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Association of six-minute walk test distance with postoperative complications in non-cardiac surgery: a secondary analysis of a multicentre prospective cohort study

Association entre la distance parcourue pendant le test de marche de six minutes et les complications postopératoires en chirurgie non cardiaque : une analyse secondaire d'une étude de cohorte prospective multicentrique

Ryan J. Ramos, BSc · Karim S. Ladha, MD, MSc · Brian H. Cuthbertson, MBChB, MD · Mark A. Shulman, MBBS, MPH · Paul S. Myles, MBBS, MPH, MD, DSc · Duminda N. Wijeysundera, MD, PhD, FAHA ⬤ on behalf of the METS Study Investigators

Abstract

Purpose The six-minute walk test (6MWT) is a simple and valid test for assessing cardiopulmonary fitness. Nevertheless, the relationship between preoperative 6MWT distance and postoperative complications is uncertain. We conducted a secondary analysis of the 6MWT nested cohort substudy of the Measurement of Exercise Tolerance before Surgery study to determine if 6MWT distance predicts postoperative complications or death.

Methods This analysis included 545 adults (≥ 40 yr) who were at elevated cardiac risk and had elective inpatient non-cardiac surgery at 15 hospitals in Canada, Australia, and New Zealand. Each participant performed a preoperative 6MWT and was followed for 30 days after surgery. The primary outcome was moderate or severe in-hospital complications. The secondary outcome was 30-day death or myocardial injury. Multivariable logistic regression modelling was used to characterize the

R. J. Ramos, BSc
Faculty of Medicine, University of Toronto, Toronto, ON, Canada

K. S. Ladha, MD, MSc · D. N. Wijeysundera, MD, PhD, FAHA (✉)
Department of Anesthesia, St Michael's Hospital, 30 Bond Street, Toronto, ON M5B 1W8, Canada
e-mail: d.wijeysundera@utoronto.ca

Li Ka Shing Knowledge Institute, St Michael's Hospital, Toronto, ON, Canada

Department of Anesthesiology and Pain Medicine, University of Toronto, Toronto, ON, Canada

Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, ON, Canada

B. H. Cuthbertson, MBChB, MD
Department of Anesthesiology and Pain Medicine, University of Toronto, Toronto, ON, Canada

Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, ON, Canada

Department of Critical Care Medicine, Sunnybrook Health Sciences Centres, Toronto, ON, Canada

M. A. Shulman, MBBS, MPH · P. S. Myles, MBBS, MPH, MD, DSc
Department of Anaesthesia and Perioperative Medicine, Alfred Hospital and Monash University, Melbourne, VIC, Australia

adjusted association of 6MWT distance with these outcomes.

Results *Seven participants (1%) terminated their 6MWT sessions early because of lower limb pain, dyspnea, or dizziness. Eighty-one (15%) participants experienced moderate or severe complications and 69 (13%) experienced 30-day myocardial injury or death. Decreased 6MWT distance was associated with increased odds of moderate or severe complications (adjusted odds ratio, 1.32 per 100 m decrease; 95% confidence interval, 1.01 to 1.73; P = 0.045). There was no association of 6MWT distance with myocardial injury or 30-day death (non-linear association; P = 0.49).*

Conclusion *Preoperative 6MWT distance had a modest association with moderate or severe complications after inpatient non-cardiac surgery. Further studies are needed to determine the optimal role of the 6MWT as an objective exercise test for informing preoperative risk stratification.*

Résumé

Objectif *Le test de marche de six minutes (6MWT) est un test simple et validé pour évaluer la santé cardiopulmonaire. Néanmoins, la relation entre la distance parcourue lors d'un 6MWT préopératoire et les complications postopératoires est inconnue. Nous avons effectué une analyse secondaire de la sous-étude de cohorte imbriquée du 6MWT dans l'étude de la Mesure de la tolérance à l'exercice avant chirurgie (Measurement of Exercise Tolerance before Surgery) afin de déterminer si la distance parcourue lors du 6MWT était prédictive de complications postopératoires ou de décès.*

Méthode *Cette analyse comprenait 545 adultes (≥ 40 ans) courant un risque cardiaque élevé et hospitalisés pour une chirurgie non cardiaque élective dans 15 hôpitaux au Canada, en Australie et en Nouvelle-Zélande. Chaque participant a exécuté un 6MWT préopératoire et a été suivi pendant 30 jours post chirurgie. Le critère d'évaluation principal touchait aux complications modérées ou graves à l'hôpital. Le critère secondaire était le décès à 30 jours ou une lésion myocardique. Un modèle de régression logistique multivariée a été employé pour caractériser l'association ajustée entre la distance parcourue lors du 6MWT et ces critères d'évaluation.*

Résultats *Sept participants (1 %) n'ont pas terminé leurs séances de 6MWT en raison de douleurs aux membres inférieurs, de dyspnée ou de vertiges. Quatre-vingt-un (15 %) participants ont souffert de complications modérées ou graves et 69 (13 %) ont subi une lésion myocardique ou sont décédés à 30 jours. La diminution de la distance parcourue au 6MWT a été associée à une augmentation du risque de complications modérées ou graves (rapport de cotes ajusté, 1,32 par diminution de 100 m; intervalle de confiance 95 %, 1,01 à 1,73; P = 0,045). Aucune association n'a été observée entre la distance parcourue au 6MWT et la lésion myocardique ou le décès à 30 jours (association non linéaire; P = 0,49).*

Conclusion *La distance parcourue lors d'un 6MWT préopératoire a été modestement associée à des complications modérées ou graves après une chirurgie non cardiaque avec hospitalisation. D'autres études sont nécessaires pour déterminer le rôle optimal du 6MWT en tant que test d'exercice objectif pour informer la stratification préopératoire des risques.*

Assessment of functional capacity is a ubiquitous component of preoperative evaluation for major surgery. A key intended purpose for evaluating functional capacity is to identify patients at increased risk of major postoperative complications. The most common method for assessing functional capacity is "subjective assessment", where a physician makes a judgement following an unstructured patient interview. Recent research has shown that subjective assessment is neither an accurate measure of preoperative cardiopulmonary fitness nor an important prognostic indicator of perioperative risk.[1] A possibly better alternative for assessing functional capacity is cardiopulmonary exercise testing (CPET), which has been described as the "gold-standard" non-invasive measurement of the integrated cardiopulmonary response to exercise.[2] Metrics derived from CPET, including peak oxygen consumption, anaerobic threshold, and inability to complete the exercise test have moderate ability to predict major postoperative complications.[1,3,4] Despite these promising data, an important practical impediment to widespread adoption of preoperative CPET is the associated need for specialized equipment and trained personnel.

A more feasible alternative may be the six-minute walk test (6MWT), which is a simple, cheap, and clinically acceptable measure of cardiopulmonary fitness.[5] The 6MWT involves walking for six minutes on a flat 30-m course while standardized instructions and encouragement are provided.[5] Performance is based on the total distance walked. The 6MWT has excellent reliability, and good construct validity based on moderate-to-strong correlation to CPET performance.[6] The test is safe, with significant adverse events being rare (1%).[6] The 6MWT has been considered a possible tool for preoperative assessment of functional capacity. In limited prior research, it was a similarly valid measure of cardiopulmonary fitness in

surgical patients, based on moderate correlation with peak oxygen consumption and anaerobic threshold measured by CPET.[7] Nonetheless, there remains uncertainty as to whether 6MWT distance predicts complications after major non-cardiac surgery. Outside the specialized context of lung cancer resection surgery,[8,9] prior relevant research consists of small studies (< 150 participants) with mixed results. Some studies found an association between 6MWT distance and complications,[10–15] while others did not.[16,17] Thus, there is a need for larger high-quality studies to better assess the role, if any, of the 6MWT in preoperative risk stratification.

We therefore conducted a secondary analysis of the 6MWT substudy of the Measurement of Exercise Tolerance before Surgery (METS) prospective cohort study. The METS study was a multicentre prospective cohort study that compared subjective assessment, CPET, natriuretic peptides, and a structured questionnaire for predicting death and major complications in 1,400 patients undergoing major non-cardiac surgery.[1] The 6MWT-METS substudy included 545 participants who underwent both 6MWT and CPET before elective inpatient non-cardiac surgery. Its primary aim was to characterize the association of 6MWT distance with two validated patient-reported outcomes: 30-day quality of recovery and one-year disability-free survival.[18] In this secondary analysis of the 6MWT-METS substudy, we sought to determine whether 6MWT distance predicted two clinically relevant postoperative adverse events (i.e., moderate or severe in-hospital postoperative complications, myocardial injury, or 30-day postoperative death), and to characterize the association between preoperative 6MWT distance and CPET performance.

Methods

Study design

We conducted a secondary analysis of the 6MWT-METS substudy. The METS study was an international multicentre prospective cohort study of adults (≥ 40 yr) who were deemed to be at elevated risk for postoperative cardiac complications and scheduled to have major elective inpatient non-cardiac surgery. The objectives, methods, and primary results of the METS study have been previously reported.[1,19] The 6MWT-METS substudy was a nested cohort study at 15 hospitals in Canada, Australia, and New Zealand. Each study centre obtained research ethics board approval before commencing recruitment, and all participants provided written informed consent.[18] Additional research ethics approval for this secondary

analysis was provided by the Unity Health Toronto Research Ethics Board.

Participants and study procedures

Participants were eligible for inclusion in the METS study if they were aged ≥ 40 yr, scheduled to have elective inpatient non-cardiac surgery, and had one or more risk factors for ischemic heart disease or postoperative cardiac complications (Appendix 1). Exclusion criteria are presented on Appendix 2. Prior to surgery, all participants underwent CPET on a cycle ergometer and underwent blood sampling to measure serum N-terminal pro-B-type natriuretic peptide (NT pro-BNP) concentrations. At the 15 hospitals participating in the substudy, all participants in the main METS study were approached to consider participation in the 6MWT-METS substudy. Participants who consented to the substudy also completed the 6MWT before surgery. Participants were followed for 30 days after surgery to ascertain mortality and specific complications (Appendix 3).

Six-minute walk test and CPET procedures

The 6MWT was conducted according to the American Thoracic Society guidelines.[20] Where possible, the 6MWT was performed on a different day from CPET; otherwise, the 6MWT was completed after CPET, with a minimum two-hour break between tests. After delivery of standardized instructions, participants completed as many laps as possible in six minutes on a flat indoor 30-m course. Walk distance (m) was calculated from the number of complete laps and distance walked in any final partial lap. This distance represents a valid test performance, regardless of the occurrence of rests or early termination. Healthcare providers were kept blinded to the 6MWT results.

Participants performed symptom-limited incremental CPET on a computer-controlled, electromagnetically braked cycle ergometer using a standardized protocol. A trained investigator at each centre used full-page graphs of the plotted local CPET data to determine peak oxygen consumption and anaerobic threshold using standardized protocols. The protocols used for the conduct and interpretation of CPET have been previously described.[1,19]

Outcomes

The primary outcome was postoperative moderate or severe in-hospital complications (including fatal events). The severity of complications was graded using a modified Clavien–Dindo classification system (Appendix 3).[21,22] The secondary outcome was myocardial injury or death

within 30 days after surgery. Myocardial injury was defined as a troponin concentration exceeding both the 99th percentile upper reference limit and threshold at which the assay coefficient of variation was 10%.[23] Participants underwent daily electrocardiogram and troponin measurements up to the third day after surgery or hospital discharge (whichever came first). Research personnel ascertaining the presence of complications were blinded to CPET and 6MWT results.

Statistical analysis

All participants who completed the 6MWT and had surgery were included in the main analyses. Descriptive statistics were initially used to characterize the sample with respect to baseline characteristics, operative features, and postoperative outcomes, both overall and across strata defined by tertiles of 6MWT distance. Categorical variables were compared using Chi square or Fisher's exact test, while continuous variables were compared using analysis of variance or the Kruskal–Wallis test.

We then applied bivariate tests to compare strata defined by the presence or absence of the primary and secondary outcomes. Categorical data were compared using the Chi square or Fisher exact test, while continuous variables were compared using the two-sample *t* test or Mann–Whitney U test. Multivariable logistic regression models were used to separately evaluate the adjusted association of preoperative 6MWT distance with these outcomes. Model covariates were selected *a priori* based on clinical sensibility, prior evidence, their inclusion in guideline-recommended assessment algorithms (i.e., Revised Cardiac Risk Index [RCRI] and natriuretic peptides for cardiac risk stratification), consistency with prior analyses of the METS study cohort,[1] and the need to prevent model overfitting. For the model predicting moderate or severe complications, the covariates were age, sex, and high-risk surgery (intraperitoneal, retroperitoneal, intrathoracic, or major vascular procedures).[1,24] For the model predicting 30-day death or myocardial injury, the covariates were age, sex, RCRI score, and NT pro-BNP concentration.[1,24] As recommended by the Canadian Cardiovascular Society guidelines, NT pro-BNP concentration was dichotomized based on a 300 ng·L^{-1} threshold.[25] To account for non-linear relationships between continuous predictor variables (i.e., 6MWT distance, age) and outcomes, we used restricted cubic spline plots to determine which transformation or categorization—if any—was necessary. Associations were expressed as adjusted odds ratios (aORs) with 95% confidence intervals (CIs). Model discrimination was characterized by the c-index, while calibration was assessed using the Hosmer–Lemeshow statistic. If a regression model showed preoperative 6MWT distance to be associated with the outcome of interest, the additional prognostic information associated with 6MWT distance was characterized by the change in the area under the receiver-operating-characteristic (ROC) curve,[26] continuous net reclassification index (NRI), and integrated discrimination improvement (IDI).[27,28]

The primary analysis was a complete case analysis because missing data were uncommon (< 6%) and largely pertained to information on baseline characteristics. We assumed that the single participant lost to follow-up between hospital discharge and the 30th postoperative day remained alive during this follow-up window. Analyses were conducted using the R statistical language (Version 4.0.2; R Foundation for Statistical Computing, Vienna, Austria) and RStudio (Version 1.3.1056; RStudio PBC, Boston, MA, USA) software. Statistical significance was defined as a two-tailed *P* value < 0.05 and no adjustment was made for multiple comparisons. The number of participants available for this substudy was determined by the sample size calculations for the METS study and 6MWT-METS substudy.[1,18,19]

Cardiopulmonary exercise testing subset analysis

To determine the correlation between 6MWT distance and measures of cardiopulmonary fitness from CPET (i.e., peak oxygen consumption, anaerobic threshold), we conducted a subset analysis of participants who underwent both 6MWT and CPET. This analysis was restricted to patients who successfully completed their exercise test (6MWT *vs* peak oxygen consumption) or who had a measurable anaerobic threshold (6MWT *vs* anaerobic threshold) because peak oxygen consumption is unlikely to represent cardiopulmonary fitness when an exercise test is terminated early for reasons (i.e., arthritis pain) other than the patient reaching their limit of tolerance, and about 9% of patients in the main METS study sample had an indeterminate anaerobic threshold.[1] The correlation between 6MWT distance and CPET measures was characterized using the Spearman coefficient.

Sensitivity analyses

We repeated the analyses after including different model covariates and using bootstrap resampling (1,000 samples) to internally validate the regression models.

Post hoc analyses

In response to comments from external peer reviewers, we conducted a *post hoc* analysis to determine whether performance of preoperative CPET and the 6MWT on the same day altered the prognostic accuracy of 6MWT

distance. First, mean 6MWT distance was compared between participants who performed the 6MWT on the same day as CPET compared with participants who did not. Second, we evaluated whether performance of CPET on the same day as the 6MWT modified the adjusted association between 6MWT distance and the primary outcome (i.e., moderate or severe complications). A multivariable logistic regression model was estimated using the following predictor variables: age, sex, high-risk surgery, 6MWT distance, same-day CPET testing, and the interaction between 6MWT distance and same-day CPET testing. Effect modification was assessed based on the statistical significance of the interaction term.

Results

Participant characteristics

From 31 July 2013 to 16 December 2015, 574 patients were recruited into the 6MWT-METS substudy (Fig. 1). All participants performed the 6MWT before surgery while 545 (95%) had surgery. The 6MWT was terminated early in seven participants (1.2%) because of dyspnea, dizziness, and lower limb pain. The sample characteristics, both overall and across tertiles of 6MWT performance, are presented in Table 1. The overall mean (standard deviation [SD]) age was 64 (11) yr, with 39% ($n = 215$) being female,

Fig. 1 Patient flow diagram showing the number of patients included in the analysis. 6MWT = 6-minute walk test; NT pro-BNP = N-terminal pro-B-type natriuretic peptide
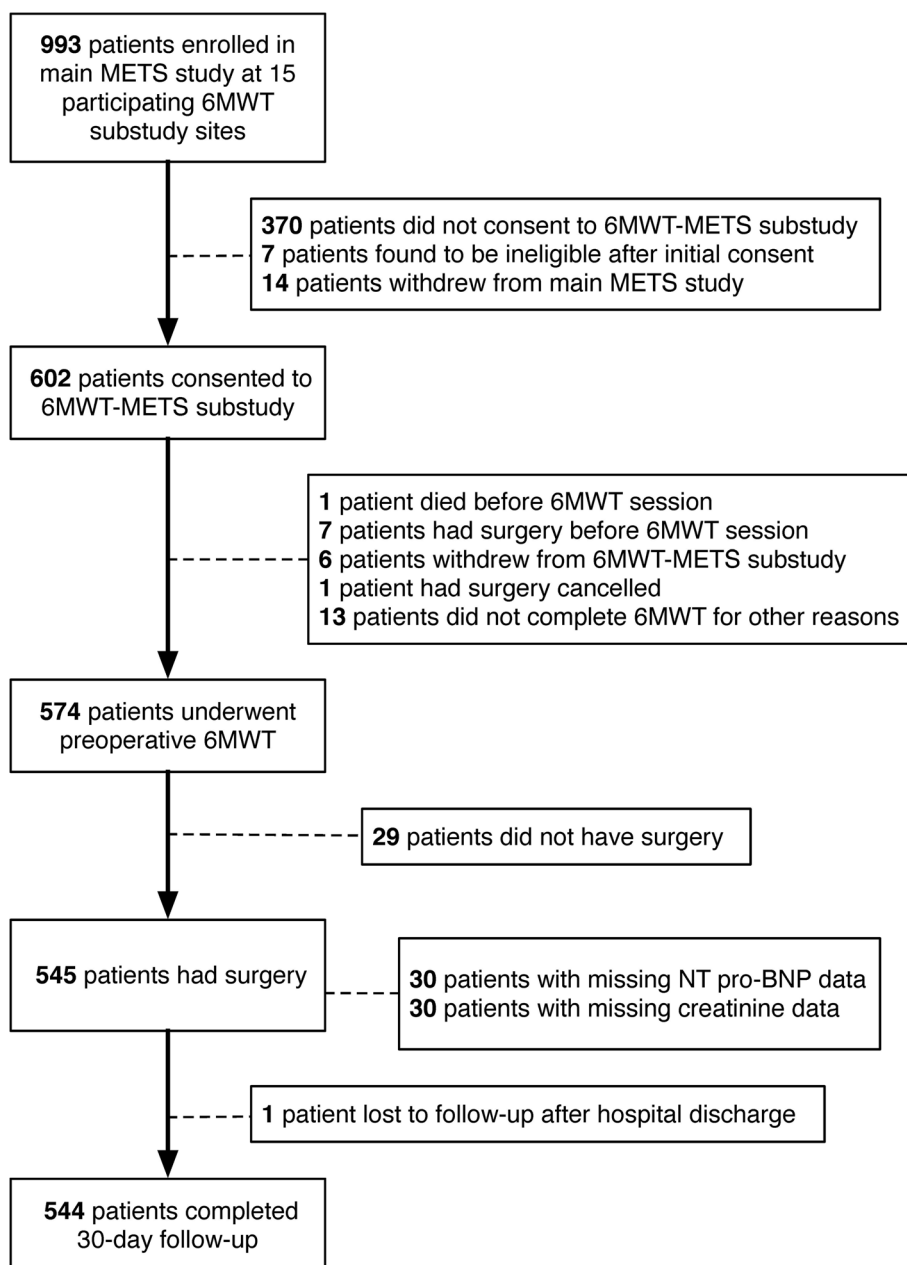
Table 1 Patient characteristics ($n = 545$) across 6MWT distance tertiles

Variable	Low (<435 m)	Middle	High (>510 m)	Total	P value
Patient characteristics					
Age (yr), mean (SD)	68 (10)	63 (11)	61 (10)	64 (11)	<0.001
Female sex, n (%)	90 (50)	72 (38)	53 (30)	215 (39)	<0.001
BMI (kg·m^{-2}), mean (SD)	31 (8)	30 (7)	29 (8)	30 (7)	0.08
Comorbidities, n (%)					
Coronary artery disease	41 (23)	34 (18)	27 (15)	102 (19)	0.16
Heart failure	11 (6)	4 (2)	3 (2)	18 (3)	0.03
Cerebrovascular disease	14 (8)	8 (4)	9 (5)	31 (6)	0.31
Peripheral artery disease	10 (6)	7 (4)	2 (1)	19 (4)	0.07
Diabetes mellitus	46 (26)	38 (20)	28 (16)	112 (21)	0.06
Hypertension	124 (69)	124 (66)	95 (53)	343 (63)	0.003
Atrial fibrillation	15 (8)	5 (3)	5 (3)	25 (5)	0.01
Recent smoker*	22 (12)	42 (23)	30 (17)	94 (17)	0.04
Obstructive lung disease[†]	35 (20)	24 (13)	18 (10)	77 (14)	0.03
Arthritis	80 (47)	52 (30)	39 (23)	171 (31)	<0.001
Renal function, (n=515), n (%)[‡]					
eGFR $\geq$ 60 mL·min^{-1} (1.73 m)$^{-2}$	139 (81)	157 (90)	159 (94)	455 (88)	0.005
eGFR 30-59 mL·min^{-1} (1.73 m)$^{-2}$	29 (17)	17 (9)	8 (5)	54 (11)	
eGFR <30 mL·min^{-1} (1.73 m)$^{-2}$ or dialysis	3 (2)	1 (1)	2 (1)	6 (1)	
Peak oxygen consumption (mL O$_2$ kg^{-1}·min^{-1}) (n=431), mean (SD)	18 (6)	21 (7)	24 (7)	21 (7)	<0.001
Anaerobic threshold (mL O$_2$ kg^{-1} min^{-1}) (n=420), mean (SD)	12 (4)	13 (5)	15 (4)	14 (4)	<0.001
Natriuretic peptide concentration (n=515), n (%)					
NT pro-BNP <100 ng·L^{-1}	71 (41)	88 (50)	111 (66)	270 (52)	<0.001
NT pro-BNP 100 ng·L^{-1} to < 300 ng·L^{-1}	54 (32)	67 (38)	42 (25)	163 (32)	
NT pro-BNP ng·L^{-1} $\geq$300 ng·L^{-1}	46 (27)	20 (12)	16 (9)	82 (16)	
ASA physical status score, n (%)					
I	5 (3)	7 (4)	10 (6)	22 (4)	0.06
II	88 (49)	109 (58)	110 (61)	307 (56)	
III	81 (45)	70 (37)	57 (32)	208 (38)	
IV	5 (3)	1 (1)	2 (1)	8 (2)	
Revised Cardiac Risk Index (n=518), n (%)[¶]					
Class 1	56 (33)	56 (32)	55 (32)	167 (32)	0.28
Class 2	66 (39)	82 (46)	84 (49)	232 (45)	
Class 3	40 (23)	28 (16)	27 (16)	95 (18)	
Class 4	9 (5)	10 (6)	5 (3)	24 (5)	
Operative characteristics					
Procedure type, n (%)					
Vascular	8 (5)	7 (4)	2 (1)	17 (3)	<0.001
Intrathoracic	6 (3)	7 (4)	9 (5)	22 (4)	
Intraperitoneal or retroperitoneal	52 (29)	74 (39)	53 (30)	179 (33)	
Urological or gynecological	37 (21)	48 (26)	72 (40)	157 (29)	
Head-and-neck	18 (10)	24 (13)	15 (8)	57 (11)	
Orthopedic	54 (30)	19 (10)	15 (8)	88 (16)	
Other	4 (2)	8 (4)	13 (7)	25 (4)	

Table 1 continued

Variable	Low (<435 m)	Middle	High (>510 m)	Total	*P* value
Postoperative hospitalization					
Postoperative length-of-stay (day), median [IQR]	4 [2–7]	4 [2–6]	4 [2–12]	4 [2–6]	0.56

Data displayed are for lower (< 435 m), middle and upper (> 510 m) tertiles of 6MWT distances. Categorical variables were compared using χ^2 or Fisher's exact test, while continuous variables were compared using analysis of variance (ANOVA) or the Kruskal–Wallis test

ASA = American Society of Anesthesiologists; BMI = body mass index; eGFR = estimated glomerular filtration rate; IQR = interquartile range; 6MWT = six-minute walk test; NT pro-BNP = N-terminal pro-B-type natriuretic peptide

*Current smoker or quit within the previous year

† Prior diagnosis of asthma, reactive airways disease, chronic obstructive lung disease, chronic bronchitis, or emphysema

‡ Estimated glomerular filtration rate was calculated using the preoperative serum creatinine concentration and Chronic Kidney Disease Epidemiology Collaboration equation

¶ Revised Cardiac Risk Index scores were calculated using a modified definition of diabetes mellitus (i.e., any prior diagnosis of diabetes mellitus, as opposed to requirement for insulin therapy)

62% (*n* = 336) having major abdominal or pelvic procedures, 63% (*n* = 327) being classified as RCRI class 2 or 3, and 16% (*n* = 82) having preoperative NT pro-BNP concentrations exceeding the high-risk threshold of 300 ng·L^{-1}. Five hundred and twenty-three (96%) patients had non-thoracic surgery. The mean (SD) preoperative 6MWT distance was 474 (100) m. When tertiles of 6MWT distance were compared, patients in the lower tertiles were more likely to be older and female, as well as more likely to have some comorbidities (e.g., arthritis, obstructive lung disease, renal insufficiency) and elevated NT pro-BNP concentrations.

Postoperative outcomes

Eighty-one (15%) participants experienced moderate or severe complications and 69 (13%) experienced myocardial injury or 30-day death. Among the 81 participants experiencing the primary outcome, common individual events included major bleeding (26%), re-operation (20%), surgical site infection (19%), and pneumonia (14%) (eTable 1 in the Electronic Supplementary Material [ESM]). Individual events associated with 30-day death or myocardial injury are presented in eTable 2 (ESM).

Prediction of moderate or severe postoperative complications

In unadjusted comparisons, participants who did or did not experience moderate or severe complications differed with respect to cardiovascular comorbidities (i.e., atrial fibrillation), NT pro-BNP concentration, RCRI score, and surgery type (Table 2). Mean (SD) 6MWT distance was 457 (97) m in patients who experienced moderate or severe

complications compared with 477 (100) m in those who did not (*P* = 0.10).

Restricted cubic spline analyses showed a linear adjusted association between 6MWT distance and complications (eFig. 1, ESM). We therefore considered 6MWT distance a continuous variable in the final multivariable regression model, where decreased 6MWT distance was associated with increased adjusted odds of postoperative complications (aOR, 1.32 per 100 m decrease; 95% CI, 1.01 to 1.73; *P* = 0.045) (Table 3). Preoperative 6MWT distance did not provide significant additional prognostic accuracy on top of age, sex, and high-risk surgery based on the change in the area under the ROC curve (increase in area from 0.67 to 0.68; *P* = 0.42), continuous NRI (0.18; 95% CI, -0.06 to 0.41; *P* = 0.14) and IDI (0.008; 95% CI, -0.0003 to 0.017; *P* = 0.06).

Prediction of 30-day death or myocardial injury

In unadjusted comparisons, the participants who did or did not experience myocardial injury or 30-day death or differed with respect to age, cardiovascular comorbidities (i.e., coronary artery disease, cerebrovascular disease), NT pro-BNP concentration, RCRI, surgery type, and 6MWT distance (eTable 3, ESM). After adjustment for RCRI score and NT pro-BNP concentration, restricted cubic spline analyses showed a non-linear association between 6MWT distance and myocardial injury or 30-day death (eFig. 2, ESM). In multivariable logistic regression analyses, the 6WMT distance was therefore modelled flexibly using a restricted cubic spline function. There was no strong association of 6MWT distance with 30-day death or myocardial injury (*P* = 0.49) (Table 4).

Table 2 Bivariate comparisons between patients who did *vs* did not experience postoperative in-hospital moderate or severe complications

Variable	Mild or no complications (n = 464)	Moderate or severe complications (n= 81)	P value
Patient characteristics			
Age (yr), mean (SD)	64 (11)	65 (11)	0.2
Female sex, *n* (%)	191 (41)	24 (30)	0.05
BMI (kg·m^{-2}), mean (SD)	30 (7)	29 (6)	0.3
Comorbidities, *n* (%)			
Coronary artery disease	85 (18)	17 (21)	0.57
Heart failure	13 (3)	5 (6)	0.12
Cerebrovascular disease	25 (5)	6 (7)	0.47
Peripheral artery disease	17 (4)	2 (3)	0.59
Diabetes mellitus	93 (20)	19 (24)	0.48
Hypertension	288 (62)	55 (68)	0.32
Atrial fibrillation	17 (4)	8 (10)	0.01
Recent smoker*	74 (16)	20 (25)	0.06
Obstructive lung disease†	68 (15)	9 (11)	0.40
Arthritis	150 (32)	21 (26)	0.25
6MWT distance in metres, mean (SD)	477 (100)	457 (97)	0.10
Renal function, (n=515), *n* (%)‡			
eGFR $\geq$ 60 mL·min^{-1} (1.73 m)$^{-2}$	393 (90)	62 (79)	0.03
eGFR 30 to 59 mL·min^{-1} (1.73 m)$^{-2}$	40 (9)	14 (18)	
eGFR < 30 mL·min^{-1} (1.73 m)$^{-2}$ or dialysis	4 (1)	2 (3)	
Natriuretic peptide concentration (n=515), *n* (%)			
NT pro-BNP <100 ng·L^{-1}	241 (55)	29 (37)	0.003
NT pro-BNP 100 ng·L^{-1} to <300 ng·L^{-1}	135 (31)	28 (36)	
NT pro-BNP ng·L^{-1} $\geq$ 300 ng·L^{-1}	61 (14)	21 (27)	
ASA Physical Status Score, *n* (%)			
I	19 (4)	3 (4)	0.48
II	267 (58)	40 (49)	
III	172 (37)	36 (44)	
IV	6 (1)	2 (1)	
Revised Cardiac Risk Index (n=518), *n* (%)¶			
Class 1	156 (34)	11 (14)	0.001
Class 2	191 (41)	41 (51)	
Class 3	76 (16)	19 (24)	
Class 4	17 (4)	7 (9)	
Operative characteristics			
Procedure type, *n* (%)			
Vascular	14 (3)	3 (4)	0.005
Intrathoracic	21 (5)	1 (1)	
Intraperitoneal or retroperitoneal	136 (29)	43 (53)	
Urologic or gynecologic	141 (30)	16 (20)	
Head-and-neck	51 (11)	6 (7)	
Orthopedic	79 (17)	9 (11)	
Other	22 (5)	3 (4)	

Table 2 continued

Variable	Mild or no complications(n = 464)	Moderate or severe complications(n= 81)	P value
Postoperative hospitalization			
Postoperative length-of-stay (day), median [IQR]	3 [2–5]	10 [7.5–16.5]	<0.001

Categorical variables were compared using χ^2 or Fisher's exact test, while continuous variables were compared using the two-sample t test or Mann–Whitney U test

ASA = American Society of Anesthesiologists; BMI = body mass index; eGFR = estimated glomerular filtration rate; IQR = interquartile range; NT pro-BNP = N-terminal pro-B-type natriuretic peptide; 6MWT = six-minute walk test; SD = standard deviation

*Current smoker or quit within the previous year

[†] Prior diagnosis of asthma, reactive airways disease, chronic obstructive lung disease, chronic bronchitis, or emphysema

[‡] Estimated glomerular filtration rate was calculated using the preoperative serum creatinine concentration and Chronic Kidney Disease Epidemiology Collaboration equation

[¶] Revised Cardiac Risk Index scores were calculated using a modified definition of diabetes mellitus (i.e., any prior diagnosis of diabetes mellitus, as opposed to requirement for insulin therapy)

Cardiopulmonary exercise testing subset analysis

Ninety-two percent ($n = 501$) of the primary analysis cohort attempted preoperative CPET. The test was terminated early in 67 patients, with the most common reason being an inability to pedal ($n = 23$) (eTable 4, ESM). There was a modest correlation between either 6MWT distance and peak oxygen consumption ($\rho = 0.390$; $P < 0.001$) or 6MWT distance and anaerobic threshold ($\rho = 0.311$; $P < 0.001$) (Fig. 2).

Sensitivity analyses

The adjusted association of the 6MWT distance with the primary and secondary outcomes was qualitatively unchanged in sensitivity analyses with bootstrap internal validation and different model covariates (eTable 4, ESM).

Post hoc analyses

Two hundred and seventy-three participants (50%) performed CPET and the 6MWT on the same day. The mean (SD) 6MWT distance did not significantly differ between participants who performed CPET and the 6MWT on the same day compared with those who did not [480 (99) m *vs* 467 (101) m, respectively; mean difference, -13 m; 95% CI, -29 to 4; $P = 0.14$]. The association of preoperative 6MWT with moderate or severe complications was modified ($P = 0.045$) by performance of CPET and the 6MWT on the same day (model presented in eTable 5, ESM). Reduced preoperative 6MWT was associated with increased odds of moderate or severe complications (aOR, 1.79 per 100 m decrease; 95% CI, 1.20 to 2.66) among individuals who did not perform CPET on the same day as the 6MWT, but not among

Table 3 Adjusted association of 6MWT distance and other clinical risk factors with moderate or severe postoperative in-hospital complications

Risk factor	Odds ratio (95% CI) for moderate or severe complications	P value
6MWT distance		
Per 100-m decrease	1.32 (1.01 to 1.73)	0.045
Surgical procedure		
Moderate-risk procedure	Reference	
High-risk procedure	3.43 (2.04 to 5.78)	< 0.001
Sex		
Male	Reference	
Female	0.62 (0.36 to 1.07)	0.09
Age		
Per 10-yr increase	1.11 (0.87 to 1.42)	0.42

Model was fit using 545 observations with complete data. The multivariable regression model had a c-index of 0.68 and Hosmer–Lemeshow goodness-of-fit statistic P value of 0.84

CI = confidence interval; 6MWT = six-minute walk test

individuals who did (aOR, 1.06 per 100 m decrease; 95% CI, 0.75 to 1.50).

Discussion

In this secondary analysis of a multicentre prospective cohort study, reduced preoperative 6MWT distance was associated with increased odds of moderate or severe in-hospital complications, even after adjusting for other easily measured clinical characteristics such as demographics and surgery type. Nonetheless, the strength of statistical evidence for this association was modest; furthermore,

Table 4 Adjusted association of 6MWT distance and other clinical risk factors with 30-day death or myocardial injury

Risk factor	Odds ratio (95% CI) for 30-day death or myocardial injury	*P* value
6MWT distance*		
500 m *vs* 600 m	1.00 (0.65 to 2.90)	
400 m *vs* 600 m	1.61 (0.72 to 3.56)	0.49
300 m *vs* 600 m	1.13 (0.46 to 2.79)	
Sex		
Male	Reference	
Female	1.03 (0.56 to 1.90)	0.91
Age		
Per 10-yr increase	1.81 (1.32 to 2.50)	< 0.001
Revised Cardiac Risk Index		
Class 1	Reference	
Class 2	1.58 (0.73 to 3.40)	0.04
Class 3	3.15 (1.35 to 7.36)	
Class 4	3.33 (1.00 to 11.08)	
NT pro-BNP concentration		
< 300 ng·L^{-1}	Reference	
≥ 300 ng·L^{-1}	1.48 (0.75 to 2.91)	0.26

Model was fit using 515 observations with complete data. The multivariable regression model had a c-index of 0.73 and Hosmer–Lemeshow goodness-of-fit statistic *P* value of 0.31

CI = confidence interval; 6MWT = six-minute walk test

*Adjusted odds ratios were extrapolated based on a restricted cubic spline function with four knots (to account for non-linear association of 6MWT distance with the outcome)

we did not find evidence that 6MWT distance provided incremental prognostic information for predicting postoperative complications. By comparison, 6MWT distance had no meaningful association with or myocardial injury or 30-day postoperative death. These overall findings were consistent after accounting for other preoperative risk factors and internal validation using bootstrap resampling.

While previous studies, including the primary report of the METS study, have shown that metrics derived from CPET performance can predict postoperative complications,[1,3] there are important practical limitations to the widespread implementation of preoperative CPET. Stated simply, it requires capital, technical, and professional costs that render it infeasible in many settings. Within that context, the 6MWT has several attractive features, including relatively low resource requirements, standardized protocols, and excellent tolerability. For example, in the cohort included in this

secondary analysis, only about 1% of 6MWT sessions were terminated early compared with 13% of CPET sessions.

Our study also confirmed the validity of the 6MWT as a measure of preoperative cardiopulmonary fitness based on the correlation of 6MWT distance with peak oxygen consumption and anaerobic threshold. Nevertheless, the magnitude of this correlation was weaker than was observed in other cohort studies where the correlations were instead in the range of 0.64 to 0.75.[7,29,30] Nonetheless, the 6MWT and CPET had similar profiles with respect to preoperative risk assessment, in that both 6MWT and peak oxygen consumption were predictive of moderate or severe complications but not myocardial injury.[1] Notably, CPET measurements were determined by investigators across 15 participating hospitals, which raises the possibility of observer and measurement bias between centres. It is possible that central interpretation of CPET data could have altered the observed correlation between 6MWT distance and CPET performance.

The results are an important addition to the literature on the validity of the preoperative 6MWT in estimating perioperative risk outside the specialized context of lung cancer resection surgery. Some prior studies have found associations between 6MWT distance and outcomes,[10–15] while others have not.[16,17] These studies typically had small sample sizes with fewer than 150 participants, and included specific subsets of surgical patients, thereby limiting the generalizability of their results. In addition, there was considerable variability in how these studies defined complications. Some studies used standardized measures such as the Clavien–Dindo classification scheme,[11,15] while others used self-defined cardiopulmonary complications[13] or solely pulmonary complications.[12,14,17] Compared with this prior work, our present study included a moderately large cohort of patients having major non-cardiac surgery and systematically followed up participants to ascertain several clinically and prognostically important outcomes.

Prior studies have focused on identifying thresholds of 6MWT performance to identify patients at elevated risk of postoperative complications, especially since simple thresholds may be attractive to clinicians.[12,14,15] Nonetheless, our results would caution against interpreting preoperative 6MWT performance based on this approach. From a methodological perspective, dichotomization of continuous predictor variables in clinical prediction models can lead to loss of statistical power, residual confounding, and serious bias.[31,32] Thus, allocation of patients into one of two risk categories based on preoperative 6MWT performance can lead to overly simple and incorrect clinical decisions. Instead, there appears to be a linear association between 6MWT distance and complications, whereby risk plausibly
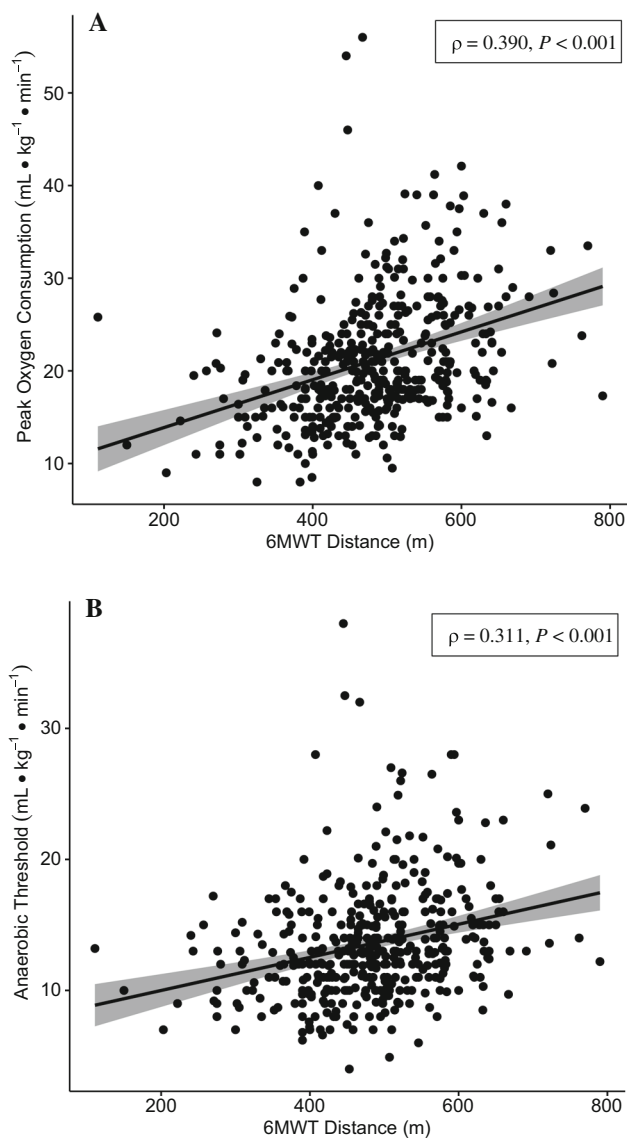
Fig. 2 Correlation between the six-minute walk test (6MWT) distance and peak oxygen consumption or VO$_2$ peak (panel A) and anaerobic threshold or AT (panel B)

increased on a *continuum* as 6MWT performance decreased. We found that each 100 m decrease in 6MWT distance was associated with an approximately 30% increase in the adjusted odds of complications. Thus, clinical prediction rules that include actual 6MWT distance may be more appropriate for risk-stratifying patients.

Our study has multiple strengths, including the prospective, international, multicentre, and diverse study cohort. There was minimal patient loss to follow-up and minimal incomplete data. The primary outcome, moderate or severe complications as defined by the modified Clavien–Dindo classification system, is an accepted measure of postoperative morbidity. In addition, the secondary outcome, 30-day death or myocardial injury, is an objective and prognostically important endpoint.

Our study has several important limitations that should be considered when interpreting the findings. First, 6MWT performance can be affected by factors other than cardiopulmonary fitness, such as patient comorbidities (e.g., peripheral artery disease, arthritis), coordination, and frailty. Second, the requirement that participants perform two preoperative exercise tests (6MWT and CPET) before surgery likely introduced selection bias, whereby healthier patients were more likely to participate in this study. Consistent with this possibility, the risk of 30-day death or myocardial infarction in the METS-6MWT substudy cohort was only one-third of that seen in more generalizable cohorts where intensive preoperative exercise testing was not required.[18,33] Thus, it is possible the substudy cohort had skewed distributions of both 6MWT results and other predictors of postoperative complications that affected the strength of association between 6MWT distance and outcomes. Third, the study design allowed for preoperative CPET and 6MWT to be performed on the same day, largely for pragmatic reasons. While such participants had to rest for at least two hours between the exercise tests, exploratory subgroup analyses suggest that preoperative 6MWT distance was predictive of moderate or severe complications only if the 6MWT and CPET were performed on separate days. From a clinical perspective, these findings suggest that participants who had performed CPET and the 6MWT on the same day were not sufficiently rested between the two exercise tests. Since subgroup analyses should be interpreted very cautiously,[34] our findings warrant replication in a future study that specifically disallows any other exercise testing on the same day as the preoperative 6MWT. Fourth, while the sample size of this study was larger than previous studies, it is likely still not sufficiently large for robust development of a clinical prediction model. Even a relatively simple multivariable regression model with the same four predictor variables used in our primary analysis (age, sex, surgical procedure, 6MWT distance) should likely include 12 parameters to allow for flexible modelling of continuous variables (age, 6MWT distance),[35] and more clinically appropriate categorization of surgical procedures.[36] Assuming the same primary outcome rate (15%) observed in the 6MWT-METS substudy, a minimum sample size of 697 is needed to develop a plausible clinical prediction model.[37]

Conclusions

In this secondary analysis of a multicentre prospective cohort study, preoperative 6MWT distance had a modest ability to predict moderate or severe complications, but not 30-day death or myocardial injury, after major inpatient

non-cardiac surgery. Further large, prospective studies are needed to determine the optimal role of the 6MWT as a simple objective exercise test to inform preoperative risk stratification for non-cardiac surgery.

Appendix 1

See Table 5.

Table 5 Inclusion criteria for the METS study (one or more had to be present)

Risk factor	Definition
Intermediate to high-risk surgery	Intraperitoneal, intrathoracic, or major vascular (supra-inguinal or lower extremity vascular) procedures
Coronary artery disease	History of angina; myocardial infarction; positive exercise, nuclear or echocardiographic stress test; resting wall motion abnormalities on echocardiogram; coronary angiography with evidence of $\geq 50\%$ vessel stenosis; or electrocardiogram with pathologic Q-waves in two contiguous leads
Heart failure	History of heart failure or diagnostic chest *x-ray* (i.e., pulmonary vascular redistribution or pulmonary edema)
Cerebrovascular disease	History of stroke or transient ischemic attack; or imaging (CT or MRI) evidence of previous stroke
Diabetes mellitus	Requirement for insulin or oral hypoglycemic therapy
Preoperative renal insufficiency	Requirement for renal replacement therapy before surgery, or estimated glomerular filtration rate ≤ 60 mL·min^{-1}·1.73 m^{-2}
Peripheral arterial disease	History of peripheral arterial disease; ischemic intermittent claudication; rest pain; lower limb revascularization procedure; peripheral arterial obstruction of $\geq 50\%$ luminal diameter; or resting ankle/arm systolic blood pressure ratio ≤ 0.90
Hypertension	Doctor's diagnosis of hypertension
Smoker	History of smoking within 1 year before surgery
Advanced age	≥ 70 yr

CT = computed tomography; MRI = magnetic resonance imaging

Appendix 2

See Table 6.

Table 6 Exclusion criteria

At the time of approach for recruitment to study, inadequate time to feasible complete CPET before surgery (defined as < 24 hr)

Planned use of CPET or 6MWT for preoperative risk stratification independent of METS study protocol

Planned surgery exclusively performed by an endovascular approach (e.g., endovascular aortic aneurysm repair)

Presence of an automated implantable cardioverter-defibrillator

Known or suspected pregnancy

Previous enrolment in the METS study

Active cardiac conditions,[38] absolute contraindications to CPET (American Thoracic Society and American College of Chest Physicians guidelines),[39] contraindications to 6MWT,[20] and conditions expected to preclude CPET or 6MWT (e.g., lower limb amputation, severe claudication, severe orthopedic impairment)

Systolic blood pressure ≥ 180 mmHg and diastolic blood pressure ≥ 100 mmHg at the time of study recruitment

CPET = cardiopulmonary exercise testing; METS = Measurement of Exercise Tolerance before Surgery; 6MWT = six-minute walk test

Appendix 3

See Table 7.

Table 7 Definitions of in-hospital postoperative complications

Complication	Definition
Non-fatal cardiac arrest	Successful resuscitation from documented (or presumed) ventricular fibrillation, sustained ventricular tachycardia, asystole, or pulseless electrical activity
Heart failure	Presence of both • clinical findings (i.e., elevated jugular venous pressure, respiratory rates, crepitations, S_3 heart sounds) • radiological findings (i.e., vascular redistribution, interstitial or frank pulmonary edema)
Stroke	New focal neurologic deficit, suspected to be vascular in origin, with signs/symptoms lasting $\geq$ 24 hr
Transient ischemic attack	Transient focal neurologic deficit that lasts less than 24 hr and is thought to be vascular in origin
Respiratory failure	Need for tracheal intubation and mechanical ventilation after patient has completed surgery, been successfully extubated, and breathing spontaneously for > 1 hr
Pneumonia	Documented hypoxemia (PaO_2/F_iO_2 ratio $\leq$ 250 mmHg) or fever (temperature > 37.5°C) with either: 1. Rales or dullness to percussion on chest examination and any of (i) new onset of purulent sputum or change in sputum character; (ii) organism isolated from blood culture; or (iii) pathogen isolated from trans-tracheal aspirate, bronchial brushing, or biopsy 2. New or progressive infiltrate, consolidation, cavitation, or pleural effusion on chest radiograph and any of (a) criteria i, ii, or iii above; (b) detection of virus or viral antigen in respiratory secretions; (c) diagnostic antibody titers; or (d) histopathologic evidence of pneumonia
Surgical site infection	Physician diagnosis of surgical site infection during: • index hospitalization • outpatient visit, hospital re-admission, or emergency room visit within 30 days after index surgery
Deep venous thrombosis	Any of the following during index hospitalization: 1. Persistent intraluminal filling defect on contrast venography 2. One or more non-compressible venous segments on B mode compression ultrasonography 3. Clearly defined intraluminal filling defect on contrast enhanced computed tomography
Pulmonary embolism	Any of the following during index hospitalization: 1. High probability ventilation/perfusion lung scan 2. Intraluminal filling defect of segmental or larger artery on a helical CT scan 3. Intraluminal filling defect on pulmonary angiography 4. A positive diagnostic test for deep venous thrombosis (e.g., positive compression ultrasound) plus low or intermediate probability ventilation/perfusion lung scan, or non-diagnostic (sub-segmental defects or technically inadequate study) helical CT scan
Significant bleeding	Blood loss with any of the following characteristics: 1. Results in drop in hemoglobin concentration of 30 g·L^{-1} or more 2. Leads to red cell transfusion or re-operation 3. Considered the cause of death
Unexpected admission to critical care unit	Unexpected admission to critical care unit, intensive care unit, step-down unit, or high-dependency unit
Re-operation	Return to operating room within index hospitalization
Severity of postoperative complications	1. Mild: only temporary harm that did not require clinical treatment 2. Moderate: required clinical treatment but without significantly prolonged hospital stay. Did not usually result in permanent harm and where this did occur, there was no associated functional limitation 3. Severe: required clinical treatment and resulted in significant prolongation of hospital stay and/or permanent functional limitation 4. Fatal: death from the complication

CT = computerized tomography; ECG = electrocardiogram; PaO_2/F_iO_2 = arterial oxygen partial pressure/fraction of inspired oxygen

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