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Association between self-reported functional capacity and major adverse cardiac events in patients at elevated risk undergoing noncardiac surgery: a prospective diagnostic cohort study

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Abstract

Background: Perioperative cardiovascular guidelines endorse functional capacity estimation, based on 'cut-off' daily activities for risk assessment and climbing two flights of stairs to approximate 4 metabolic equivalents. We assessed the association between self-reported functional capacity and postoperative cardiac events.

Methods: Consecutive patients at elevated cardiovascular risk undergoing in-patient noncardiac surgery were included in this predefined secondary analysis. Self-reported ability to walk up two flights of stairs was extracted from electronic charts. The primary endpoint was a composite of cardiac death and cardiac events at 30 days. Secondary endpoints included the same composite at 1 yr, all-cause mortality, and myocardial injury.

Results: Among the 4560 patients, mean (standard deviation) age 73 (SD 8 yr) yr, classified as American Society of Anesthesiologists physical status $\geq$3 in 61% (n=2786/4560), the 30-day and 1-yr incidences of major adverse cardiac events were 5.7% (258/4560) and 11.2% (509/4560), respectively. Functional capacity less than two flights of stairs was associated with the 30-day composite endpoint (adjusted hazard ratio 1.63, 95% confidence interval [CI] 1.23–2.15) and all other endpoints. The addition of functional capacity information to the revised cardiac risk index (RCRI) significantly improved risk classification (functional capacity plus RCRI *vs* RCRI: net reclassification improvement $[NRI]_{Events}$ 6.2 [95% CI 3.6–9.9], $NRI_{Nonevents}$19.2 [95% CI 18.1–20.0]).

Conclusions: In patients at high cardiovascular risk undergoing noncardiac surgery, self-reported functional capacity less than two flights of stairs was independently associated with major adverse cardiac events and all-cause mortality at 30 days and 1 yr. The addition of self-reported functional capacity to surgical and clinical risk improved risk classification.

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Editor's key points

- Exercise capacity and fitness are associated with perioperative risk.
- The relationship between self-reported functional status and postoperative cardiac events is unclear.
- This study found that self-reported poor functional capacity was independently associated with major adverse cardiac events at 30 days and 1 yr after surgery.
- These findings support the use of self-reported functional capacity to improve preoperative cardiac risk assessment.

The estimated worldwide need for surgical interventions based on the burden of disease exceeds 320 million procedures per year,[1] and approximately one-third of these consist of major procedures in patients with high cardiovascular risk.[2] In a cohort of 10 000 patients undergoing major noncardiac surgery, 30-day major adverse cardiac events including cardiac mortality, myocardial infarction, congestive heart failure, non-fatal cardiac arrest, and cardiac revascularisation were reported in more than 8% of patients.[3]

Considering this impressive burden, anaesthesiologists and cardiologists are keenly interested in cardiovascular assessment before noncardiac surgery for accurate risk-stratification,[2,4–6] to inform shared decisions, to guide monitoring options intraoperatively and postoperatively (e.g. screening for myocardial injury using troponin[5,7]), and to decide which patients should be submitted to preoperative cardiologic workup and optimisation of co-existing cardiac conditions.[2,4]

Functional capacity can be measured using cardiopulmonary exercise testing[8] or estimated either formally using a validated questionnaire[8,9] or semi-quantitatively comparing self-reported functional activity with cut-off reference activities (e.g. the ability to climb two flights of stairs is considered to approximate 4 metabolic equivalents).[2,4] Although measured functional capacity did not improve preoperative risk stratification in the Measurement of Exercise Tolerance before Surgery study,[8] formal estimation using the score derived from the Duke Activity Status Index questionnaire was associated with cardiac events and death.[2,4,9] However, depending on the social, cultural, and geographical setting, patients might not be able to answer all questions of the Duke Activity Status Index. Further, the application of the full questionnaire might appear long in busy preoperative clinics and estimation of functional capacity using the self-reported ability to conduct reference activities (in short self-reported functional capacity) is endorsed by guidelines[2,4] despite limited evidence. We hypothesised that self-reported functional capacity estimated by the ability of climbing less than two flights of stairs was independently associated with adverse cardiac events and that the addition of functional capacity to existing risk scores, such as the revised cardiac risk index (RCRI)[10] and surgical risk class, improved risk stratification.

Methods

This is a preplanned secondary analysis from a large prospective diagnostic cohort study accompanying a systematic screening program for perioperative cardiovascular complications in consecutive patients undergoing noncardiac surgery at the University Hospital Basel and at the Cantonal Hospital Aarau, Switzerland.[11–14] Patients were eligible for this analysis if they provided written informed consent to registration in a dedicated prospective database. Patients were recruited between October 2014 and October 2017. The study was approved by the local ethics committee (EKNZ2015-301, NCT 02573532).

Study population

According to the institutional routine screening, high-sensitivity cardiac troponin T (hs-cTnT, in Basel) and sensitive cardiac troponin I (s-cTnI) (in Aarau; see Supplementary material) were measured preoperatively and on the first and second postoperative day in patients undergoing in-patient visceral, orthopaedic, trauma, vascular, urologic, spinal, and thoracic procedures and aged ≥65 yr or ≥45 yr in the presence of a history of coronary artery disease, peripheral arterial disease, or stroke. Patients were excluded from the screening if they underwent cardiac surgery within 14 days before the noncardiac surgery procedure. Additional exclusion criteria for the present analysis were: (1) repeated surgery within 1 yr (while repeat-screening for clinical monitoring purpose was conducted if ≥5 days had elapsed); (2) no consent for registration in the prospective database; and (3) missing information on functional capacity.

Assessment of functional capacity

As part of the routine assessment during the preoperative visit in the preoperative anaesthesia clinic, the attending anaesthesiologists (in training or consultant) ask the patients about their ability to walk up two flights of stairs, which approximates 4 metabolic equivalents.[2,4] This self-reported information is collected in the electronic anaesthesia charts using a check box (checking=yes able to climb two flights of stairs), with the option to provide details in the form of free text. Although the electronic chart can be saved and closed without providing this entry, this rarely occurred, as indicated by the minimal number of patients missing this information (22/5946). For the study, data for the ability to walk up two flights of stairs was prospectively extracted from the clinical documentation (automatically using the check boxes and supplemented by search of the corresponding free-text entries) and stored in the dedicated study database.

Endpoints and methods of follow-up and adjudication

The primary endpoint was time to a composite of cardiac death, myocardial infarction (fulfilling the fourth definition),[15] acute heart failure, and life-threatening arrhythmia within 30 days (major adverse cardiac events). Secondary endpoints included time to the same composite within 1 yr, time to all-cause mortality within 30 days, and 1 year. Further, we assessed perioperative myocardial injury (defined as an absolute delta of 14 ng L^{-1} for hs-cTnT[14] and of 45 ng L^{-1} for s-cTnI, each corresponding to the 99th percentile of the healthy population) detected during the screening period. At 1 yr, we contacted patients by mail, or in cases of non-response via phone, to obtain information on adverse cardiovascular events or death. If the patients or next of kin reported a hospital admission, study personnel obtained all relevant documentation from the treating hospitals or the general practitioner. Local death registries were checked for information in cases of protracted non-response.

Perioperative myocardial injury was further classified in 'cardiac' or 'primarily extracardiac' if a clear primarily extracardiac disease, such as sepsis, stroke, or pulmonary embolism, triggered it.[14] Perioperative troponin elevations (I or T) were centrally assessed by cardiologists and anaesthesiologists. The other events were extracted from the medical charts according to predefined criteria.

Statistical analysis

The analyses followed a predefined analysis plan specifying aims, population, primary and secondary endpoints, subgroups, and statistical approach. The calculation of net reclassification was conditional on the detection of a significant association to align results presentation with the Measurement of Exercise Tolerance before Surgery study.[8] The analysis plan is available upon request.

Descriptive data are reported as count (percentage) and mean (standard deviation) or median (inter-quartile range). Appropriate descriptive statistics were utilised for data that did not satisfy parametric assumptions.

We conducted Cox regression analysis with right-censoring after assessment of non-violation of the proportional hazard assumption. Confounders were predefined (see Supplementary material for detailed list) and forced-entered into the model. Collinearity was assessed using SPSS (STATISTICS COLLIN TOL ZPP) that provides the variance inflation factor, Eigenvalue, condition index, and variance proportion. In the presence of 258 primary endpoints, using the rule of thumb of 10–12 events per predictor,[16] adjustment with up to 25 predictors would have been possible. The area under the curve of the model (discrimination) was calculated using Harrel's C statistic. Model calibration was assess using Brier's Score (Spiegelhalter Z-statistics) and by comparing observed *vs* predicted event rates.[17] We conducted complete-case analysis.

We assessed the association in the following predefined subgroups: (1) patients undergoing low-risk surgery according to the classification published in the European Society of Anaesthesiology (ESA) guidelines,[2] as the guidelines do not recommend the assessment of functional capacity in this group; (2) patients undergoing hip and knee replacement, spine surgery, or major vascular surgery of the lower limbs, as their ability to climb stairs may be affected by noncardiac causes. To assess interaction, product interaction terms were generated, entered into the Cox regression model, and assessed for significance.

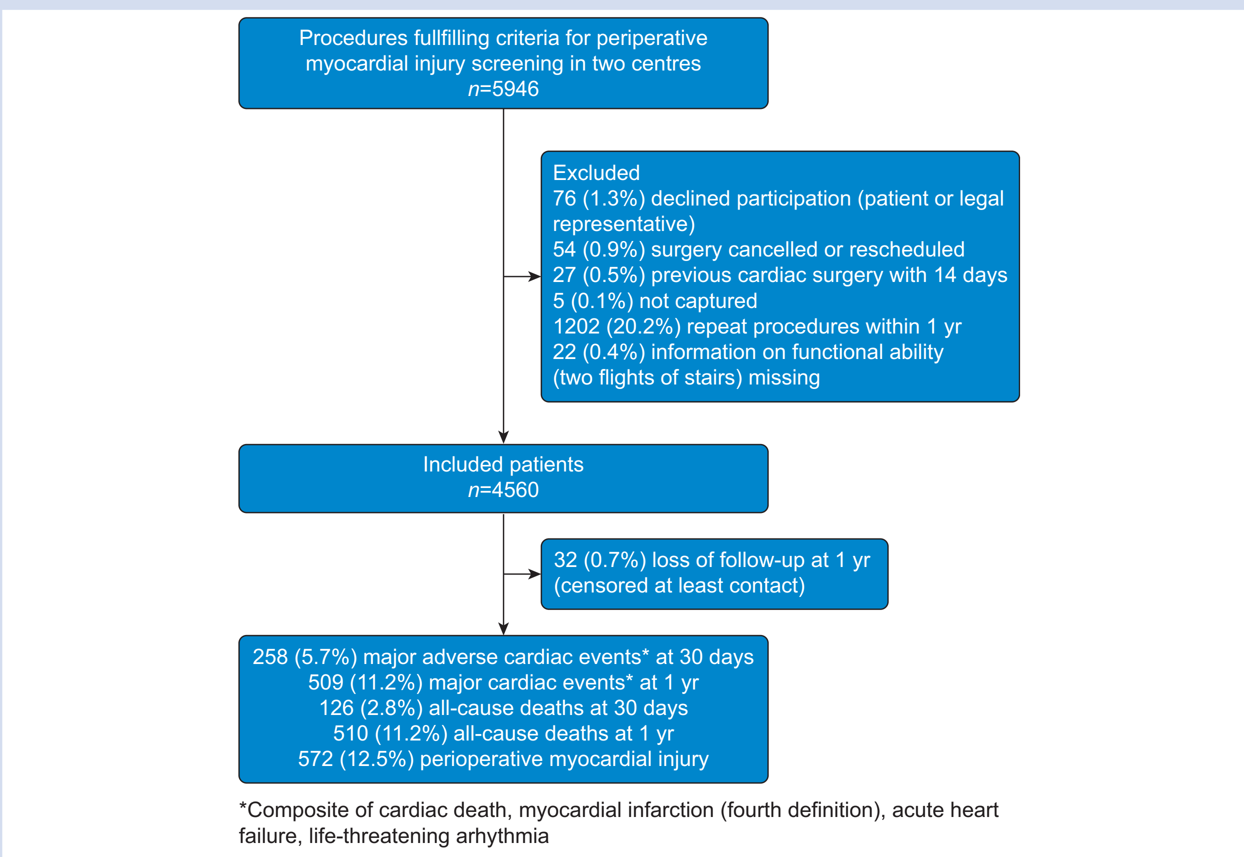


Figure 1. Study flowchart. Major adverse cardiac events (MACE) were the composite of cardiac mortality, myocardial infarction (fulfilling the fourth universal definition of myocardial infarction),[15] acute heart failure, and life-threatening arrhythmia.

For perioperative myocardial injury detected during the screening period, we conducted logistic regression adjusting for the same variables.

To assess the impact of self-reported functional capacity on risk stratification, we calculated the net reclassification improvement (NRI)[18] for events and non-events. After exclusion of acute conditions, the American College of Cardiology/American Heart Association algorithm[4] starts by estimating the risk for major adverse cardiac events based on 'combined clinical/surgical risk' and refers to the RCRI and other risk calculators; the next branch divides patients at elevated risk (≥1%) by functional capacity. The ESA/European Society of Cardiology algorithm starts with the risk of the surgical procedure,[2] then applies the assessment of functional capacity in intermediate or high-risk procedures. As such, we estimated the risk for major adverse cardiac events at 30 days based on the RCRI *vs* the functional capacity plus RCRI, and on surgical risk *vs* functional capacity plus surgical risk. Risk classes were defined as <1%, 1–5%, and >5%.[2] We then calculated the NRI and its 95% confidence interval (95% CI). SPSS 24 was used for the analyses. Null hypotheses were considered refuted if $P<0.05$ (two-tailed).

Results

Of the 5946 patients perioperatively monitored using cardiac troponin measurement, 4560 fulfilled the inclusion criteria. One-year follow-up was complete in 4528/4560 (99.3%). Complete-case analysis consisted of 4559/4560 patients (ASA class missing in one [0.02%] patient). Event rates are reported in Fig 1. Table 1 summarises the prevalence of confounding factors.

Association between self-reported functional capacity less than two flights of stairs and major adverse cardiac events

After a median (inter-quartile range) follow-up duration of 30 (30–30) days, we registered 172/1862 (9.2%) composite events in patients with self-reported functional capacity less than two flights of stairs and 86/2698 (3.2%) in patients with preserved functional capacity ($P<0.001$) (Fig 2). After a median follow-up duration of 365 (365–365) days, we registered 337/1862 (18.1%) composite events *vs* 172/2698 (6.4%) ($P<0.001$). After a median follow-up duration of 30 (30–30) days, we registered 98/1861 (5.3%) deaths *vs* 28/2694 (1.0%) ($P<0.001$). After a median follow-up duration of 365 (365–365) days, the number of deaths showed a similar pattern (351/1861 [18.9%] *vs* 169/2694 [6.3%], $P<0.001$). After multivariable adjustment, self-reported functional capacity less than two flights of stairs was significantly associated with the 30-day major adverse cardiac events (hazard ratio [HR] 1.63, 95% CI 1.23–2.15) and all secondary endpoints (Table 2). The variance inflation factor was <1.5 for all variables. The Brier's score was 0.0552 (Brier's score lower values indicate better calibration; Spiegelhalter z=3.077) for the 30-day major adverse cardiac events model and for the 1-yr major adverse cardiac events model, respectively. The model underestimated 30-day major adverse cardiac events rates in patients at lower risk (Supplementary Table S3).

The proportional hazard assumption was not violated ($P=0.23$ and $P=0.89$ for the 30-day and the 1-yr composite endpoint, respectively). The association between self-reported functional capacity <2 flights of stairs and major adverse cardiac events seemed consistent throughout the study population. Specifically, the adjusted HR (95%CI) of self-reported functional capacity <2 flights of stairs for the primary endpoint was 1.44 (95% CI 0.68–3.05) in low vs. 1.59 (95%CI 1.17–2.16) in intermediate/high risk surgery patients (interaction $P=0.103$). The adjusted HR (95% CI) of self-reported functional capacity <2 flights of stairs was 1.25 (95%CI 0.62–2.52) in patients submitted major lower extremity vascular procedures vs. 1.68 (95%CI 1.24–2.29) in non-lower extremity vascular surgery patients (interaction $P=0.121$). Similarly, we did not find any indication for significant interaction with hip and knee replacement and spine surgery

Table 1 Baseline characteristics of the whole cohort and stratified by 30-day major adverse cardiac events (MACE: cardiac mortality, myocardial infarction [fulfilling the fourth universal definition of myocardial infarction],[15] acute heart failure, and life-threatening arrhythmia). Further details are available in the Supplementary material. American Society of Anesthesiologists (ASA) physical status: $n=4559$ because of one missing value. Values are counts and percentages unless stated otherwise.

	30-Day MACE ($n=258$)	No MACE ($n=4302$)	All patients ($n=4560$)
Age (yr), mean (SD)	77 (8)	73 (8)	73 (8)
Female	11 (43.0)	1928 (44.8)	2039 (44.7)
ASA physical status ≥3	222 (86.0)	2564 (59.6)	2786 (61.1)
Surgery risk class			
Intermediate	159 (61.6)	2528 (58.8)	2687 (58.9)
High	52 (20.2)	462 (10.7)	514 (11.3)
Surgical urgency			
Urgent (≤1 day)	49 (19.0)	523 (12.2)	572 (12.5)
Semi-elective (2–7 days)	73 (28.3)	712 (16.6)	785 (17.2)
RCRI class			
1 Risk factor	92 (37.5)	1407 (32.7)	1499 (32.9)
2 Risk factors	72 (27.9)	604 (14)	676 (14.8)
≥3 Risk factors	43 (16.7)	255 (5.9)	298 (6.5)
History of heart failure			
LVEF<40%	26 (10.1)	145 (3.4)	171 (3.8)
LVEF 40–50%	15 (5.8)	108 (2.5)	123 (2.7)
LVEF>50%	20 (7.8)	96 (2.2)	116 (2.5)
LVEF not quantified	3 (1.2)	7 (0.2)	10 (0.2)
History of PAVD	78 (30.2)	723 (16.8)	801 (17.6)
History of stroke/TIA	46 (17.8)	422 (9.8)	468 (10.3)
History of diabetes mellitus			
Non-insulin-dependent	46 (17.8)	579 (13.5)	635 (13.7)
Insulin-dependent	44 (17.1)	347 (8.1)	391 (8.6)
Renal failure			
I–II	82 (31.8)	1319 (30.7)	1401 (30.7)
≥III	59 (22.9)	504 (11.7)	563 (12.3)
Dialysis	11 (4.3)	84 (2.0)	95 (2.1)
COPD	50 (19.4)	604 (14.0)	654 (14.3)
Cancer surgery	30 (11.6)	723 (16.8)	753 (16.5)
History of CAD	117 (45.3)	1102 (25.6)	1219 (26.7)
Self-reported functional capacity less than two flights of stairs	172 (66.7)	1690 (39.3)	1864 (40.8)

CAD, coronary artery disease; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; Hx, history; KIDGO, Kidney Disease: Improving Global Outcomes; LVEF, left ventricular ejection fraction; PAVD, peripheral arterial vascular disease; RCRI, revised cardiac risk index; SD, standard deviation; TIA, transient a ischaemic attack.

(n=1272/4560; interaction P=0.608). The adjusted association between self-reported functional capacity less than two flights of stairs was odds ratio (OR) 1.62 (95% CI 1.32–1.99) for perioperative myocardial injury detected by postoperative cardiac troponin elevation (for definitions details, please refer to the endpoint section).

Reclassification improvement by addition of self-reported functional capacity

Addition of self-reported functional capacity to surgical and clinical risk stratification according to the algorithms of the American College of Cardiology/American Heart Association and of the ESA/European Society of Cardiology guidelines improved risk stratification both in events and in non-events patients (Table 3). Expressed in absolute numbers, the addition of functional capacity to the RCRI, for example, led to correct reclassification of 879 and incorrect classification of 35 of 4560 patients. Reclassification tables are presented in the Supplementary material.

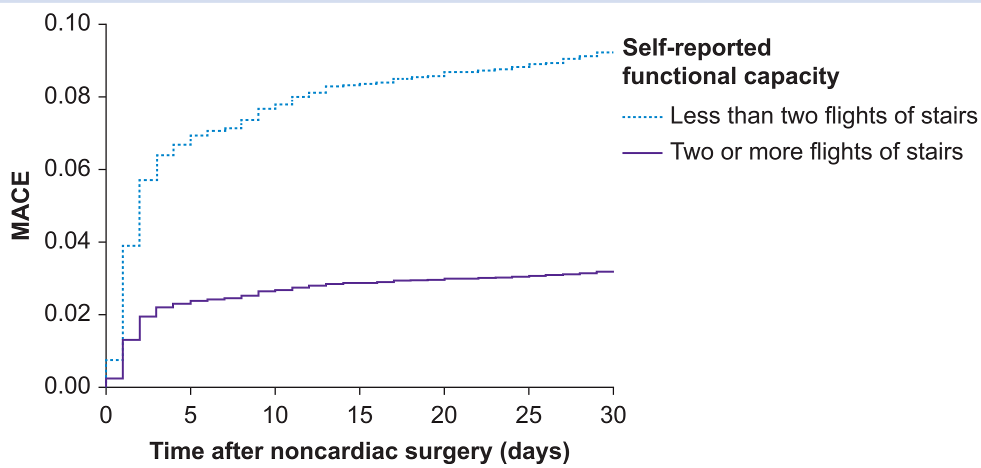
Discussion

Main results

This secondary analysis of prospectively collected data indicated that self-reported functional capacity less than two flights of stairs was independently associated with major adverse cardiac events at 30 days and 1 yr in patients at high cardiovascular risk undergoing inhospital noncardiac surgery. This association was detectable also in patients undergoing procedures for pathologies potentially affecting ambulation. Furthermore, the addition of self-reported functional capacity less than two flights of stairs to surgical risk and clinical risk stratification following both the algorithms endorsed by the American and the European guidelines,[2,4] respectively, resulted in significant reclassification improvement both for events and in particular non-events. As such, these findings provide strong support for the use of self-reported functional capacity for preoperative cardiac risk assessment, in contrast to previous work.[8]

Comparison with previous studies

Wiklund and colleagues[19] estimated metabolic equivalents in more than 5900 patients undergoing inhospital noncardiac surgery. Major cardiovascular events or cardiac mortality occurred in 1.6% (94/5939). The area under the curve for adverse cardiac events of metabolic equivalents based on daily activities amounted to 0.664 and metabolic equivalents was not independently associated with cardiac events. Limitations of this study included the potential for misclassification resulting from event extraction from administrative data and the inclusion of patients at lower cardiovascular risk as indicated by the low event rate. Reilly and colleagues[20] asked 600 patients undergoing major noncardiac surgery to estimate the number of blocks and the number of stairs they were able to walk. Patients unable to walk four blocks or two flights of stairs were considered to have low exercise tolerance. This definition resulted in a likelihood ratio of 1.3 for any perioperative complications. Poor exercise tolerance was independently associated with any complication (adjusted OR 1.94 [95% CI 1.19–3.17]) but not with cardiovascular complications (age-



	Day 0	Day 10	Day 20	Day 30
Less than two flights of stairs				
At risk	1861	1705	1666	1639
Cumulative MACE	0	140	159	172
Two or more flights of stairs				
At risk	2697	2612	2600	2587
Cumulative MACE	0	75	82	86

Figure 2. Kaplan–Meier curves for major adverse cardiac events (MACE) after inhospital noncardiac surgery in patients with self-reported functional capacity (ability to climb two flights of stairs). MACE were a composite of cardiac mortality, myocardial infarction (fulfilling the fourth universal definition of myocardial infarction),[15] acute heart failure, and life-threatening arrhythmia).

Table 2 Adjusted hazard ratio for time to primary and secondary endpoints. Major adverse cardiac events (MACE: consisted in a composite of cardiac mortality, myocardial infarction [fulfilling the fourth definition],[15] acute heart failure, and life-threatening arrhythmia). Complete-case analysis including 4559/4560 patients (ASA physical status missing in one [0.02%] patient).

	30-Day MACE	1-Yr MACE	30-Day all-cause mortality	1-Yr all-cause mortality
Harrel's C statistic (95% CI)	0.778 (0.760−0.810)	0.770 (0.761−0.801)	0.857 (0.834−0.889)	0.799 (0.781−0.817)
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Age (yr)	1.04 (1.02−1.06)	1.04 (1.03−1.05)	1.06 (1.04−1.09)	1.05 (1.04−1.07)
Female	1.02 (0.78−1.32)	0.91 (0.75−1.10)	0.90 (0.62−1.32)	0.83 (0.69−1.00)
ASA physical status ≥3	1.83 (1.24−2.71)	2.05 (1.55−2.72)	5.81 (2.48−13.58)	2.76 (2.04−3.72)
Surgery risk class				
Intermediate	1.83 (1.32−2.55)	1.11 (0.90−1.36)	2.08 (1.26−3.44)	1.14 (0.93−1.41)
High	2.45 (1.61−3.73)	1.51 (1.14−2.01)	4.14 (2.28−7.52)	1.92 (1.46−2.54)
Surgical urgency				
Urgent (≤1 day)	2.03 (1.44−2.87)	1.53 (1.17−1.99)	5.74 (3.63−9.10)	2.40 (1.85−3.11)
Semi-elective (2−7 days)	1.86 (1.37−2.52)	1.64 (1.32−2.04)	3.11 (1.98−4.90)	2.07 (1.66−2.58)
History of heart failure				
LVEF<40%	1.681 (1.09−2.60)	2.17 (1.63−2.91)	1.73 (0.92−3.24)	1.81 (1.31−2.49)
LVEF 40−50%	1.35 (0.78−2.32)	1.58 (1.09−2.27)	1.25 (0.53−2.93)	1.30 (0.840−2.00)
LVEF>50%	2.07 (1.29−3.31)	2.09 (1.48−2.96)	0.53 (0.17−1.67)	1.06 (0.70−1.61)
LVEF not quantified	3.75 (1.17−11.97)	2.86 (1.06−7.75)	1.56 (0.21−11.43)	1.29 (0.32−5.22)
History of PAVD	1.20 (0.84−1.63)	1.36 (1.10−1.69)	0.95 (0.60−1.50)	1.11 (0.88−1.40)
History of stroke/TIA	1.54 (1.11−2.14)	1.24 (0.97−1.58)	1.74 (1.10−2.74)	1.21 (0.94−1.56)
History of diabetes mellitus				
Non-insulin-dependent	1.22 (0.87−1.70)	1.29 (1.02−1.63)	0.96 (0.57−1.61)	1.22 (0.96−1.54)
Insulin-dependent	1.51 (1.05−2.16)	1.53 (1.19−1.97)	1.55 (0.93−2.59)	1.28 (0.98−1.67)
Renal failure				
I−II	1.20 (0.88−1.63)	1.31 (1.05−1.64)	0.83 (0.53−1.30)	1.16 (0.93−1.44)
≥III	1.35 (0.96−1.91)	1.60 (1.26−2.04)	0.87 (0.52−1.45)	1.37 (1.07−1.75)
Dialysis	1.66 (0.86−3.18)	1.86 (1.20−2.89)	2.19 (0.95−5.07)	3.16 (2.08−4.77)
COPD	1.12 (0.81−1.54)	1.23 (0.98−1.53)	1.16 (0.74−1.82)	1.15 (0.92−1.44)
Cancer surgery	0.92 (0.62−1.37)	1.64 (0.68−1.91)	2.83 (1.79−4.47)	4.36 (3.56−5.34)
History of CAD	1.45 (1.07−1.85)	1.22 (1.01−1.49)	0.94 (0.63−1.41)	0.83 (0.67−1.01)
Self-reported functional capacity less than two flights of stairs	1.63 (1.23−2.15)	1.64 (1.34−2.00)	2.54 (1.64−3.95)	2.11 (1.72−2.57)

CAD, coronary artery disease; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; Hx, history; KIDGO, Kidney Disease: Improving Global Outcomes; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac events; PAVD, peripheral arterial vascular disease; TIA, transient a ischaemic attack.

adjusted OR 1.81 [0.94−3.46]).[20] The evidence on the association between the inability to climb one flight of stairs and perioperative complications was inconclusive (OR 1.8 [95% CI 0.7−4.6]) in a small cohort (n=79) addressing patients undergoing either thoracic or abdominal surgery.[21] This study,[21] however, suffers from a limited sample size.

More recently, the Measurement of Exercise Tolerance before Surgery study[8] indicated that functional capacity formally assessed using the Duke Activity Status Index questionnaire was associated with myocardial infarction or death by an OR 0.96 (95% CI 0.92−0.99) in approximately 1400 patients undergoing in-patient noncardiac surgery, aged ≥40 yr and with at least one cardiovascular risk factor. These results

Table 3 Net reclassification improvement and C-statistic for 30-day cardiac mortality and major adverse cardiac events by the addition of functional capacity information to surgical and clinical risk estimation. Major Adverse Cardiac Events consisted in a composite of cardiac mortality, myocardial infarction (fulfilling the fourth definition),[15] acute heart failure, and life-threatening arrhythmia. AUC, area under the curve; MET, metabolic equivalent; NRI, net reclassification improvement; RCRI, revised cardiac risk index.

Restratification approach	*n* Events/ Total	NRI events (95% CI)	NRI non-events (95% CI)	AUC (95% CI)
Self-reported metabolic equivalents plus RCRI *vs* RCRI	258/ 4560	6.2 (3.6 −9.9)	19.2 (18.1 −20.0)	0.716 (0.689−0.750) *vs* 0.667 (0.645−0.712)
Self-reported metabolic equivalents plus RCRI *vs* RCRI—excluded low-risk patients based on RCRI	207/ 2473	11.6 (7.6 −16.7)	36.5 (34.5 −38.6)	0.661 (0.613−0.689) *vs* 0.608 (0.555−0.683)
Self-reported metabolic equivalents plus surgical risk *vs* surgical risk	258/ 4560	9.7 (6.4 −14.0)	24.3 (23.0 −25.1)	0.675 (0.647−0.710) *vs* 0.585 (0.552−0.623)
Self-reported metabolic equivalents plus surgical risk *vs* surgical risk—excluded low-risk patients based on surgical risk	211/ 3201	11.8 (7.8 −16.9)	0.52 (0.50 −0.54)	0.642 (0.608−0.683) *vs* 0.544 (0.504−0.588)

were confirmed in a more detailed analysis of those data offering insights on cut-off Duke Activity Status Index scores.[9] In contrast, in the Measurement of Exercise Tolerance before Surgery study, functional capacity semi-quantitatively estimated by the attending physicians (n=1351) was not independently associated with all-cause mortality and myocardial infarction.[8] We consider the divergent findings may arise from a difference in the study population: patients in the present analysis were older (mean 73 *vs* 65 yr), more burdened by comorbidities (27% *vs* 12% coronary artery disease; 9% *vs* 1% heart failure; ASA≥3 61% *vs* 34%), which is reflected also in the higher prevalence of functional capacity <4 metabolic equivalents (41% in the present, here approximated by less than two flights of stairs, *vs* 8% in the Measurement of Exercise Tolerance before Surgery study[8]). Further, the primary endpoint in the present study, while including life-threatening arrhythmia and congestive heart failure (in addition to myocardial infarction), focused on cardiac mortality rather than all-cause mortality. Finally, the Measurement of Exercise Tolerance before Surgery study registered only a minimal number of events (two at 30 days and four at 1 yr) in the subgroup of patients with functional capacity <4 metabolic equivalents.[8]

Strengths and limitations

Strengths of our study in terms of selection include a cohort of consecutive patients based on broad inclusions criteria and minimal missing data in terms of exposure, follow-up, and covariables. Misclassification bias in terms of self-reported functional capacity cannot be excluded (i.e. overestimation or underestimation of fitness by the patients), however, (1) this is reflective of clinical routine, and (2) can be expected to be non-differential because of the prospective approach.

We are aware of the following limitations: first, the data were generated in two centres only. Second, the routine functional capacity assessment was binary (self-reported ability to climb less than 2 flights of stairs) (i.e. we were not able to address the impact of other daily activities to approximate other metabolic equivalents cut-off, e.g. 10 metabolic equivalents). Third, we used self-reported functional capacity based on cut-off daily activities only and did not apply any validated formal functional capacity assessment tool. However, the estimation based on 'cut-off' daily activities is guideline-endorsed.[24]

Fourth, in this analysis we focused on 30-day cardiac death and other major adverse cardiac events, whereas the primary endpoint in the parent study (NCT 02573532) was 1-year all-cause mortality. The preference of this endpoint as a primary endpoint was driven by its perceived better alignment with the use of self-reported functional capacity endorsed by the guidelines.

Fifth, perioperative myocardial injury was determined based on hs-cTnT and s-cTnI. However, perioperative myocardial injury was not the primary outcome and all the myocardial infarctions included in the primary composite endpoint fulfilled the fourth universal definition.[22]

Sixth, the full model underestimated 30-day major adverse cardiac events in the lower quintiles. However, first, our aim was to assess the independent association between functional capacity and major adverse cardiac events and not to derive a new model for risk classification; second, for the calculation of net reclassification, we did not use the model but applied the RCRI, one of the risk stratification tools recommended by the guidelines.[2,4]

Finally, the use of reclassification has been criticised.[23,24] However, we provided desegregated values for events and non-events and the 'crude' reclassification tables in the Supplementary material. Further, to avoid influence by the choice of categories, we used published categories and reported the continuous NRI as well.

In conclusion, in patients at high cardiovascular risk undergoing inhospital noncardiac surgery, self-reported functional capacity less than two flights of stairs, one of the daily activities used by guidelines to estimate 4 metabolic equivalents, was independently associated with cardiovascular death and major adverse cardiac events at 30 days and 1 yr. The addition of self-reported functional capacity information to surgical risk and clinical risk stratification resulted in significant reclassification improvement in a large number of patients.

Authors' contributions

Design, analysis, interpretation, drafting: GLB, CP, DMG, CM
Data acquisition, revision for important intellectual content, final approval of the version to be published, agreement to be accountable for all aspects of the work; all authors, Basel-PMI Investigators listed below.

Declarations of interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2020.08.041.

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