



Physical performance tests and in-hospital outcomes in elective open chest heart surgery

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ARTICLE INFO

Keywords:

Open chest heart surgery
Mortality
Hand grip
Timed up and go

ABSTRACT

Background: Physical performance tests are essential for a comprehensive health assessment, and have been described as predictors of disability and muscle mass decline after open chest heart surgery (OHS). We evaluated the association between physical performance tests with clinical outcomes after OHS in younger and older patients. Moreover, the ability of physical performance tests and European System for Cardiac Operative Risk Evaluation (Euroscore II) to predict death was assessed.

Methods: Elective OHS patients were evaluated before surgery with handgrip strength (HGS), 30-s Chair-Stand Test (30sCST), and timed up and go test (TUGT). The outcomes were post-surgical complications, total length of stay (LOS), time to walk (TW), time in invasive mechanical ventilation (TIMV), and in-hospital mortality. Data were stratified between patients < 60 (younger) and ≥ 60 years old (older).

Results: A total of 166 patients were included in the study (older, n = 89). The only physical test associated with mortality in the adjusted models was HGS in older patients (p = 0.03). Among older patients, both Euroscore II (AUC = 0.77) and HGS (AUC = 0.80) demonstrated good ability to predict death. Combining HGS and Euroscore II did not increase accuracy for mortality prediction (AUC = 0.83).

Conclusion: HGS performance was comparable to a well-established surgical risk score in evaluating in-hospital mortality after OHS, only in older patients. Functional testing before OHS could be a tool to improve risk stratification in these patients. Future intervention studies aiming to improve functional capacity before elective OHS can further clarify the impact of physical fitness in surgical recovery.

1. Introduction

Physical performance tests are health assessment tools which evaluate mobility, muscle performance, and sensation in various degrees and combinations [1], and are employed in a wide range of clinical settings. The timed up and go test (TUGT), handgrip strength (HGS), and 30-s chair-stand test (30sCST) are simple and easy to perform tests, previously shown as valid and reliable [2,3]. These tests are key components of health assessment in the elderly, which are susceptible to frailty and functional decline [4], but have also been used in the diagnosis of functional loss of younger patients as well [5]. The association between functional status and adverse outcomes has been previously observed in stable coronary artery disease [6], after myocardial heart infarction [7], and heart failure [2]. In open chest heart surgery (OHS), risk scores are

designed to predict mortality, in which the European System for Cardiac Operative Risk Evaluation (Euroscore II) is one of the most employed worldwide [8]. One potential limitation of traditional risk scores is their lack of evaluation of specific patient characteristics, mainly frailty and physical performance [9]. There are only few studies examining the association between physical performance tests and OHS outcomes [10,11]. The present study evaluated the association between performance in a set of physical tests and clinical outcomes after OHS, in younger and older patients. Additionally, the ability of physical performance tests and Euroscore II to predict death was assessed.

Abbreviations: HGS, handgrip strength; LOS, length of stay; OHS, open chest heart surgery; SC, surgical complications; TIMV, time in mechanical ventilation; TUGT, timed up and go test; TW, time to walk; 30sCST, 30-s chair-stand test.

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<https://doi.org/10.1016/j.ijcha.2022.101164>

Received 8 August 2022; Received in revised form 9 December 2022; Accepted 11 December 2022

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2. Methods

2.1. Study design and patients

This is a prospective longitudinal study including adult patients admitted to National Institute of Cardiology (Ministry of Health, Rio de Janeiro, Brazil) that underwent elective OHS (coronary artery bypass grafting [CABG] and valve surgery [VS]). An active search was performed to recruit patients during hospital admission and before surgery. Inclusion criteria were age ≥ 18 years and indication for OHS. The exclusion criteria were patients unable to comprehend the objective of the study, unable to walk without assistance, pregnancy, and patients with contact or respiratory isolation due to clinical suspicion or diagnosis of COVID-19.

The indications for OHS were established according to international Guidelines [12,13], by a heart team comprised by multiple professionals (clinicians, surgeons, nurse staff) independent from the study team. Combined surgery was indicated for patients that presented simultaneous valve and coronary artery disease.

The study was approved by the local Institutional Review Board (IRB) under protocol # CAAE 03908818.8.0000.5272, and informed consent approved by the IRB was obtained from all participants.

2.2. Measurements

Anthropometry (height, body weight, and body mass index), comorbidities, blood biochemistry, and left ventricular ejection fraction (LVEF, measured with transthoracic echocardiogram using the Teicholz method) were obtained from medical records. LVEF and laboratory data were considered when obtained in the previous 12 months before recruitment. Euroscore II was calculated using an online tool (www.euroscore.org). The post-surgical complications outcome was a composite of new atrial fibrillation, hemodynamic shock, cardiac tamponade, reoperation due to bleeding or ischemia, reintubation, acute kidney failure, mediastinitis, endocarditis or suture dehiscence. The in-hospital outcomes after surgery were length of hospital stay (LOS), time to walk (TW, equivalent to intensive care unit length of stay), time in invasive mechanical ventilation (TIMV), and in-hospital mortality.

2.3. Physical performance evaluation

Three different tests were employed to evaluate physical performance before OHS: TUGT, HGS, and 30sCST. The TUGT test was performed to evaluate patient's dynamic stability and mobility. The patient was asked to stand up from an armless chair, to walk a 3-meter distance, return and sit down at the fastest pace possible, under supervision [14]. Lower extremity strength was evaluated by the 30sCST. The patient started seated up straight in an armless chair, with the feet flat on the floor and arms held across the chest. After the instruction, the patient was asked to stand up and sit down repeatedly, as quickly as possible, for 30 s. The number of completed stands was registered [15]. Upper limb strength was evaluated with HGS using a Kratos hydraulic dynamometer (Model ZM, Manual Inc., Brazil). The patient seated on an armless chair with the elbow flexed at 90° and asked to exert maximal force with dominant hand [16]. Three measurements were performed with one minute interval, with the highest value recorded.

2.4. Statistical analysis

Following a clinical rationale, data analyses were stratified between patients < 60 (younger) and ≥ 60 years old (older). Variables were tested for normality using the Shapiro-Wilk normality test. Comparisons of numerical variables with normal distribution were analyzed by Student-*t* test, and variables with non-Gaussian distribution were analyzed by Mann-Whitney test. Categorical variables were analyzed by Chi-Square. Descriptive statistics consisted of mean and standard deviation

for continuous variables and frequency and percentage for categorical variables. The association between exposure variables (physical performance tests before surgical procedure) and outcomes were determined by either logistic regression (SC and in-hospital mortality) or linear regression (LOS, TW, and TIMV) models, depending on the nature of the outcome variable. Three different models were fitted: model 1: unadjusted; model 2: adjusted for age and sex; model 3: adjusted for Euroscore II. Residual plots for each regression model were visually inspected and did not demonstrate major deviations. Receiver operating characteristic (ROC) curves were drawn with determination of the area under the curve (AUC) to analyze the accuracy for the association between physical performance test, Euroscore II or the combination of both with in-hospital mortality, that were compared using a test for the equality of the AUC. Statistical analyses were performed using Stata 13.0. Statistical significance was set at $p \leq 0.05$.

3. Results

3.1. Subject characteristics, physical tests and surgical outcomes

Between May 2019 and January 2021, 391 patients were eligible for the study. Patients were recruited consecutively; however, elective OHS was temporarily suspended between March and August 2020, as a consequence of the COVID-19 pandemic. After use of exclusion criteria ($n = 151$), surgical withdrawals ($n = 52$), and patient refusal to participate ($n = 22$), 166 patients were included in the evaluation. Anthropometric and clinical characteristics of patients stratified by age groups are presented in Table 1. Preoperative physical performance is presented in Table 2. Surgical variables and outcomes are presented in Table 3. The older group displayed more frequently hypertension ($p < 0.001$), osteoarthritis ($p = 0.002$) and higher Euroscore II values ($p < 0.001$). Although younger patients displayed higher force on HGS, higher number of repetitions on 30sCST and shorter time on TUGT, the differences were not significant when compared to older group. All patients had pulse oximetry over 95 % at the beginning of physical evaluation. There were no adverse events associated with any of the physical tests used (i.e., shortness of breath, chest pain, syncope, pre-syncope or other symptoms requiring emergency evaluation). Regarding surgical data, younger patients presented higher frequency of CABG ($p = 0.002$) while older patients presented higher frequency of combined surgery ($p = 0.012$), had higher frequency of surgical complications (p

Table 1
Anthropometric and clinical characteristics of patients by age group.

Parameter	Younger (n = 77)	Older (n = 89)	P-Value
Age (years)	48.9 \pm 9.5	66.2 \pm 4.5	< 0.001
Male n (%)	50 (64.9)	58 (65.2)	0.975
Body mass index (kg/m ²)	26.9 \pm 4.9	27.1 \pm 3.9	0.842
Creatinine (mg/dl)	1.03 \pm 0.34	1.03 \pm 0.31	0.927
Osteoarthritis n (%)	0	10 (11.9)	0.002
Hypertension n (%)	48 (64)	77 (88.5)	< 0.001
Diabetes n (%)	21 (28.4)	31 (36.5)	0.278
Dyslipidemia n (%)	16 (21.3)	28 (32.2)	0.122
Atrial fibrillation n (%)	11 (15.7)	11 (13.1)	0.644
Previous stroke n (%)	6 (8.1)	8 (9.5)	0.122
NYHA class III/IV (%)	30.6	51.4	0.014
LVEF (% Teicholz)	58.4 \pm 14.9	60.4 \pm 16.2	0.523
Euroscore II	2.1 \pm 1.6	3.6 \pm 3.3	< 0.001

Body mass index n = 124, Creatinine n = 67, Osteoarthritis n = 159, Hypertension n = 162, Diabetes n = 159, Dyslipidemia n = 162, Atrial fibrillation n = 154, Previous Stroke n = 158, NYHA class III/IV n = 134, LVEF n = 95, Euroscore II n = 150.

The results are presented as the mean \pm SD. Comparisons of numerical variables were analyzed by Student-*t* test, and categorical variables were analyzed by Chi-Square.

Abbreviations: Euroscore II, European System for Cardiac Operative Risk Evaluation; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

Table 2
Physical tests results of patients by age group.

Test	Younger (n = 77)	Older (n = 89)	P-Value
HGS (Kgf)	27.1 ± 9.7	24.8 ± 9.8	0.14
30sCST (repetitions)	9.8 ± 4	9.1 ± 3.2	0.21
TUGT (seconds)	11.5 ± 4.6	12.6 ± 5.1	0.124

The results are presented as the mean ± SD. Comparisons were analyzed by Student-t test.

Abbreviations: 30sCST, 30-s Chair-Stand Test; HGS, handgrip strength; TUGT, timed up and go test.

Table 3
Surgical variables and outcomes after elective open-heart surgery.

Variable	Younger (n = 77)	Older (n = 89)	P-Value
CABG, n (%)	36 (46.7)	63 (70.8)	0.002
vS n (%)	44 (57.1)	40 (44.9)	0.117
Combined, n (%)	3 (3.9)	14 (15.7)	0.012
ECC use, n (%)	77 (100)	82 (96.5)	0.096
ECC time (minutes)	118.5 ± 52.3	129.6 ± 56.8	0.205
SC, n (%)	7 (9.1)	21 (28)	0.006
TIMV (minutes)	1,290 ± 3,168	1,235 ± 1,239	0.885
TW (minutes)	6,702.82 ± 3,880.95	13,797.13 ± 4,5321	0.204
LOS (days)	17.1 ± 11.8	17.6 ± 9.1	0.762
In-hospital mortality, n (%)	2 (2.6)	10 (11.2)	0.032

ECC use n = 159, ECC time n = 157, Surgical complications n = 145, TIMV n = 155, LOS n = 153.

The results are presented as the mean ± SD. Comparisons of numerical variables were analyzed by Student-t test, and categorical variables were analyzed by Chi-Square.

Abbreviations: CABG, coronary; artery bypass grafting; ECC, extracorporeal circulation; vS valve surgery; LOS, length of stay; SC, surgical complications; TIMV time in mechanical ventilation; TW, time to walk.

Table 4
Association between preoperative physical tests and outcomes after open-heart surgery in younger patients (<60 years old).

Physical performance test	Outcome	Model 1		Model 2		Model 3	
HGS		β (95 %CI)	p-value	β (95 %CI)	p-value	β (95 %CI)	p-value
	TIMV	-13.41 (-89.2 to 62.4)	0.726	-49.61 (-143.3 to 44.0)	0.29	-16.63 (-104.5 to 71.3)	0.70
	TW	-106.69 (-203.6 to -9.7)	0.03	-80.91 (-202.0 to 40.1)	0.18	-50.35 (-142.6 to 41.9)	0.27
	LOS	-0.045 (-0.330 to 0.239)	0.75	-0.069 (-0.425 to 0.285)	0.69	-0.018 (-0.340 to 0.303)	0.91
30sCST	SC	OR (95 %CI)	p-value	OR (95 %CI)	p-value	OR (95 %CI)	p-value
		0.964 (0.88 to 1.05)	0.43	0.96 (0.87 to 1.07)	0.54	0.98 (0.89 to 1.09)	0.81
	Mortality	0.98 (0.85 to 1.14)	0.87	1.03 (0.79 to 1.35)	0.79	1.00 (0.85 to 1.17)	0.96
		β (95 %CI)	p-value	β (95 %CI)	p-value	β (95 %CI)	p-value
	TIMV	-21.02 (-202.5 to 160.4)	0.81	-36.76 (-225.8 to 152.3)	0.69	-27.42 (-231.2 to 176.4)	0.78
	TW	-20.81 (-250.3 to 208.7)	0.85	57.62 (-175.6 to 290.8)	0.62	-4.44 (-212.0 to 203.1)	0.96
TUGT	LOS	-0.003 (-0.69 to 0.68)	0.99	0.011 (-0.70 to 0.73)	0.97	0.001 (-0.75 to 0.75)	0.99
	SC	OR (95 %CI)	p-value	OR (95 %CI)	p-value	OR (95 %CI)	p-value
		0.87 (0.68 to 1.11)	0.27	0.88 (0.70 to 1.12)	0.33	0.79 (0.57 to 1.10)	0.18
	Mortality	0.94 (0.64 to 1.37)	0.76	0.80 (0.42 to 1.51)	0.49	0.96 (0.67 to 1.37)	0.83
		β (95 %CI)	p-value	β (95 %CI)	p-value	β (95 %CI)	p-value
	TIMV	36.42 (-120.4 to 193.2)	0.64	45.20 (-114.9 to 205.3)	0.57	39.67 (-133.0 to 212.4)	0.64
Mortality	TW	128.62 (-81.9 to 339.1)	0.22	71.98 (-142.2 to 286.1)	0.50	174.39 (-8.13 to 356.9)	0.06
	LOS	0.23 (-0.35 to 0.82)	0.42	0.23 (-0.36 to 0.83)	0.44	0.29 (-0.32 to 0.92)	0.34
	SC	OR (95 %CI)	p-value	OR (95 %CI)	p-value	OR (95 %CI)	p-value
		1.00 (0.83 to 1.20)	0.96	0.99 (0.82 to 1.20)	0.96	1.05 (0.86 to 1.28)	0.62
	Mortality	1.04 (0.79 to 1.36)	0.76	1.18 (0.73 to 1.91)	0.48	1.03 (0.76 to 1.38)	0.84

The results of logistic regression (SC and in-hospital mortality) or linear regression (LOS, TIMV, and TW). Three different models were fitted for each association: model 1: unadjusted; model 2: adjusted for age and sex; model 3: adjusted for Euroscore II.

Model 1 and 2 (TIMV n = 76, TW n = 67, LOS n = 74, SC n = 70, Mortality n = 77).

Model 3 (TIMV n = 68, TW n = 59, LOS n = 66, SC n = 65, Mortality n = 69).

Abbreviations: LOS, length of stay; SC, surgical complications; TIMV, time in mechanical ventilation; TW, time to walk.

= 0.006) and higher in-hospital mortality after surgery (p = 0.032).

3.2. Association between preoperative physical performance tests and surgical outcomes

The results of logistic regression (SC and in-hospital mortality) or linear regression (LOS, TW, and TIMV) are presented in Table 4 for younger patients and Table 5 for older patients. In younger group, HGS was associated with TW in the unadjusted model (p = 0.03). There was a trend towards association between TUGT and TW in the model adjusted for Euroscore II (p = 0.06). No other associations between physical performance tests and surgical outcomes were observed in this group. In older group, there was an association between HGS performance and in-hospital mortality, either in the unadjusted and the adjusted for Euroscore II models (p = 0.008 and p = 0.03, respectively). There was a trend for association between 30sCST and surgical complications, either in the model adjusted for age and sex (p = 0.08) as well as in the analysis adjusted for Euroscore II (p = 0.07). There was also a trend for the association between 30sCST and mortality in the model adjusted for age and sex (p = 0.08).

The AUC for the associations between HGS and in-hospital mortality in younger and older groups are depicted in Figs. 1 and 2, respectively. In younger group, neither HGS nor Euroscore II alone demonstrated good accuracy for the association with in-hospital mortality (AUC = 0.52 and 0.65, respectively). The combination of HGS and Euroscore II presented a nonsignificant increase in accuracy (AUC = 0.70, p = 0.34 versus Euroscore II alone). In older group, HGS was similar to Euroscore II (AUC = 0.80 and 0.77, respectively) alone, and the combination of HGS and Euroscore II suggested an additive although nonsignificant effect (AUC = 0.83, p = 0.180 versus Euroscore II alone).

4. Discussion

4.1. Physical performance tests and surgical outcomes

With the current expansion of the scope of percutaneous interventions for treatment of advanced cardiac disease, OHS is reserved

Table 5

The association between preoperative physical tests and outcomes after open-heart surgery in older patients (≥ 60 years old).

Physical performance test	Outcome	Model 1		Model 2		Model 3	
		β (95 %CI)	<i>p</i> -value	β (95 %CI)	<i>p</i> -value	β (95 %CI)	<i>p</i> -value
HGS	TIMV	-11.80 (-40.7 to 17.1)	0.41	-33.12 (-74.5 to 8.3)	0.11	-5.62 (-33.1 to 21.9)	0.68
	TW	104.5 (-1097.9 to 1307.0)	0.86	-368.0 (-2164.4 to 1428.3)	0.68	255.6 (-1165.7 to 1677.1)	0.72
	LOS	-0.05 (-0.26 to 0.15)	0.60	0.04 (-0.24 to 0.34)	0.73	0.01 (-0.20 to 0.23)	0.90
	SC	OR (95 %CI)	<i>p</i> -value	OR (95 %CI)	<i>p</i> -value	OR (95 %CI)	<i>p</i> -value
	Mortality	0.97 (0.92 to 1.03)	0.45	0.99 (0.92 to 1.07)	0.88	1.01 (0.95 to 1.08)	0.66
30sCST	TIMV	0.88 (0.80 to 0.96)	0.008	1.00 (0.87 to 1.14)	0.98	0.89 (0.80 to 0.99)	0.03
	TW	β (95 %CI)	<i>p</i> -value	β (95 %CI)	<i>p</i> -value	β (95 %CI)	<i>p</i> -value
	LOS	45.54 (-38.3 to 129.4)	0.28	44.74 (-50.1 to 139.6)	0.35	36.81 (-40.6 to 114.3)	0.34
	SC	-1175.1 (-4486.7 to 2136.3)	0.48	-1951.4 (-5643.5 to 1740.6)	0.29	-1137.1 (-4979.6 to 2705.4)	0.55
	Mortality	-0.33 (-0.95 to 0.27)	0.27	-0.27 (-0.95 to 0.39)	0.41	-0.08 (-0.71 to 0.55)	0.80
TUGT	SC	OR (95 %CI)	<i>p</i> -value	OR (95 %CI)	<i>p</i> -value	OR (95 %CI)	<i>p</i> -value
	Mortality	1.11 (0.95 to 1.29)	0.17	1.16 (0.98 to 1.38)	0.08	1.18 (0.98 to 1.41)	0.07
	TIMV	0.97 (0.79 to 1.20)	0.82	1.32 (0.96 to 1.82)	0.08	1.07 (0.83 to 1.37)	0.59
	TW	β (95 %CI)	<i>p</i> -value	β (95 %CI)	<i>p</i> -value	β (95 %CI)	<i>p</i> -value
	Mortality	-22.62 (-76.0 to 30.8)	0.40	-24.12 (-88.1 to 39.9)	0.45	-19.13 (-68.9 to 30.7)	0.44

The results of logistic regression (SC and in-hospital mortality) or linear regression (LOS, TIMV, and TW). Three different models were fitted for each association: model 1: unadjusted; model 2: adjusted for age and sex; model 3: adjusted for Euroscore II. Model 1 and 2 (TIMV n = 79, TW n = 60, LOS n = 79, SC n = 75, Mortality n = 89). Model 3 (TIMV n = 73, TW n = 54, LOS n = 73, SC n = 70, Mortality n = 83). Abbreviations: LOS, length of stay; SC, surgical complications; TIMV, time in mechanical ventilation; TW, time to walk.

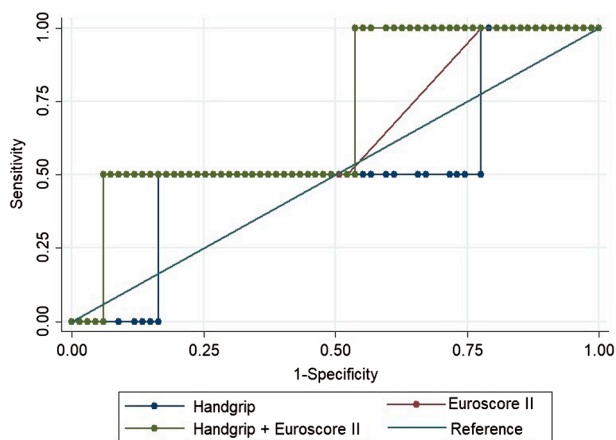


Fig. 1. Receiver operator curves (ROC) of hand grip strength (HGS), Euroscore II and the combination of both methods in younger patients for in-hospital mortality.

to higher risk patients [17]. Accordingly, more patients with advanced age, frailty, and comorbidities undergo OHS, which requires improved methods of risk evaluation. Functional physical tests, previously associated with outcomes in clinical and surgical patients, may serve for this purpose.

The greater incidence of OHS complications in the older group of patients (23.5 %) in the present study is in line with previous findings in literature, where higher frequency of complications is associated with the elderly [18,19]. Notwithstanding, in order to assess the independent contribution of physical performance to surgical outcomes, age adjustment was performed within each age group (younger and older), either directly in model 2, and indirectly through Euroscore II (which includes the age of patient) in model 3.

In our study, performance in TUGT was marginally associated with time to walk in the younger group of patients, but not in older group. While TUGT has been previously shown to identify functional mobility deficits even in children [20], osteoarthritis was present in 12 % of

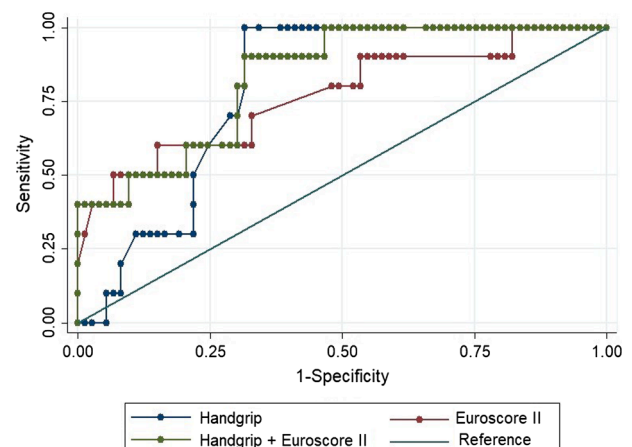


Fig. 2. Receiver operator curves (ROC) of hand grip strength (HGS), Euroscore II and the combination of both methods in older patients for in-hospital mortality.

individuals of older group, which could have impaired the performance of TUGT [21], a test relying essentially in mobility skills. This comorbidity may have limited the test capacity to measure associations with outcomes in OHS patients. In contrast, 30sCST offered a trend towards association with surgical complications and mortality, in older group only. This test measures lower limb endurance and physical capacity, and was previously associated with sarcopenia in elderly [22]. The most consistent results with OHS outcomes in our study were obtained with HGS in older group, with significant associations with in-hospital mortality.

In a previous study, da Silva et al. evaluated HGS in 50 elective OHS patients, finding correlations between HGS and TIMV or LOS, with no data regarding mortality [10]. In our study, an increased sample size allowed stratification by age groups, and the use of more robust regression analysis, which found no association of HGS with TIMV, TW or LOS. In a post hoc analysis of 1,245 older patients (age 74 ± 6.6

years) undergoing CABG and/or vS, Fountotos et al. found an association of HGS with 1-year and 30-day mortality, and with LOS [11]. Our present study, in which the older group was on average 8 years younger than Fountotos' study, could expand the age frame in which HGS performance can be associated with surgical mortality.

4.2. Comparison between HGS and Euroscore II

The comparison of HGS (the only physical performance test that was significantly associated with in-hospital mortality in the present study) with Euroscore II, a reference multisystem risk prediction tool, demonstrated similar accuracy. The prediction capacity of a risk score may differ in distinct populations, which can be attributed to differences of risk factors [23]. In the original description of Euroscore II, the population had a sex (women, 30.9 %) and age distribution (64.6 ± 12.5 years) similar to our older set of patients [8]. Our results indicate that HGS, a simple and suited for bedside physical test, could perform similar to Euroscore II in mortality prediction in elective OHS.

5. Study limitations

The present study was performed with patients from a single healthcare center, and therefore may not be representative of a large population of OHS patients. Functional tests impairments can be associated with nutritional deficits [24], which were not evaluated in the present study. In addition, although we performed adjusted analysis considering the most important confounders, we cannot exclude the possibility of residual confounding for the relationships between physical performance tests and surgical outcomes.

6. Conclusions

Taken together, our data suggest that in older patients, HGS performance has accuracy equivalent to a well-established risk score in evaluating short-term mortality risk after elective OHS. With increasing evidence from multiple studies describing a critical role of physical performance in OHS patients, more research is needed to develop and test the effects of comprehensive strategies, designed to enhance muscle strength before surgery, in order to improve outcomes in elective OHS.

Declarations

Ethics approval and consent to participate:

The present study was conducted in accordance with the Declaration of Helsinki, and this study was approved by the Institutional Review Board of the National Institute of Cardiology in Rio de Janeiro, Brazil, under protocol # CAAE 03908818.8.0000.5272. Written informed consent to participate in the study was obtained from all participants.

Availability of data and materials.

Not applicable.

Consent for publication.

Not applicable.

Funding.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

The authors would like to thank Isabella Verena Santos and Giovana Ruffier for the assistance in data collection.

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