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BRIEF COMMUNICATION

Preoperative Factors Predict Memory Decline After Coronary Artery Bypass Grafting or Percutaneous Coronary Intervention in an Epidemiological Cohort of Older Adults

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BACKGROUND: Durable memory decline may occur in older adults after surgical (coronary artery bypass grafting [CABG]) or nonsurgical (percutaneous coronary intervention) coronary revascularization. However, it is unknown whether individual memory risk can be predicted. We reanalyzed an epidemiological cohort of older adults to predict memory decline at ≈1 year after revascularization.

METHODS AND RESULTS: We studied Health and Retirement Study participants who underwent CABG or percutaneous coronary intervention at age ≥65 years between 1998 and 2015 and participated in ≥1 biennial postprocedure assessment. Using a memory score based on direct and proxy cognitive tests, we identified participants whose actual postprocedure memory score was 1–2 ("mild") or >2 ("major") SDs below expected postprocedure performance. We modeled probability of memory decline using logistic regression on preoperatively known factors and evaluated model discrimination and calibration. A total of 1390 participants (551 CABG, 839 percutaneous coronary intervention) underwent CABG/percutaneous coronary intervention at 75±6 years old; 40% were women. The cohort was 83% non-Hispanic White, 8.4% non-Hispanic Black, 6.4% Hispanic ethnicity, and 1.7% from other groups masked by the HRS (Health and Retirement Study) to preserve participant confidentiality. At a median of 1.1 (interquartile range, 0.6–1.6) years after procedure, 267 (19%) had mild memory decline and 88 (6.3%) had major memory decline. Factors predicting memory decline included older age, frailty, and off-pump CABG; obesity was protective. The optimism-corrected area under the receiver operator characteristic curve was 0.73 (95% CI, 0.71–0.77). A cutoff of 50% probability of memory decline identified 14% of the cohort as high risk, and was 94% specific and 30% sensitive for late memory decline.

CONCLUSIONS: Preoperative factors can be used to predict late memory decline after coronary revascularization in an epidemiological cohort with high specificity.

Key Words: memory ■ neurocognitive disorder ■ postoperative cognitive decline ■ prediction ■ surgery

Durable cognitive decline, including major and minor postoperative neurocognitive disorder (PND), is a feared outcome following coronary revascularization procedures such as coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI). Based on data for postoperative cognitive decline (POCD), the incidence of PND >6 months after CABG is likely to be 25% to 38%[1]; 3-month POCD after elective left heart catheterization occurs in 8% to 13%.[2] POCD is associated with decreased quality of life and functional capacity, earlier departure from the workforce, future Alzheimer' disease and Alzheimer' disease–related dementias, and premature mortality.[3,4]

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Calls for broadly discussing PND/POCD as part of informed consent preoperatively have been largely unheeded, and a better understanding of individualized risk for PND may help with preoperative risk discussions. While some cohort average risk factors have been described (eg, older age, preoperative low cognition, preoperative depression, and postoperative delirium[5]), there are currently no predictive models for anticipated postoperative cognitive outcome after coronary revascularization. We recently showed that there is no population-average change in memory performance or dementia risk in older adults following CABG versus PCI.[6] However, there was a group of individuals who underwent CABG or PCI and met adapted criteria for PND based on memory decline at cognitive testing 0 to 2 years after their procedure. We reanalyzed the cohort of older adults from this study to establish whether preoperative factors predict long-term memory decline after coronary revascularization with CABG or PCI.

METHODS

We analyzed a previously described[6] cohort of participants in the HRS (Health and Retirement Study), linked to Medicare fee-for-service billing data. HRS is a prospective, longitudinal survey of US adults that collects economic, health, family, and lifestyle data via biennial detailed interviews. HRS's sampling schema deliberately oversamples participants from minority racial and ethnic backgrounds. Participants in the HRS gave verbal informed consent for participation in the study, and data collection practices are approved by the University of Michigan, which administers the HRS. The University of California, San Francisco, Committee on Human Research waived the requirement for participant consent for this analysis. HRS public data are available from the University of Michigan under conditions of data use available at https://hrs.isr.umich.edu/data-products. The analytic code used in this study is available from the corresponding author upon reasonable request.

We analyzed community-dwelling participants who enrolled in the HRS between 1992 and 2010 and underwent CABG or PCI identified by *International Classification of Diseases, Ninth Revision* (*ICD-9*) procedure codes between 1998 and 2015. Using results from the HRS's direct or proxy cognitive assessments according to established methodology, we calculated a "memory score" (analogous to a *z*-score) for cognitive performance for each participant at the pre- and postprocedure interviews.[7] The actual change in memory score from pre- to postprocedure was adjusted by the expected cognitive change derived from a group of age- and sex-matched older adults without reported cardiac disease. We used the SD of the preprocedure memory score for CABG/PCI recipients to identify participants whose adjusted postprocedure memory score was >2 SDs below their expected score (major memory decline) or 1 to 2 SDs below expectation (mild memory decline).[6,8] No preoperative diagnoses of cognitive impairment were made; the absolute amount of cognitive change from pre- to postprocedure was used for cognitive outcome stratification.

Predictor variables were drawn from the closest HRS interview within 3 years before the procedure. Where possible, cleaned and processed variables prepared by the RAND Center for the Study of Aging were used. Candidate variables included procedure type (CABG with cardiopulmonary bypass, off-pump CABG, or PCI), age at procedure, sex, marital status (partnered versus not partnered), total financial assets dichotomized at the median value of $168 274, educational attainment, 4-category body mass index (BMI), patient-reported history of diabetes, heart problems, or stroke, depressive symptoms measured by a modified 8-item Centers for Epidemiologic Studies Depression Scale dichotomized using a cut point of 3, frailty operationalized by translation of the "functional domains" model into variables available through the HRS core interview,[9] independence in instrumental activities of daily living, duration between the procedure and the postprocedure interview (ie, recovery time), and baseline memory score. While the HRS does collect race or ethnicity data (participant-reported, but categorized according to investigator-defined categories), race and ethnicity were intentionally not used in modeling because of the unmeasured complexity of social, structural, and medical racism (eg, limited access to care). Categories used to describe the cohort were non-Hispanic White, non-Hispanic Black, Hispanic ethnicity, and other, a category used by the HRS to preserve participant confidentiality which includes masked classifications (Asian, Pacific Islander, American Indian, and Alaska Native).

Multiple imputation with chained equations was used to address missingness in Centers for Epidemiologic Studies Depression Scale (5.3%), frailty (3.2%), financial assets (1.0%), and BMI (0.5%); remaining variables had <0.5% missingness. We used ordered logistic regression for Centers for Epidemiologic Studies Depression Scale (8 levels), and linear regression for total financial assets and BMI. Since these 3 predictors were operationalized as binary (depression and assets) or multilevel variables (BMI) in the final model, we then passively imputed their categorical values based on their imputed values. The largest fraction of missing information was 0.225, so we used 25 imputations; the average relative variance increase was 0.0192, suggesting that missing data had a small effect on the variance of the estimates, and the interpretation of the findings was no different for a model run on the data before imputation.

Statistical Analysis

Analysis was carried out in Stata/MP 17 (StataCorp, College Station, TX). Unadjusted associations between 3-level memory decline categories (ie, no, mild, and major memory decline) and preoperatively known characteristics were assessed with χ^2 tests for binary and categorical variables and ordinal regression by memory category for continuous variables. The primary analytic strategy was a logistic regression model for any memory decline (mild or major) incorporating all variables described above. Predictor variables were entered into the model without regard to statistical significance or variable selection. Sensitivity analysis with ordinal regression by memory category resulted in substantially similar findings. Model discrimination was assessed with the area under the receiver operator characteristic curve, and calibration with a calibration plot (module pmcalplot for Stata). We calculated an optimism-corrected area under the receiver operator characteristic curve using bootstrapping with 1250 replications (ie, 50 replicates per multiply-imputed data set) with replacement, and calculated the location-shifted bootstrap CI. Lack of model sensitivity to death as a competing risk was assessed by constructing a prediction model for a composite of death before cognitive assessment *or* mild or major memory decline; model interpretation was not substantively different. Author ELW had full access to the data in the study, and takes responsibility for integrity of the data and its analysis.

RESULTS

There were 1390 HRS participants who underwent a coronary revascularization procedure and contributed cognitive data at ≥1 postprocedure interview; 40% were women. The cohort was 83% non-Hispanic White, 8.4% non-Hispanic Black, 6.4% Hispanic ethnicity, and 1.7% from other groups masked by the HRS to preserve participant confidentiality. Of these, 267 (19%) met criteria for mild memory decline and 88 (6.3%) met criteria for major memory decline (Table 1), at a median of 1 year after the procedure. Participants who met memory decline criteria were, on average, older and less likely to be overweight or obese, and were more likely to meet criteria for frailty, and to report difficulty with at least 1 instrumental activity of daily living before the procedure.

In adjusted analysis, statistically significant independent predictors of mild or major memory decline included off-pump CABG (odds ratio [OR], 1.75 [1.14–2.69]), age at procedure (OR, 1.18 [1.15–1.22] per additional year), and frailty (OR, 1.96 [1.42–2.69]). Overweight and obese BMI were associated with lower risk of memory decline, and the likelihood of memory decline decreased with additional time since the procedure (OR, 0.69 [0.56–0.86] per additional year). Table 1 includes adjusted ORs for all variables included in the model.

The uncorrected area under the receiver operator characteristic curve for the logistic regression model was 0.75 (0.72–0.78) (Figure [A]); after optimism correction, the area under the receiver operator characteristic curve was 0.73 (0.71–0.77). Calibration was excellent across the range of predicted memory decline probability (Figure [B]). A cutoff of 50% predicted probability for memory decline, which attempted to prioritize specificity, identified 14.1% of older adults as "high risk." At that cutoff, the prediction model was 94% specific for any memory decline, although sensitivity was only 30%. Of individuals with a <50% predicted probability of memory decline, 96.3% were free of major memory decline at the postprocedure cognitive interview. For those with >50% probability, 37% met criteria for mild memory decline and 37% for major memory decline; only 25% were free of memory decline (Table 2).

DISCUSSION

A model using preoperatively known factors predicted older adults who would meet a definition for durable memory decline analogous to PND, adapted for use with epidemiological data, after coronary revascularization. Using a 50% probability cutoff, which identified 14% of older adults as being at elevated risk of memory decline, 75% met mild or major memory decline criteria at an average of 1 year after their procedure. Participants with <50% probability of memory decline had less than a 4% chance of meeting adapted criteria for major PND.

The goal of this study was to generate a predictive model for memory decline using factors known before coronary revascularization, not to make causal conclusions about potential contributors to PND. Associations between PND/POCD and age and comorbid medical disease have been previously demonstrated. The protective association between overweight and obesity and subsequent neurocognitive disorder parallels well-demonstrated associations between low body weight[10] and/or weight loss[11] and subsequent dementia. A variety of causal mechanisms for this association have been proposed, including apathy, hormonal changes, and reduced olfactory function in preclinical dementia.[12] In this cohort, lower BMI may have identified older adults who are on a trajectory of accelerated cognitive decline and/or in preclinical stages of dementia.

Frailty, which was associated with an OR of 1.95 (1.42–2.69) for memory decline, and difficulty with instrumental activities of daily living (OR, 1.48 [0.99–2.21] for memory decline, which approached but did

Table 1. Characteristics of the Analytic Cohort and Unadjusted and Adjusted Associations With Memory Decline

	No memory decline N=1035	Mild memory decline N=267	Major memory decline N=88	Univar *P* value*	Adjusted OR†	Adjusted *P* value
Procedure						
PCI	643 (62%)	148 (55%)	48 (55%)	0.063	(reference)	
CABG	301 (29%)	86 (32%)	26 (30%)		1.30 (0.96–1.76)	0.087
OPCAB	91 (8.8%)	33 (12.4%)	14 (16%)		1.75 (1.14–2.69)	**0.010**
Age	74±5.9 y	77±6.3 y	80±6.2 y	<0.001	1.18 (1.15–1.22) per y	**<0.001**
Male sex	643 (62%)	149 (56%)	46 (52%)	0.048	1.21 (0.88–1.67)	0.235
Unpartnered‡	306 (30%)	91 (34%)	40 (45%)	0.005	0.96 (0.69–1.33)	0.821
Financial assets >$168 274§	553 (54%)	141 (53%)	43 (49%)	0.718	0.80 (0.59–1.09)	0.158
Education						
<HS/GED	324 (31%)	77 (29%)	31 (35%)	0.685	1.03 (0.73–1.47)	0.862
HS degree	328 (32%)	92 (34%)	32 (36%)		(reference)	
Some college	194 (19%)	51 (19%)	11 (13%)		0.89 (0.60–1.31)	0.547
College+	189 (18%)	47 (18%)	14 (16%)		0.81 (0.54–1.22)	0.320
Body mass index						
<18.5	6 (0.6%)	2 (0.8%)	1 (1%)	0.001	0.95 (0.21–4.26)	0.945
18.5–25	253 (25%)	96 (36%)	32 (36%)			
25–30	483 (47%)	109 (41%)	41 (47%)		0.68 (0.50–0.93)	**0.015**
>30	288 (28%)	58 (22%)	14 (16%)		0.58 (0.39–0.85)	**0.005**
Diabetes	303 (29%)	82 (31%)	31 (35%)	0.485	1.27 (0.94–1.71)	0.126
Previously diagnosed heart problems	480 (46%)	114 (43%)	33 (38%)	0.187	0.74 (0.56–0.97)	**0.031**
Stroke	127 (12%)	32 (12%)	16 (18%)	0.265	1.12 (0.75–1.66)	0.574
Depressive sx	213 (22%)	55 (21%)	25 (29%)	0.284	0.95 (0.66–1.36)	0.771
Frailty	278 (28%)	97 (37%)	37 (42%)	0.001	1.96 (1.42–2.69)	**<0.001**
Difficulty with at least 1 IADL	146 (14%)	38 (14%)	27 (31%)	<0.001	1.48 (0.99–2.21)	0.058
Years between procedure and postprocedure assessment	1.1 (0.7–1.6)	0.9 (0.4–1.5)	0.9 (0.4–1.4)	0.001	0.69 (0.56–0.86) per y	**0.001**
Preprocedure memory score	0.82±0.47	0.89±0.45	0.75±0.49	0.415	1.19 (1.14–1.24) per 0.1 memory unit	**<0.001**
Postprocedure memory score	0.83±0.44	0.41±0.49	−0.44±0.62	<0.001		

Odds ratios are displayed as point estimate (95% CI). CABG indicates coronary artery bypass grafting; HS, high school; HS/GED, high school or General Education Degree; IADL, instrumental activity of daily living; OPCAB, off-pump CABG; OR, odds ratio; and PCI, percutaneous coronary intervention.

*Assessed with χ^2 tests for categorical variables or ordinal regression for continuous variables.

†Adjusted OR is from the logistic regression for any memory decline (ie, model with reported performance characteristics, which combined mild and major memory decline as the primary outcome).

‡Includes single, divorced, and widowed.

§$168 274 is the weighted median value from the previously described cohort of n=1680 older adults who underwent coronary revascularization, regardless of participation in postprocedure interview; current study sample is limited to those who contributed postprocedure cognition data.

Bold values indicates $P < 0.05$.

not achieve statistical significance) are relatively novel predictors in this area. Our findings are qualitatively consistent with the association between frailty and adverse cognitive outcomes in a small study of older patients after cardiac surgery.[13] As appreciation of the importance of function and geriatric syndromes in perioperative care grows, routine assessment of frailty and/or function may help patients understand their risk for a variety of untoward postoperative outcomes.

Our approach was strengthened by the use of an epidemiological cohort, with better representation of historically excluded racial and ethnic minority groups and those of low socioeconomic status and/or low educational attainment compared with typical inception cohort studies of this topic.[14] However, there are important limitations to our approach. First, cognitive testing in this epidemiological cohort was not linked to any health event; therefore, assessments are randomly spaced with respect to coronary revascularization, limiting the granularity of memory assessment timing. Second, cognitive assessments were also limited to memory, because of the testing performed by the HRS; deficits in executive function are often described as part of POCD/PND, but we lack the data to assess predictors of executive function change. Third, sensitivity at the 50% predicted probability cutoff was only

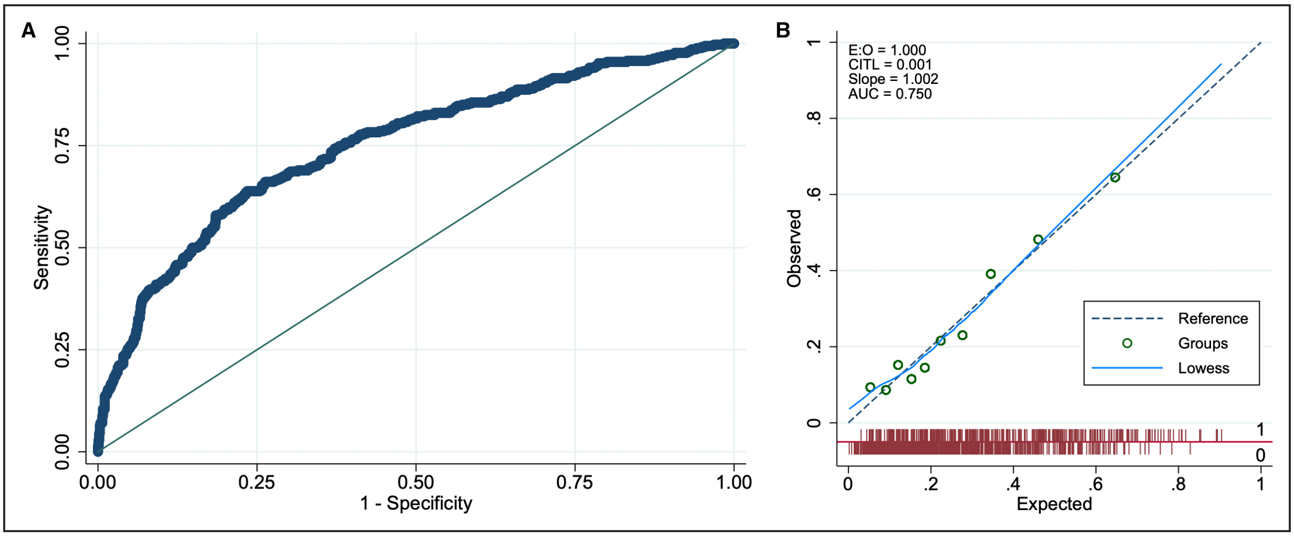

Figure. Discrimination and calibration of the prediction model.
Discrimination was assessed by receiver operator characteristic curve (**A**) and calibration using a calibration plot (**B**). AUC indicates area under the receiver operator characteristic curve; E:O, expected-to-observed ratio; and CITL, calibration-in-the-large.

Table 2. Categorization of Participants According to Expected Versus Actual Category of Memory Decline Using 50% Predicted Probability Cutoff for <50% Versus >50% Predicted Risk

	No memory decline	Mild memory decline	Major memory decline
Model predicts <50% risk	968 (80%)	202 (17%)	45 (3.7%)
Model predicts >50% risk	64 (37%)	64 (37%)	43 (25%)

The 50% predicted probability cutoff was 94% specific and 30% sensitive for any memory decline.

30%, although the model was 94% specific. While a less stringent cutoff would increase sensitivity, it would compromise specificity. Selection of a predicted probability cutoff should depend on what clinical actions might occur after a "high-risk" screen. Fourth, participants who died after surgery were by definition excluded from analysis of late cognitive outcomes; thus, this model would only be generalizable to those who survive, an outcome that cannot be known at the time of surgery. However, cognitive trajectories previously modeled in this cohort of older adults were not sensitive to the competing risk of death.[6]

Despite no evidence for population-level differences in long-term cognitive outcome after CABG versus PCI, there is clinically significant heterogeneity in individual cognitive outcomes after coronary revascularization. A model using preoperatively known factors performs with high specificity to identify older adults at high risk for long-term memory decline before coronary revascularization with CABG or PCI. Understanding the predictive role of individual-level factors for memory decline, which here included older age, frailty, and lower BMI, may facilitate preoperative risk discussion and, potentially, intra- and postoperative interventions to optimize cognitive outcomes.

ARTICLE INFORMATION

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Disclosures

None.

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