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Postoperative myocardial injury phenotypes and self-reported disability in patients undergoing noncardiac surgery: a multicentre observational study

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Abstract

Background: Postoperative myocardial injury (PMI) comprises a spectrum of mechanisms resulting in troponin release. The impact of different PMI phenotypes on postoperative disability remains unknown.

Methods: This was a multicentre prospective cohort study including patients aged ≥50 yr undergoing elective major noncardiac surgery. Patients were stratified in five groups based on the occurrence of PMI and clinical information on postoperative adverse events: PMI classified as myocardial infarction (MI; according to fourth definition), PMI plus adverse event other than MI, clinically silent PMI (PMI without adverse events), adverse events without PMI, and neither PMI nor an adverse event (reference). The primary endpoint was 6-month self-reported disability (assessed by WHO Disability Assessment Schedule 2.0 [WHODAS]). Disability-free survival was defined as WHODAS ≤16%.

Results: We included 888 patients of mean age 69 (range 53–91) yr, of which 356 (40%) were women; 151 (17%) patients experienced PMI, and 625 (71%) experienced 6-month disability-free survival. Patients with PMI, regardless of its phenotype, had higher preoperative disability scores than patients without PMI (difference in WHODAS; β: 3.3, 95% confidence interval [CI]: 0.5–6.2), but scores remained stable after surgery (β: 1.2, 95% CI: −3.2–5.6). Before surgery, patients with MI (n=36, 4%) were more disabled compared with patients without PMI and no adverse events (β: 5.5, 95% CI: 0.3–10.8). At 6 months, patients with MI and patients without PMI but with adverse events worsened in disability score (β: 11.2, 95% CI: 2.3–20.2; β: 8.1, 95% CI: 3.0–13.2, respectively). Patients with clinically silent PMI did not change in disability score at 6 months (β: 1.39, 95% CI: −4.50–7.29, P=0.642).

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Conclusions: Although patients with postoperative myocardial injury had higher preoperative self-reported disability, disability scores did not change at 6 months after surgery. However, patients experiencing myocardial infarction worsened in disability score after surgery.

Keywords: disability; myocardial infarction; noncardiac surgery; postoperative myocardial injury; troponins

Editor's key points

- Perioperative cardiac events are a common and important cause of poor outcomes in the months and years after major surgery.
- The mechanism of perioperative cardiac events is debated with some arguing that the dominant cause is plaque rupture coronary thrombosis (classic MI), whereas others believe the problem is multifactorial.
- Understanding the aetiology of this important patient problem is key to developing effective treatments.
- The findings of this study shed further light on the complexity of this problem, with different long-term outcomes for patients with different patterns of cardiac events.

Annually, several hundred million patients undergo noncardiac surgery worldwide.[1,2] Approximately one out of each six of these patients will develop a complication, most commonly an infection.[3] Cardiovascular events are another major cause of postoperative morbidity and mortality.[4–10] However, ischaemic cardiac events are often asymptomatic and go unrecognised.[6] Accordingly, guidelines have suggested postoperative biomarker surveillance to identify patients at risk for such complications.[11–14]

Postoperative myocardial injury (PMI), or an elevated serum troponin concentration,[11,15] occurs in 11–19% of patients undergoing noncardiac surgery.[4–10] Besides cardiac ischaemia, PMI has been associated with a broad spectrum of clinical phenotypes, including myocardial infarction (MI), heart failure, arrhythmia, respiratory failure, pulmonary embolism, renal failure, and sepsis.[4,7–11,16–18] Although the association of PMI and increased mortality has repeatedly been reported, it is unclear how PMI affects patient-centred outcomes such as long-term disability. Research regarding such patient-reported outcomes is important as patients prioritise these over traditional outcomes, such as complications or length of hospital stay.[19,20] Based on the International Classification of Functioning, Disability and Health (ICF), disability is defined as difficulties in different functional domains, including cognition, mobility, self-care, getting along, life activities, and participation during the previous 30 days.[8,21–23]

The primary objective of this study was to characterise the associations between different PMI phenotypes and 6-month self-reported disability in patients undergoing major noncardiac surgery. We hypothesised that PMI, regardless of its phenotype, is associated with increased postoperative disabilities.

Methods

Study design and population

This multicentre, prospective, cohort study included patients undergoing noncardiac surgery at the University Health Network (UHN; Toronto, Canada), the University Medical Center Utrecht (UMCU; Utrecht, The Netherlands), and Erasmus Medical Center (EMC; Rotterdam, The Netherlands). Eligible patients undergoing elective major noncardiac surgery under general or spinal anaesthesia with an expected postoperative hospital stay exceeding 24 h were included. At the UMCU and EMC, patients aged ≥60 yr were included as those patients are part of a standard postoperative troponin monitoring protocol, whereas UHN included patients aged ≥50 yr. Enrolment took place from June 26, 2014 to June 12, 2015, and from January 29, 2018 to April 10, 2021. In the 2014–15 period, patients were recruited at UHN as part of a pilot study aiming to compare postoperative disability in patients with *vs* without PMI (results were never published). Based on the WHO Disability Assessment Schedule 2.0 (WHODAS 2.0) data, the sample size for the presented study was updated and additional patients were recruited in the 2018–21 period resulting in a final study population.

All participants provided written informed consent and the local ethics committees approved the study protocol prior to patient recruitment (Utrecht Medical Research Ethics Committee; 17–673/M and University Health Network Research Ethics Board; 17–5092). Before initiation, the study was registered on ClinicalTrials.gov (NCT02146560, registered on May 26, 2014 and NCT03408522, registered on January 24, 2018). This study was reported in accordance with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement.[24]

Procedures

Patients underwent blood sampling prior to surgery and daily until the third postoperative day or hospital discharge (whichever came first). At UHN and UMCU, high sensitive cardiac troponin (hsTn) was analysed using the ARCHITECT STAT High Sensitive Troponin-I assay (Abbott Diagnostics, Lisnamuck, Longford, Ireland). At EMC, high sensitive troponin T was measured using the Cobas e602 Troponin T hs STAT assay (Roche Diagnostics, Germany). In the analysis, the highest value of all postoperative measurements for each patient was used. Treating physicians were blinded to the biomarker results except if they requested them as part of clinical care. At the UMCU, routine troponin measurements are part of the standard postoperative care protocol and are accordingly always available in clinical practice. At postoperative day 1, a 12-lead ECG was performed and assessed by a cardiologist for signs of ischaemia. Additional diagnostic tests or initiation of therapy was left at the cardiologist's discretion which was done in deliberation with the responsible surgeon.

Data collection and definitions

All data were collected from electronic medical and administrative records. Data were obtained for patient characteristics, comorbidities including active malignancy and the Revised

Cardiac Risk Index (RCRI),[25] chronic medication use (i.e. beta blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, antiplatelets statins, and insulin), surgical characteristics (i.e. specialty, type of anaesthesia, intraoperative blood loss), length of hospital stay, and the occurrence of postoperative adverse events. History of ischaemic heart disease was defined as previous MI, coronary revascularisation, or both; systolic heart failure was defined as a left ventricular ejection fraction ≤40%.

Postoperative adverse events assessed were MI defined by the Fourth Universal Definition of Myocardial Infarction,[11] heart failure requiring consultation and treatment by a cardiologist, arrhythmia diagnosed on 12-lead ECG or cardiac monitor, cerebrovascular accident (defined as radiologically confirmed ischaemic or haemorrhagic stroke or transient ischaemic attack), radiologically confirmed deep venous thrombosis and pulmonary embolism, sepsis as clinically diagnosed by the treating physician and requiring ICU admission, respiratory failure requiring ICU admission, pneumonia requiring antibiotics, acute kidney injury (AKI) defined as an increase in creatinine of 26.4 μmol L^{-1} or 50% from the preoperative creatinine value according to the Acute Kidney Injury Network (AKIN) criteria,[26] reoperations, and in-hospital mortality.

Postoperative myocardial injury phenotypes

PMI was defined as elevated hsTn exceeding the 99th percentile of the used assay with a 10% coefficient of variation.[11,15] In case of preoperative elevated hsTn above the 99th percentile, PMI was defined as an increase of ≥20% of the preoperative hsTn.[15] Patients were stratified in five groups (i.e. PMI phenotypes) based on the combination of the occurrence of PMI or the aforementioned postoperative adverse events. Patients with PMI were divided as: (1) PMI classified as MI (defined according to fourth universal definition of MI[11]); (2) clinically silent PMI (defined as elevated postoperative troponins but not meeting the criteria of MI and occurring without any other postoperative adverse events); and (3) PMI plus occurrence of adverse events other than MI. Patients without PMI were divided as: (1) experiencing an adverse postoperative event; and (2) no adverse events (reference group).

Disability assessment and outcome definitions

Disability was assessed before surgery and then again at 6 months after surgery. Self-reported disability was measured using the 12-item WHODAS 2.0.[23] The WHODAS 2.0 is an easy-to-use and clinically valid tool for measuring postoperative disability.[21,27,28] It was administered by telephone, scored as previously described, and calculated to a percentage, with low scores indicating no/low disability. Patients who died were defined as fully disabled and were therefore assigned a score of 100%. Data on 6-month mortality were retrieved through electronic medical records and the municipal personal records database. Disability-free survival was defined as being alive with a postoperative WHODAS 2.0 score ≤16%.[21] Clinically significant disability was defined as a postoperative WHODAS 2.0 score ≥35%. Patients with a postoperative WHODAS 2.0 score of 17–34% had some disability. New-onset clinically significant disability was defined as an absolute increase of ≥5% in WHODAS 2.0 score in association with a postoperative score of ≥35%. Minimal clinically important difference was defined as an absolute change of ≥5% in WHODAS 2.0 score.[21,27] Patients without at least one complete WHODAS 2.0 assessment were excluded from the analysis.

Sample size

A previously conducted pilot study in major noncardiac surgery (ClinicalTrials.gov: NCT02146560) found a mean 6-month postoperative disability score (as measured by WHODAS 2.0) of 29% in patients with PMI compared with 15% in patients without PMI. Based on these results and using a level of significance of 0.05 and a power of 0.8, 104 patients with PMI were needed. With an expected PMI incidence of 11%, a total of 832 patients were needed. Accounting for 10% loss to follow-up, we aimed to include 900 patients.

Statistical analysis

Baseline characteristics were compared among the PMI phenotypes and presented as mean (standard deviation), median (interquartile range [IQR]), or count (percentage), as appropriate. Categorical variables were compared using the χ^2 test and continuous variables were compared using the one-way ANOVA and Kruskal–Wallis test, as appropriate. Generalised linear mixed models were used to investigate the association between PMI phenotypes and 6-month self-reported disability (on a continuous scale). We assessed whether PMI phenotypes were associated with disability prior to surgery (i.e. coefficients for PMI phenotypes) and with change in disability scores at 6 months after surgery (i.e. interaction between PMI phenotypes and timepoint of disability assessment, i.e. preoperative *vs* postoperative). Patients without PMI and no adverse events served as the reference group.

Multivariable analyses were conducted by adding *a priori* selected confounders to the fixed part of the model. These included age (continuous), sex (dichotomous), RCRI score[25] (categorical; 0, 1, 2, and 3 or more risk factors), and cancer diagnosis (dichotomous). The random part of the model included a random intercept per individual. Restricted maximum likelihood estimation was used to generate unbiased variance estimates. Estimates represent difference in WHODAS 2.0 scores and are expressed as linear regression coefficients (β) with 95% confidence intervals (95% CIs). Thereafter, multivariable Poisson regression analyses were performed to examine the association between PMI phenotypes and the secondary outcomes (i.e. disability-free survival, clinically significant disability, and new-onset clinically significant disability). We used Poisson regression models with robust standard errors to present effect estimates as risk ratios (RRs, with 95% CI) as the aforementioned disability outcomes were relatively common and the rare disease assumption would not hold.[29] The models were adjusted for the same confounders as described before. The complete analytical approach was repeated using PMI as the exposure to assess the association of PMI on 6-month self-reported disability and secondary outcomes. Missing data were observed in, for example, hsTn and WHODAS 2.0 scores, and multiple imputation using the *mice* library was performed to limit bias in effect estimates.[30,31] All aforementioned analyses were performed in 50 imputed datasets and results were pooled using Rubin's rule. Original (i.e. non-imputed) preoperative and 6-month WHODAS 2.0 scores were used in the linear mixed-effects model analyses as imputation of missing outcome data in such models does not increase estimate precision.[32] A

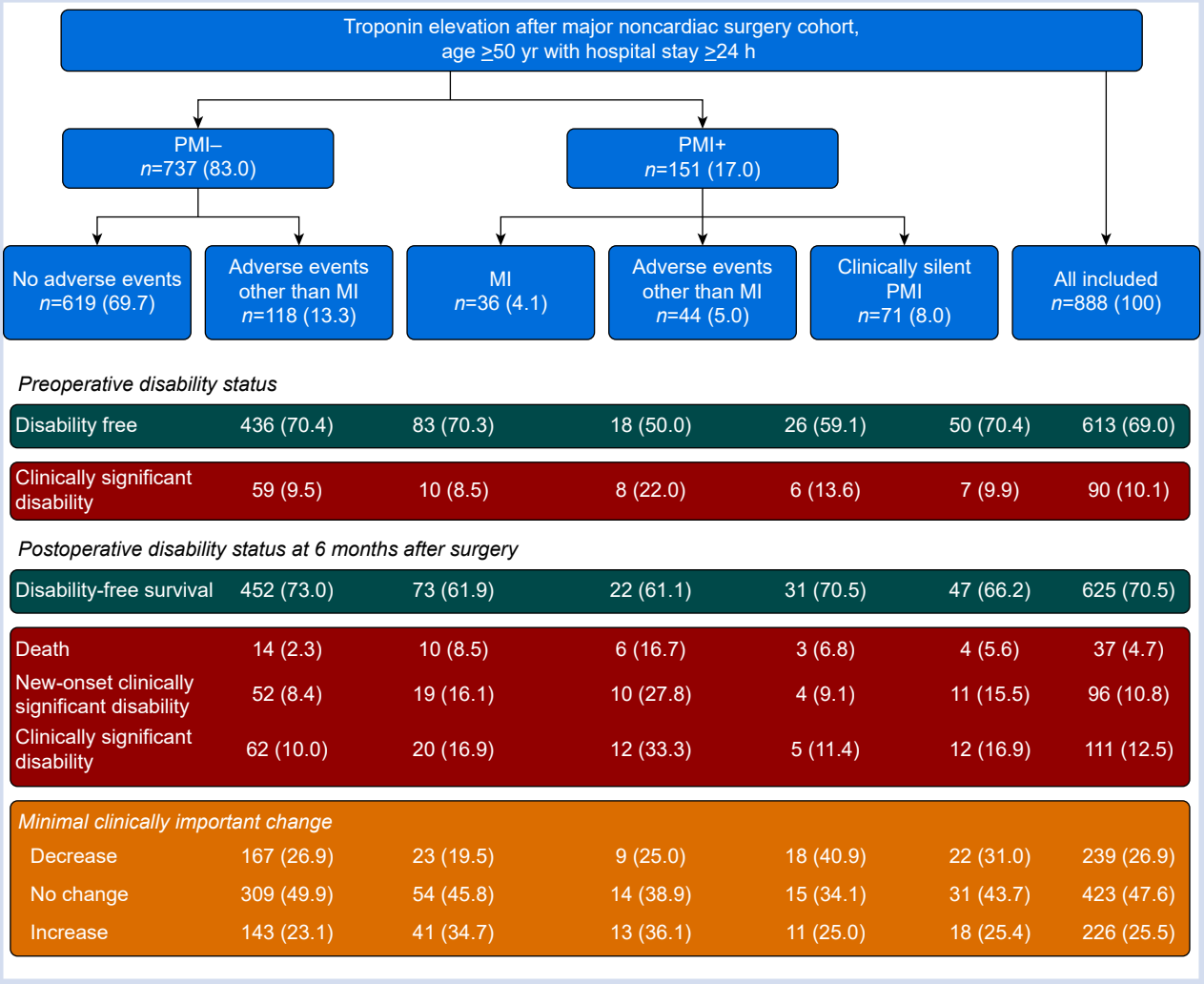

Fig 1. Patient flow with disability status. Clinically significant disability, WHODAS 2.0 score >35%; Disability free or disability-free survival, WHODAS 2.0 score ≤16%; MI, myocardial infarction; minimal clinically important change, ≥5% change in WHODAS 2.0 from preoperative measurement; new-onset clinically significant disability, WHODAS score ≥35% AND worsening in WHODAS 2.0 score ≥5%; non-MI events, in-hospital complications except myocardial infarction; PMI, postoperative myocardial injury; WHODAS, World Health Organization Disability Assessment Score.

two-sided *P*-value of 0.05 was considered statistically significant. Statistical analyses were performed in R Foundation for Statistical Computing, Vienna, Austria (Version 4.0.3 – © 2020-10-10, R, Inc., for Windows).

Results

Patient baseline characteristics

In total, 902 eligible patients provided written informed consent, of whom 14 (1.6%) were excluded because of unexpected discharge on the same day as hospitalisation (n=5), or not completing at least one of the two WHODAS 2.0 questionnaires (n=9). Thus, 888 patients were included in the final analysis. In 126 (14%) patients, only one WHODAS 2.0 questionnaire was available, of whom 58 (7%) had a missing preoperative questionnaire and 68 (8%) had a missing postoperative questionnaire. Prior to surgery, troponin was elevated in 46 (5%) patients. Postoperative troponin was elevated in 185 (21%) patients, of whom 151 (17%) met criteria for PMI. During hospitalisation, 198 (22%) patients suffered one or more complications and 36 (4%) developed an MI (Fig. 1).

The study sample was predominantly male (60%). A substantial proportion of the sample had high-risk surgery according to the RCRI criteria (56%) and had a preoperative diagnosis of cancer (46%) (Table 1). Patients with one available WHODAS 2.0 score had higher RCRI scores, but incidences of preoperative troponin elevation and PMI were similar as were the available WHODAS 2.0 scores (Supplementary Table S1). Patients with PMI, regardless of its phenotype, were older (68.5 *vs* 74.7 yr, P<0.001), underwent more often vascular surgery (19% *vs* 42%, P<0.001), and had more often elevated preoperative troponins (4% *vs* 12%, P<0.001, Supplementary Table S2). Although magnitudes of self-reported disability-free survival

Table 1 Baseline characteristics in patients over the postoperative myocardial injury phenotypes. ACE inhibitor, angiotensin-converting enzyme inhibitor; ENT, ear, nose, and throat; *MI, myocardial infarction; non-MI events, in-hospital complications except myocardial infarction; PMI, postoperative myocardial injury; RCRI, Revised Cardiac Risk Index.

	Overall	No adverse events, PMI −	Adverse events other than MI, PMI−	Myocardial infarction, PMI +	Adverse events other than MI, PMI+	Clinically silent PMI, PMI +	P-value
n	888	619	118	36	44	71	
Age (mean (range))	69.0 (53–91)	68.4 (53–87)	69.0 (55–86)	70.8 (59–86)	71.4 (59–86)	72.4 (57–91)	<0.001
Female (%)	356 (40.1)	244 (39.4)	46 (39.0)	17 (47.2)	13 (29.5)	36 (50.7)	0.177
RCRI score (%)							0.01
0	244 (27.5)	181 (29.2)	27 (22.9)	7 (19.4)	11 (25.0)	18 (25.4)	
1	408 (45.9)	280 (45.2)	63 (53.4)	14 (38.9)	13 (29.5)	38 (53.5)	
2	172 (19.4)	114 (18.4)	24 (20.3)	8 (22.2)	16 (36.4)	10 (14.1)	
≥3	64 (7.2)	44 (7.1)	4 (3.4)	7 (19.4)	4 (9.1)	5 (7.0)	
Revised Cardiac Risk Index (%)							
High-risk surgery	493 (55.5)	340 (54.9)	71 (60.2)	23 (63.9)	26 (59.1)	33 (46.5)	0.317
Ischaemic heart disease	156 (17.6)	107 (17.3)	16 (13.6)	12 (33.3)	10 (22.7)	11 (15.5)	0.074
Heart failure	31 (3.5)	21 (3.4)	2 (1.7)	2 (5.6)	2 (4.5)	4 (5.6)	0.606
Cerebrovascular disease	112 (12.6)	71 (11.5)	16 (13.6)	3 (8.3)	7 (15.9)	15 (21.1)	0.163
Insulin-dependent diabetes mellitus	98 (11.0)	65 (10.5)	11 (9.3)	8 (22.2)	6 (13.6)	8 (11.3)	0.246
Preoperative creatinine >177 μmol dl^{-1}	25 (2.8)	10 (1.6)	6 (5.1)	3 (8.3)	6 (13.6)	0 (0.0)	<0.001
Preoperative elevated troponin (%)	46 (5.2)	23 (3.7)	5 (4.2)	4 (11.1)	5 (11.4)	9 (12.7)	0.002
Malignancy (%)	412 (46.4)	292 (47.2)	59 (50.0)	17 (47.2)	15 (34.1)	29 (40.8)	0.363
Surgical specialty (%)							<0.001
ENT and dental	131 (14.8)	98 (15.8)	17 (14.4)	3 (8.3)	4 (9.1)	9 (12.7)	
General	180 (20.3)	126 (20.4)	29 (24.6)	8 (22.2)	6 (13.6)	11 (15.5)	
Neurosurgery	60 (6.8)	47 (7.6)	9 (7.6)	1 (2.8)	0 (0.0)	3 (4.2)	
Orthopaedic	89 (10.0)	69 (11.1)	12 (10.2)	2 (5.6)	3 (6.8)	3 (4.2)	
Thoracic	45 (5.1)	24 (3.9)	10 (8.5)	5 (13.9)	4 (9.1)	2 (2.8)	
Urological and gynaecological	179 (20.2)	138 (22.3)	18 (15.3)	6 (16.7)	6 (13.6)	11 (15.5)	
Vascular	204 (23.0)	117 (18.9)	23 (19.5)	11 (30.6)	21 (47.7)	32 (45.1)	
Chronic medication use (%)							
Antiplatelet	313 (35.2)	195 (31.5)	45 (38.1)	17 (47.2)	25 (56.8)	31 (43.7)	0.001
Beta blocker	257 (28.9)	149 (24.1)	38 (32.2)	18 (50.0)	20 (45.5)	32 (45.1)	<0.001
Calcium antagonist	198 (22.3)	126 (20.4)	24 (20.3)	13 (36.1)	21 (47.7)	14 (19.7)	<0.001
ACE inhibitor	293 (33.0)	198 (32.0)	38 (32.2)	11 (30.6)	17 (38.6)	29 (40.8)	0.553
Statin	405 (45.6)	267 (43.1)	53 (44.9)	24 (66.7)	28 (63.6)	33 (46.5)	0.008
Centre (%)							<0.001
University Medical Center, Utrecht	492 (55.4)	354 (57.2)	86 (72.9)	12 (33.3)	18 (40.9)	22 (31.0)	
University Health Network, Toronto	313 (35.2)	230 (37.2)	27 (22.9)	20 (55.6)	12 (27.3)	24 (33.8)	
Erasmus Medical Center, Rotterdam	83 (9.3)	35 (5.7)	5 (4.2)	4 (11.1)	14 (31.8)	25 (35.2)	

Table 2 In-hospital complications over the different postoperative myocardial injury phenotypes. IQR, interquartile range; MI, myocardial infarction; NA, not applicable; PMI, postoperative myocardial injury. As patients could experience more than one complication, numbers do not count to the total number of patients per group.

	Overall	No adverse events, PMI −	Adverse events other than MI, PMI−	Myocardial infarction, PMI +	Adverse events other than MI, PMI+	Clinically silent PMI, PMI +	P-value
n	888	619	118	36	44	71	
In-hospital death (%)	10 (1.1)	NA	4 (3.4)	4 (11.1)	2 (4.5)	NA	<0.001
Myocardial infarction (%)	36 (4.1)	NA	0 (0.0)	36 (100.0)	0 (0.0)	NA	<0.001
Arrythmia (%)	31 (3.5)	NA	17 (14.4)	6 (16.7)	8 (18.2)	NA	<0.001
Heart failure (%)	6 (0.7)	NA	1 (0.8)	0 (0.0)	5 (11.4)	NA	<0.001
Deep venous thrombosis (%)	4 (0.5)	NA	3 (2.5)	0 (0.0)	1 (2.3)	NA	0.001
Cerebrovascular accident (%)	9 (1.0)	NA	6 (5.1)	0 (0.0)	3 (6.8)	NA	<0.001
Pulmonary embolism (%)	21 (2.4)	NA	15 (12.7)	3 (8.3)	3 (6.8)	NA	<0.001
Acute kidney injury (%)	62 (7.0)	NA	37 (31.4)	6 (16.7)	19 (43.2)	NA	<0.001
Respiratory failure (%)	24 (2.7)	NA	10 (8.5)	7 (19.4)	7 (15.9)	NA	<0.001
Pneumonia (%)	48 (5.4)	NA	30 (25.4)	5 (13.9)	13 (29.5)	NA	<0.001
Sepsis (%)	11 (1.2)	NA	5 (4.2)	4 (11.1)	2 (4.5)	NA	<0.001
Reoperation (%)	47 (5.3)	NA	25 (21.2)	9 (25.0)	13 (29.5)	NA	<0.001
Length of stay in days (median [IQR])	5 [3–8]	4 [2–7]	9 [6–13]	8 [6–21]	9 [6–17]	4 [3–7]	<0.001
Intraoperative blood loss (%)							<0.001
0–500 ml	713 (80.3)	528 (85.3)	76 (64.4)	21 (58.3)	31 (70.5)	57 (80.3)	
500–1000 ml	93 (10.5)	59 (9.5)	18 (15.3)	6 (16.7)	5 (11.4)	5 (7.0)	
>1000 ml	82 (9.2)	32 (5.2)	24 (20.3)	9 (25.0)	8 (18.2)	9 (12.7)	

varied among the PMI phenotypes and appeared higher among individuals who developed an MI after surgery (Fig. 1), these differences were not statistically significant (χ^2=8.9, df=4, *P*=0.065).

In-hospital adverse events

In total, 309 complications occurred in 198 patients, of which AKI (*n*=62, 20%), pneumonia (*n*=48, 16%), and reoperation (*n*=47, 15%) were diagnosed most frequently (Table 2). In the 151 patients experiencing PMI, 36 (24%) developed an MI. Patients with PMI frequently also had other complications such as respiratory failure, arrhythmia, AKI, or had to undergo a reoperation (Table 2). Patients with PMI had higher estimated blood loss during surgery (>1 L; 17% *vs* 8%, *P*=0.001) and longer hospital stay (median [IQR] in days: 7 [4–13] *vs* 4 [3–8], *P*<0.001) than patients without PMI.

Disability outcomes at 6 months after surgery

At 6 months, 625 (71%) patients were alive and disability-free, and 152 (17%) patients had some disability. Furthermore, 96 (11%) patients experienced new-onset clinically significant disability, of whom 37 (5%) died. Of the 96 patients with new-onset clinically significant disability after surgery, 38 (4%) patients had no disability before surgery, 37 (4%) patients had some disability before surgery, and 21 (2%) patients were already clinically significantly disabled before surgery but worsened to a higher disability score (e.g. from a WHODAS 2.0 score of 40%–50%) (Fig. 1).

Overall, 6-month disability-free survival rates did not differ significantly across the five groups (*P*=0.083). However, patients who experienced complications suffered clinically significant disability or new-onset clinically significant disability more frequently than patients without adverse events (18.7% *vs* 10.7%, *P*=0.004 and 16.7% *vs* 9.1% *P*=0.004, respectively). In approximately half of all included patients, disability scores changed <5% and a quarter had a minimal clinically important decrease of at least 5% (i.e. improvement) in disability score, which was not different among the PMI phenotypes (*P*=0.181 and *P*=0.079, respectively). Figure 2 shows the transition in disability status from before surgery to 6 months after surgery for the PMI phenotypes. Multivariable Poisson regression models showed no statistically significant associations between any of the PMI phenotypes with disability-free survival, clinically significant disability, nor new-onset clinically significant disability (Supplementary Tables S3 and S4).

Association between postoperative myocardial injury phenotypes and disability scores

Patients diagnosed with malignancy had better disability scores prior to surgery, as their difference in WHODAS 2.0 (i.e. β) was −4.81 (95% CI −6.80 to −2.83, *P*<0.001) compared with patients without malignancy (Table 3). Similarly, females scored worse after surgery (β: 3.25, 95% CI: 1.26–5.24, *P*=0.001). Those who experienced an MI after surgery had a higher preoperative disability score than patients with no PMI and without adverse postoperative events (β: 5.52, 95% CI: 0.25–10.8, *P*=0.040).

Overall, WHODAS 2.0 did not change between the preoperative measurement and 6 months after surgery (β: 0.96, 95% CI: −1.01 to 2.92, *P*=0.340). However, patients who developed an MI and those without PMI experiencing adverse events worsened in disability score at 6 months compared with patients with no PMI and without adverse events (β: 11.23, 95% CI: 2.29–20.2, *P*=0.014 and β: 8.08, 95% CI: 3.02–13.15, *P*=0.002, respectively). This means that, for example, patients who developed an MI had a 16.75%-point higher WHODAS 2.0 (i.e. 5.52+11.23=16.75) at 6 months after surgery than patients with no PMI and without adverse events. Patients with clinically silent PMI had similar preoperative disability scores compared with those with no PMI and without adverse events (β: 2.31, 95% CI: −1.69–6.31, *P*=0.257) and did not change in disability score at 6 months (β: 1.39, 95% CI: −4.50–7.29, *P*=0.642).

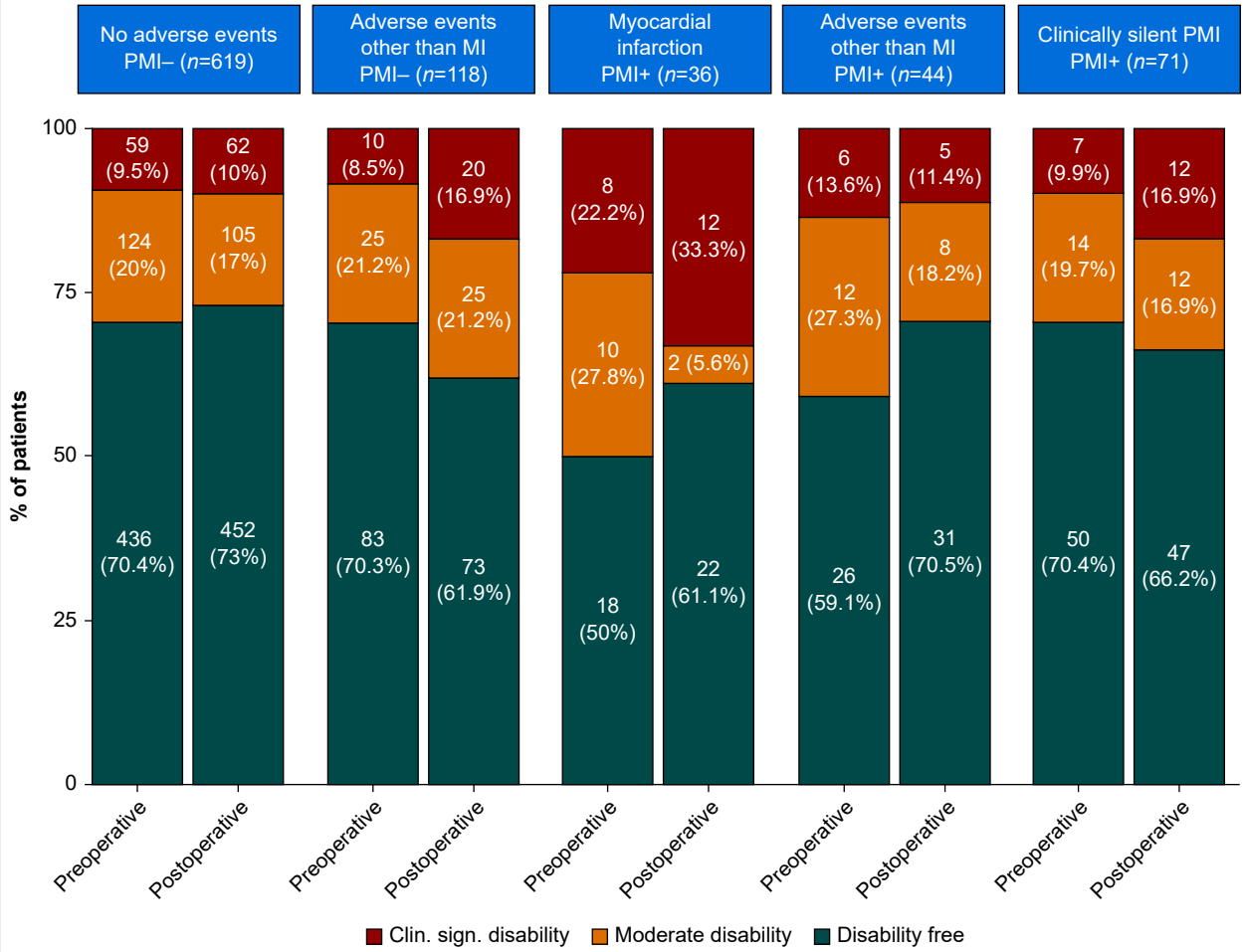

Fig 2. Disability status prior to and 6 months after surgery over the different postoperative myocardial injury (PMI) phenotypes. Clin. sign. disability, clinically significant disability; MI, myocardial infarction.

Patients with PMI, regardless of its phenotype, had higher disability scores prior to surgery (β: 3.33, 95% CI: 0.51–6.15, P=0.021), but disability scores at 6 months were not different from patients without PMI (β: 1.20, 95% CI: −3.19–5.58, P=0.592, Supplementary Table S4).

Discussion

We investigated the relationship between different PMI phenotypes and disability 6 months after major noncardiac surgery. This prospective multicentre study has several main findings. Firstly, experiencing an MI was associated with a worsened self-reported disability score at 6 months after surgery (i.e. change in WHODAS 2.0 score was 11% points compared with before surgery). Moreover, patients diagnosed with MI after surgery already were more disabled prior to surgery than patients without PMI and without adverse postoperative events. Secondly, regardless of its phenotype, PMI was associated with more disabilities prior to surgery, but disability scores 6 months after surgery were similar to patients without PMI. Thirdly, patients experiencing PMI were also often diagnosed with other cardiac and noncardiac complications such as pneumonia, respiratory failure, and AKI.

PMI has been associated with a broad spectrum of different phenotypes of which MI is the best known.[4,7–11,16–18] As most of these (ischaemic) complications are not recognised because typical symptoms are absent in the postoperative period, several guidelines have recommended routine cardiac biomarker surveillance to facilitate early detection.[11–14] In our sample, 151 (17%) patients had PMI and without routine troponin surveillance, many MIs (n=36, 24% of PMI cases) and clinically silent PMI (n=71, 47% of PMI cases) would not have been detected. Patients who developed an MI often also had other complications, such as arrhythmia (n=6, 17%), respiratory failure (n=7, 19%), and pneumonia and (n=5, 14%). Patients who experienced PMI with adverse events other than MI most often suffered AKI, pneumonia, or had to undergo another surgery. PMI can be considered as a biomarker of adversity in patients at high risk for complications (i.e. both cardiac and noncardiac events), disability, or death. Accordingly, further research should focus on prognostication of postoperative disabilities aiming to inform patients prior to surgery or during hospital admission and on interventions

Table 3 Mixed model analyses of the association between postoperative myocardial injury (PMI) phenotype and 6-month self-reported disability score. CI, confidence interval; MI, myocardial infarction; Ref, reference; WHODAS, World Health Organization Disability Assessment Score. *The β coefficients with 95% CI represent the differences in WHODAS 2.0 scores. For example, the β for myocardial infarction indicates a 5.52 higher WHODAS 2.0 score prior to surgery compared with patients with no adverse events. In general, WHODAS 2.0 remains stable between the preoperative and postoperative measurement (β with 95% CI: 0.96 [−1.01 to 2.92]). The interaction between timing of disability assessment and PMI phenotype presents the change in WHODAS 2.0 over time (i.e. postoperative *vs* preoperative measurement) for each PMI phenotype (e.g. β with 95% CI: 11.23 [2.29–20.16]). This means that patients who developed a myocardial infarction had a 16.75%-point higher WHODAS 2.0 (5.52+11.23=16.75) at 6 months after surgery than patients who did not suffer any adverse events.

	β	95% CI	*P*-value
(Intercept)	18.96	(8.98–28.94)	<0.001
Patient characteristics			
Age (yr)	−0.06	(−0.20 to 0.08)	0.380
Female sex	3.25	(1.26–5.24)	0.001
Malignancy	−4.81	(−6.80 to −2.83)	<0.001
Revised Cardiac Risk Index			
0	Ref	Ref	Ref
1	-4.43	(−6.76 to −2.11)	<0.001
2	0.94	(−2.00 to 3.88)	0.531
≥3	6.10	(1.76–10.43)	0.006
PMI phenotype			
No adverse events	Ref	Ref	Ref
Adverse events other than MI, PMI−	0.80	(−2.24 to 3.85)	0.604
Myocardial infarction (MI)	5.52	(0.25–10.78)	0.040
Adverse events other than MI, PMI+	3.65	(−1.05 to 8.35)	0.128
Clinically silent PMI	2.31	(−1.69 to 6.31)	0.257
Preoperative vs postoperative			
Timing disability assessment	0.96	(−1.01 to 2.92)	0.340
No adverse events * timing disability assessment	Ref	Ref	Ref
Adverse events other than MI, PMI− * timing disability assessment	8.08	(3.02–13.15)	0.002
Myocardial infarction * timing of disability assessment	11.23	(2.29–20.16)	0.014
Adverse events other than MI, PMI+ * timing of disability assessment	-1.84	(−9.44 to 5.76)	0.635
Clinically silent PMI * timing of disability assessment	1.39	(−4.50 to 7.29)	0.642

(e.g. lifestyle or cardiac workup) in these patients at increased risk in an attempt to avoid disability or death.

Currently, patient-centred outcome measures including health-related quality of life, days alive and out of hospital, and long-term disability-free survival are becoming increasingly important.[22,33–35] These measures are important to assess as the patient-centred impact of complications such as MI or stroke on long-term recovery may vary considerably. [28] Disability-free survival has been of particular interest in multiple studies[34,36,37]; however, comparison of different types of patients in a heterogeneous surgical population is challenging. Firstly, consider the patient undergoing a hip replacement, who is disabled before surgery because of limited mobility, likely experiences long-term disability-free survival because surgery resolves the disability. In a heterogeneous surgical population, the orthopaedic patient is compared with someone undergoing surgery for cancer. The oncologic patient often has no presurgical disability but may become severely disabled after surgery as a result of disease progression. Subgroup analyses or future investigations, such as based on surgical specialty, might be beneficial to provide better individualised treatment recommendations to improve postoperative patient-centred outcomes. Beattie and colleagues[8] previously found that each of the PMI subtypes was associated with reduced disability-free survival 1 yr after surgery. This study underlines that patients developing a postoperative MI, including silent MIs which are not apparent in routine clinical practice without active troponin surveillance, are already more disabled prior to surgery and become worse after surgery. This means that postoperative MI is still a severe complication and regardless of efforts to avoid MI (and also PMI), appropriate treatment, or both,[38,39] patients are more disabled after surgery than patients without any adverse events. However, the current investigation cannot reproduce the finding of Beattie and colleagues[8] that PMI phenotypes other than MI are associated with more postoperative disabilities. This may be because of the different tools that were used to assess disability-free survival, a different follow-up period (i.e. 6 months *vs* 1 yr), and the considerably smaller sample size of the current study. However, we did find that patients with PMI regardless of its phenotype were more disabled before surgery, but disability scores did not change after surgery. Although numerous studies showed associations between PMI and postoperative mortality,[4,6,7] our study shows that these patients did not worsen in disability scores at 6 months after surgery. More research is needed to validate this result. This includes that a larger number of patients in each of the PMI groups would be required to compare the effects on disability and death.

To the best of our knowledge, this is the first study reporting on the relation between PMI with its different phenotypes and disability 6 months after major surgery. Although this was a prospective multicentre study enabling generalisability to a wide variety of surgical patients, several limitations must be addressed. Firstly, some in-hospital complications, such as pulmonary embolism or MI occurring after the third postoperative day, might have been missed as these were not always recognised in clinical practice.[6,40,41] Adjudication of complications was solely based on the clinical, laboratory, and diagnostic work-up data that was available as part of routine

clinical care. This could have resulted in an underestimation of the true incidence of these complications. Furthermore, we did not collect information on the timing of occurrence of postoperative adverse events, meaning that we do not know whether PMI occurred before or after an adverse event. We hypothesise that PMI is secondary to other adverse events meaning that PMI most likely occurs after development of postoperative events.[9] Secondly, the troponin assay used at UMCU and UHN (hsTnI) was different from the assay used at EMC (hsTnT), indicating that the assays could have different sensitivities. For the definition of PMI, the assay-specific URL was used as recommended in current guidelines.[11–14]

Thirdly, regarding the outcome measures, the definition of new-onset clinically significant disability does not differentiate patients who worsened from no disability to clinically significant disability (e.g. from a WHODAS 2.0 score of 10%–50%) from patients who were already disabled before surgery but worsened further (e.g. from a WHODAS 2.0 score of 40%–50%), although it may be relevant to distinguish these patients from each other. Nevertheless, we believe that the disability definitions as proposed by Shulman and colleagues[21] currently best reflect the true patients' outcomes.

Fourthly, the number of patients in whom disability status was known both before and after surgery was smaller (N=725) than the anticipated sample size (N=832). Also, the number of patients with disability in each of the five groups was small, which may have led to an underpowered analysis.

Finally, all adverse events other than MI were combined into one outcome. Although it would be of interest to analyse these separately, the numbers of patients in the five groups did not allow this.

Conclusions

Patients with postoperative myocardial injury after surgery had more preoperative disabilities, but after surgery disability scores were not different from those of patients without postoperative myocardial injury. However, the subgroup of patients with postoperative myocardial injury developing a postoperative myocardial infarction worsened significantly in disability score after surgery. Postoperative myocardial infarction still is a severe complication, not only resulting in increased mortality but also in more disabilities. Early recognition and management of myocardial infarction and other complications after noncardiac surgery might not only prevent mortality but also improve long-term disability-free survival.

Authors' contributions

Study conception and design: LMV, JvW, WAvK, WSB.
Data acquisition: LMV, JvW, RBG, FvL, SF, MM, MMcK, WAvK, WSB.
Data analysis: LMV, JvW, WAvK, WSB.
Data interpretation: LMV, JvW, RBG, WAvK, WSB.
Drafting of manuscript: LMV, JvW, WAvK, WSB.
Revising of manuscript critically for important intellectual content: all authors.
Final approval of manuscript: all authors.
All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Declaration of interest

The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

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