, and atrial fibrillation) revised cardiac risk index (RCRI) and geriatric sensitive cardiac risk index (GSCRI) with a bootstrap resampling validation for predicting the risk major adverse cardiac event (MACE) in the training set. The dashed line indicated the ideal model in which the predicted and the actual probabilities were perfectly identical, the dotted line indicated actual performance with apparent accuracy, and the solid line presented a bootstrap corrected estimate of the calibration curve.

Many differences between the current study and the original validating studies of both indices may explain their poor performance when externally validated in our patients.

The mean age was 66 and 74 years in the RCRI and GSCRI cohorts, respectively, which is lower than the mean age in the current study (85.9 years). Our results showed that those with MACE had a statistically significantly higher age compared to those without MACE (median age, 87 vs 85 years, $p = 0.0001$). The regression analysis showed that MACE incidence increased progressively with age. Many other studies have also proved the role of age as a risk factor for postoperative MACE.^{31–34}

The urgency and types of surgeries were different. While Lee et al in the RCRI validating study¹⁸ have only included elective surgeries and Alrezk et al in the GSCRI validating study¹⁹ have excluded emergency surgeries, we have included elective and non-elective surgeries including trauma surgery and emergency vascular surgeries.

Both indices have considered surgery as a predictive risk factor from different points of view. RCRI has classified surgeries based on their risk (low, moderate, high) while GSCRI has stratified surgeries anatomically; yet, the study spectrum of both indices did not include trauma surgery.

Many other research teams have proved that urgent and emergency surgeries increased the incidence of MACE by OR ranging from 1.6 to 2.8.^{32,35–37} Trauma surgery, in particular, carries two hazardous aspects: being non-elective

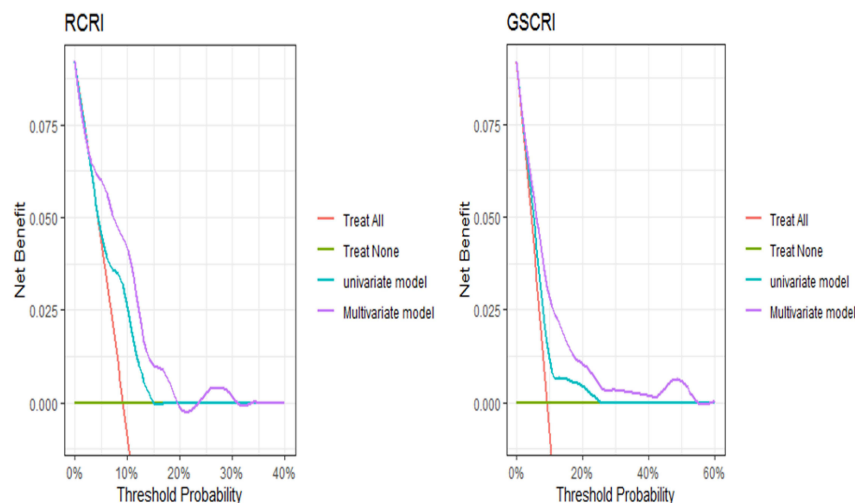


Figure 5 Decision curve analysis. The curve with the highest value of net benefit at a particular risk threshold has the highest clinical utility. Patients must have at least a 10% chance of having the hazard outcome to be checked by the index. The Orange and green lines assume that all patients are treated as high-risk or low-risk, respectively. The multivariate model of RCRI has a slightly better net benefit than the univariate model, while the multivariate GSCRI shows superior net benefit compared to the univariate model. Multiplying the value of net benefit by 1000 gives the number of net true positives per 1000 patients.

Abbreviations: RCRI, revised cardiac risk index; GSCRI, geriatric sensitive cardiac risk index.

surgery and being associated with an imbalanced systemic inflammation that causes various perioperative complications^{38,39} which leads to worse cardiovascular outcomes.⁴⁰ This supports our results that identified trauma surgery as a risk predictor, increasing the odds of postoperative in-hospital MACE by 203%.

AF as a predictive risk factor was not considered in the design of both indices, where it was statistically significantly prevalent in those with MACE in the current study. The regression analysis has also shown that AF increases the odds of in-hospital postoperative MACE by 377%. AF is one of the most common perioperative cardiac arrhythmias encountered during orthopedic surgery^{41,42} and has been extensively studied as a cause of perioperative morbidity and worse outcomes.^{43–45}

In a retrospective orthopedic study⁴⁶ including 906 total knee arthroplasty under epidural anesthesia, patients with AF were 2.6, 3.3, and 2.6 times more likely to have postoperative acute MI, ventricular tachycardia, and HF, respectively.

The role of AF as a risk factor for postoperative MACE was also supported by Puelacher et al results³⁷ that confirmed its significant association with postoperative MI after non-cardiac surgery.

By introducing age, trauma surgery, and AF as risk predictors into both indices (multivariate RCRI and multivariate GSCRI), we have noticed that the discriminative ability of the RCRI and the GSCRI has increased by 14.80% and 8.06%, respectively. The bootstrap analysis of the multivariate GSCRI confirmed an improved predictive ability up to a 40% MACE risk. This result seems to be satisfactory, as the highest recorded risk of postoperative MACE following non-cardiac surgery was 19.4%.³³

However, the bootstrap analysis of the multivariate RCRI has proven its limited predictive ability even after the implementation of the previously mentioned risk factors. Compared to RCRI, GSCRI considers the ASA class and the functional status of patients as predicting factors and is specific to patients over 65 years old. This may explain why multivariate GSCRI has better predictive ability than multivariate RCRI. The influence of the clinical condition and the frailty status of the patients on the postoperative MACE incidence was shown in a recently published study⁴⁷ where the risk of 30-day mortality, MI, and CA was 0.35% in the low frailty risk group and 2.12% in the high-risk frailty group in the patients with RCRI class I.

Of interest in this study is that the prevalence of some established preoperative cardiovascular risk factors, such as prior cerebrovascular events, coronary artery disease, and HF, which are supposed to increase the incidence of MACE according to both indices, was not statistically significantly different when comparing patients with and without in-

Table 8 Correlation of Clinically Relevant Perioperative Parameters and Both Indices. There is Statistically Significant Evidence of Negligible Correlations Between Both Indices and the Perioperative Blood Pressure and Heart Rate Changes, Vasopressor Requirements, Postoperative IMC/ICU Admission, and Length of Hospital Stay. The Correlation Coefficients are Less Than 0.3 in All Cases

Parameters	Correlation Coefficient (Sig. (2-Tailed))	
	RCRI	GSCRI
Systolic blood pressure 0	−0.092 (0.008)	−0.063 (0.068)
Diastolic blood pressure 0	−0.067 (0.053)	−0.022 (0.519)
Intraoperative systolic blood pressure Low	−0.096 (0.005)	−0.124 (0.000)
Intraoperative diastolic blood pressure Low	−0.117 (0.001)	−0.149 (0.000)
Systolic blood pressure End	−0.105 (0.002)	−0.105 (0.002)
Diastolic blood pressure End	−0.085 (0.014)	−0.101 (0.003)
Heart rate 0	−0.017 (0.622)	0.016 (0.647)
Intraoperative heart rate low	−0.059 (0.089)	−0.012 (0.735)
Vasopressor need	0.059 (0.089)	0.097 (0.005)
PACU systolic blood pressure low	−0.083 (0.032)	−0.085 (0.028)
PACU diastolic blood pressure low	−0.142 (0.000)	−0.148 (0.000)
Postoperative IMC admission	0.168 (0.000)	0.206 (0.000)
Postoperative ICU admission	0.140 (0.000)	0.109 (0.002)
Length of hospital stay	0.170 (0.000)	0.144 (0.000)

Abbreviations: RCRI, revised cardiac risk index; GSCRI, geriatric sensitive cardiac risk index; 0, at baseline; low, lowest value; End, values at the end of the operation; PACU, post-anesthesia care unit.

hospital MACE. Moreover, the regression analysis has shown that the association of the previously mentioned preoperative cardiovascular risk factors with in-hospital postoperative MACE does not reach statistical significance.

Our observation regarding the cerebrovascular events being of non-predictive value in the current study may explain why the GSCRI has overestimated the MACE incidence in risk class E. By revising the data of the GSCRI risk class E, we have found that the total number of patients was 69, and 91.3% of them (63/69) had a prior history of cerebrovascular events, which is considered a risk factor in the GSCRI but not in the current study. Similarly, another recent study³³ could not identify cerebrovascular events as an independent risk factor for perioperative cardiac complications in patients over 80 years with coronary artery disease undergoing non-cardiac operations. The prevalence of preoperative cerebrovascular events in that study was not significantly different in those with and without postoperative in-hospital MACE (18.8% vs 18.9%, OR: 1.003, $p = 0.99$).

Besides the role of the recent advances in coronary artery disease management and the extensive use of percutaneous interventions, which help in the reduction of short-term mortality, cardiac death, and MI,^{48,49} the nature of the operations in this study (trauma, vascular, and urological surgeries), which required only T10 sensory level block, could reduce the hypotensive effect of SA and subsequently limit the coronary hypoperfusion. This may explain the statistically non-significant prevalence of coronary artery disease between those with and without MACE and the regression analysis results.

SA may be a good choice for patients with HF because of the less reduction in blood pressure, the avoidance of tachycardia, and the preservation of myocardial contractility when compared to general anesthesia. This may explain the non-significant difference in the prevalence of HF between those with and without postoperative MACE and the

regression analysis results. However, the lack of data concerning the phenotype, duration, and severity of HF limits the interpretation.

Aortic stenosis and pulmonary hypertension are expected to increase the incidence of postoperative adverse cardiovascular outcomes, especially under SA, which is contraindicated in severe cases. In agreement with this came our results, which indicated that the prevalence of aortic stenosis and pulmonary hypertension was statistically significantly higher in those with postoperative MACE than those without, and the regression analysis has shown that they are statistically significantly associated with postoperative MACE. The current study included 46 (5.5%) patients with aortic stenosis, of whom 11 were diagnosed with a severe degree, and 16 (1.9%) patients with pulmonary hypertension. The plausible explanation for providing SA to patients with severe aortic stenosis might be due to their submission to emergency operations. This did not allow for complete preoperative cardiac assessment, and severe aortic stenosis was most probably first diagnosed after the occurrence of complications.

Another difference between our study and the derivation studies of both indices is the restriction to one type of anesthesia (SA) in the current study. Neuraxial anesthesia was found to improve postoperative cardiac outcome (reduced postoperative MI, pulmonary embolism, and mortality by about one-third)⁵⁰ or at least was not associated with altered odds of adverse cardiovascular outcomes in high-risk patients undergoing non-cardiac surgeries.⁵¹

Although the POISE trial⁵² concluded that the neuraxial block was associated with an increased risk of adverse cardiovascular outcomes, SA as a sole anesthetic technique was not associated with a high incidence of MACE (OR 0.89) or MI (OR 0.74) when compared with general anesthesia in that trial. This discrepancy is most likely attributed to including patients who had combined general anesthesia and thoracic epidural block under the category of a “neuraxial block”, which led to high odds of MACE in the neuraxial group when compared to patients who had only general anesthesia.

The in-hospital postoperative MACE incidence was 7.5% in the current study. Sazgary et al⁵³ have reported a higher postoperative MACE incidence of 15.2% in high-risk cardiac patients. The anesthetic technique (general and spinal versus only spinal), the study period (30 days versus the in-hospital outcome), and the screening for detection of non-symptomatic MACE compared to the only clinically based diagnosis in our study may explain the higher incidence of MACE in the compared study.

In another study, which included patients over 80 years old with coronary artery disease, the incidence of postoperative MACE was 19.4%.³³ The differences between that study and ours are the longer study period of 30 days and the use of general and neuraxial anesthesia.

Sabaté et al,⁵⁴ on the other hand, have reported a lower MACE incidence of 4.3%, which may be attributed to the lower age (mean 67 compared to 85.9 years), a better ASA score (55.4% ASA II against 85.1% ASA III and IV), and the small percentage of emergency (7.1 versus 54.1%) and high-risk (5.2% versus 7.17%) surgeries in the compared and current study, respectively. Besides that, the surgery spectrum in the Sabaté et al study did not include trauma surgeries.

Our results showed statistically significant evidence of a negligible correlation between the two indices and the postoperative ICU admission, LOS, intraoperative and immediate postoperative blood pressure and heart rate changes, and vasopressor requirements. This result was expected because both indices underestimated the likelihood of postoperative MACE that is always associated with ICU admission, prolonged LOS, and hemodynamic instability with subsequent use of vasopressors. In contrast to our results, Ackland et al⁵⁵ have found that a RCRI score ≥ 3 was associated with a significant increase in postoperative LOS and ICU admission. This may be explained by their elective ICU admission based on the preoperative cardiac risk severity according to the RCRI, while we have almost depended on the perioperative clinical evaluation of the patients for postoperative ICU admissions.

Our study has the following limitations: first, the retrospective and single-center design. Second, the number of events was smaller than the recommended 100,⁵⁶ yet we have recorded 81 events which is more than those recorded in the original validation set of the RCRI (36 events), and other validating studies.^{29,57} This number of events is also accepted as a required sample size for external validation of risk models for binary outcomes, according to a recently published study.⁵⁸ Third, this study, being retrospective, is also limited by the short-term (in-hospital) outcome.

Furthermore, we could not find details about the perioperative management of anticoagulant therapy in patients with AF, but there was no single recorded epidural hematoma among our patients. Also, some important laboratory parameters such as serum lactate level were not measured.

Although the age restriction (≥ 80 years) and anesthetic approach (only SA) can limit the generalizability of our findings, we consider this a powerful aspect because we targeted a clinically relevant subgroup in which precise preoperative cardiovascular risk stratification is very essential. To our knowledge, this is the first study to address the type of anesthesia and to include only the oldest-old patients in the external validation of postoperative cardiovascular risk indices. Conclusion: Both RCRI and GSCRI had limited ability to predict postoperative in-hospital MACE and correlated poorly with postoperative ICU admission and LOS following surgery under SA in the oldest-old patients. Updated versions by introducing age, AF, and trauma surgery had improved the predictive ability and the clinical utility of the multivariable GSCRI, while the multivariable RCRI was still of limited predictive and clinical utility.

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Disclosure

The authors declare that they have no competing interests.

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