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Clinical outcomes in older surgical patients with mild cognitive impairment

Annie M. Racine, PhD^{a,f,*}, Tamara G. Fong, MD, PhD^{a,b,*}, Yun Gou, MA^a, Thomas G. Trivison, PhD^a, Douglas Tommet, MS^a, Kristen Erickson, MA^a, Richard N. Jones, ScD^e, Bradford C. Dickerson, MD^f, Eran Metzger, MD^{a,c}, Edward R. Marcantonio, MD^{a,d}, Eva M. Schmitt, PhD^a, and Sharon K. Inouye, MD, MPH^{a,d}

^aAging Brain Center, Institute for Aging Research, Hebrew SeniorLife, Harvard Medical School, Boston, MA

^bDepartment of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

^cDepartment of Psychiatry, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

^dDepartment of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

^eDepartments of Psychiatry and Human Behavior and Neurology, Brown University Warren Alpert Medical School, Providence RI

^fDepartment of Neurology and Massachusetts Alzheimer's Disease Research Center, Massachusetts General Hospital, Harvard Medical School, Boston, MA

Abstract

INTRODUCTION—Older adults, including those with mild cognitive impairment (MCI), are increasingly undergoing surgery.

METHODS—Relative risks of MCI alone or with delirium on adverse outcomes were estimated in an ongoing prospective, observational cohort study of 560 non-demented adults 70 years old.

RESULTS—MCI (n=61, 11%) was associated with increased relative risk (RR) of delirium (RR=1.9, p<.001) and delirium severity (RR=4.6, p<.001). Delirium alone (n=107), but not MCI alone (n=34), was associated with multiple adverse outcomes including more major post-operative complication(s) (RR=2.5, p=.002) and longer length of stay (RR=2.2, p<.001). Patients with concurrent MCI and delirium (n=27) were more often discharged to a post-acute facility (RR=1.4, p<.001) and had synergistically increased risk for new impairments in cognitive functioning (RR=3.6, p<.001).

Corresponding author: Dr. Tamara Fong, 1200 Centre Street, Boston, MA 02131, Phone: 617-971-5390, Fax: 617-971-5309, tfong@bidmc.harvard.edu.

*Contributed equally as co-first authors; Tamara Fong is the corresponding author

DISCUSSION—MCI is associated with increased risk of delirium incidence and severity. Patients with delirium and MCI have synergistically elevated risk of developing new difficulties in cognitively demanding tasks.

Keywords

Mild Cognitive Impairment; prodromal Alzheimer's disease; surgery; delirium; post-operative

1. INTRODUCTION

Adults 65 years and older undergo over 19 million surgeries each year in the U.S.[1] and represent over 50% of all surgical admissions[2] despite comprising only 15% of the population. The number of surgical procedures in this age group increased by 30% between 2000–2010[1]; total knee replacement increased by 100%, from 31 to 62 per 10,000 patients from 1991–2010[3]. Current projections indicate that surgeries in seniors will increase by 50–600% by 2030, with the variation depending on surgical type[4].

Accompanying the growing rates of surgery in older adults is a rise in persons with mild cognitive impairment (MCI) undergoing surgery. MCI has been proposed as a transitional stage between the cognitive changes of normal aging and dementia in which individuals have impairments in one or more cognitive domains but not severe enough to interfere with normal day to day activities [5]. While 10–15% of individuals with MCI with memory impairment progress to dementia due to Alzheimer's disease (AD) each year compared to 1–2% of the general elderly population[6, 7], MCI can also lead to non-AD dementia, revert to normal cognition or remains stable. Previous studies have found that MCI is often present but undiagnosed at time of surgery,[8, 9] and is associated with increased rates of various postoperative complications[8, 10–14] including delirium[9, 12, 15–20]. Postoperative delirium is the most common surgical complication in older adults generally, occurring in 5% to 50% of this population.[21] Little is known about whether MCI and delirium exert disparate or synergistic effects on adverse postoperative outcomes during hospitalization and follow-up. A better understanding of both the distinct and combined risks of MCI and delirium holds important clinical implications, with the potential to strongly influence surgical management of this vulnerable and growing segment of the older population.

The objectives of the present study were: 1) to examine the rates of MCI at baseline in a large prospective cohort of older adults without dementia before undergoing major scheduled surgery; 2) to determine whether MCI was associated with increased risk for incidence or higher severity of post-operative delirium; 3) to evaluate the association between MCI and other adverse clinical outcomes during hospitalization and at one-month follow-up; and 4) to evaluate potential interactions between delirium and MCI on risk of clinical outcomes. We hypothesized that baseline MCI would be associated with increased risk and severity of post-operative delirium, and worse clinical outcomes during hospitalization and at one-month follow-up. We further hypothesized based on prior work demonstrating that delirium can accelerate cognitive decline in patients with Alzheimer's Disease[22, 23] that delirium and MCI would have synergistic deleterious effects on clinical outcomes, particularly for new functional impairments related to cognition.

2. METHODS

2.1. Study population

The Successful Aging after Elective Surgery (SAGES) study is an ongoing prospective, observational cohort study of older adults without dementia undergoing major elective surgery. The study design and methods have been described in detail previously[24, 25]. In brief, eligible participants were age 70 years and older, English speaking, scheduled to undergo elective surgery at one of two Harvard-affiliated academic medical centers and with an anticipated length of stay of at least 3 days. Eligible surgical procedures included: total hip or knee replacement, lumbar, cervical, or sacral laminectomy, lower extremity arterial bypass surgery, open abdominal aortic aneurysm repair, and open or laparoscopic colectomy. Exclusion criteria were evidence of dementia, delirium, or hospitalization within 3 months, terminal condition, legal blindness, severe deafness, history of schizophrenia or psychosis, and history of alcohol abuse or withdrawal. A total of 566 patients met all eligibility criteria and were enrolled between June 18, 2010 and August 8, 2013; thus, recruitment is complete but longitudinal follow-up is ongoing. Six subjects were excluded after enrollment due to suspected dementia, determined by neuropsychological testing and clinical review by an expert multi-disciplinary panel, leaving a final sample of 560 participants. Written informed consent for study participation was obtained from all participants according to procedures approved by the institutional review boards of Beth Israel Deaconess Medical Center and Brigham and Women's Hospital, the two study hospitals, and Hebrew SeniorLife, the coordinating center for the study.

2.2. Data collection

Participants underwent baseline assessment in their homes. From the first postoperative day through discharge, participants underwent a daily delirium assessment (detailed below). Participants were interviewed one month later, and medical record review was completed. All study interviews were conducted by experienced interviewers, who underwent 2–4 weeks of intensive training and standardization[24]. Inter-rater reliability assessment and standardization on all key study variables, including delirium assessment, was conducted every 6 months continually throughout the study and coding questions were addressed in weekly meetings of all study staff.

2.3. Assessment of cognitive function and MCI

Prior to surgery and after one-month, patients were tested with a standardized neuropsychological battery consisting of the Hopkins Verbal Learning Test-Revised (HVLT), Visual Search and Attention Test, Trail Making Test (TMT) Parts A and B, Digit Symbol Substitution Test, Digit Span Test Forward and Backward, Verbal Fluency, Category Fluency, Boston Naming Test (BNT), and copying pentagons, to assess attention, memory, language, visuospatial and executive functioning.

MCI was defined according to clinical consensus or psychometric criteria. For consensus-MCI, cases were first identified by a decline in cognitive performance greater than 1.5 standard deviations (SD) from the age-adjusted mean on any memory test, or greater than one SD on two or more neuropsychological tests, one of which was a memory test [26].

Cases were subjected to rigorous review by a multi-disciplinary expert panel (one neurologist, two neuropsychologists, two geriatricians, and two geriatric psychiatrists). The participant's medical history, demographics, and neuropsychological testing results, proxy report of cognitive function (Informant Questionnaire on Cognitive Decline in the Elderly, IQCODE) and basic and instrumental activities of daily living (ADLs and IADLs, respectively) were provided to the clinical consensus panel[24]. Using a modified Delphi approach, and the National Institute on Aging-Alzheimer's Association (NIA-AA) Criteria for Mild Cognitive Impairment[5], patients were adjudicated as consensus-MCI taking into account all the above data.

Psychometric-MCI was defined based on neuropsychological test performance[27]. Specifically, scores >2.0 SD below the mean on a single test of memory (either HVLT total or delayed recall), or >1.5 SD below the mean on a memory test and one test in another cognitive domain, were used to define MCI by psychometric criteria. As both approaches have been applied in prior studies of MCI, we opted to use a combined approach to maximize sensitivity for the present study (Supplementary Table A1). Because both definitions required impairment on a memory test, all cases described herein refer to the amnesic variant of MCI.

2.4. Primary outcomes

Delirium assessment included daily brief cognitive testing,[24, 28] Delirium Symptom Interview (DSI),[29] and family and nurse interviews. Delirium was rated using the Confusion Assessment Method (CAM),[29] a standardized approach with high sensitivity (94–100%), specificity (90–95%)[30, 31], and high reliability (kappa statistic= 0.92 in 71 paired ratings in SAGES). The DSI was used to rate the symptoms on the CAM. Combined with a validated chart review method,[32, 33] patients were classified as delirious if either the CAM or chart review criteria were met. The combined method is the preferred approach for maximizing sensitivity in the detection of delirium.[33]

Delirium severity was rated with the CAM-S long form, which is a score created from the 10 features from the full CAM instrument: acute onset or symptom fluctuation, inattention, disorganized thinking, altered level of consciousness, disorientation, memory impairment, perceptual disturbances, psychomotor agitation, psychomotor retardation, and sleep-wake cycle disturbance. With the exception of fluctuation which was rated 0 (absent) or 1 (present), each symptom was rated 0–2 for absent (0), mild (1) or marked (2). The sum of these ratings yielded a CAM-S long form score from 0 to 19, with higher scores indicating more severe delirium. In 73 paired ratings, the CAM-S demonstrated an overall agreement of 97% and intraclass correlation coefficient of 0.88[35]. The CAM-S was selected as the delirium severity measure used in this study because it is scored based on items from the CAM, which is the main instrument used for the detection of delirium in our study. The CAM-S is quick and simple to use, has good psychometric properties and high inter-rater reliability, can be administered by trained research assistants, and, importantly, has strong association with clinical outcomes related to delirium [34]. In the current study, CAM-S peak, the highest single CAM-S rating during hospitalization, was used as our primary severity measure. We categorized delirium severity (peak CAM-S) using pre-specified

scores of 0–2, 3–7, and 8–19 points. The first group (CAM-S scores of 0–2 points) represents the group without delirium, since a minimum of 3 features is required for CAM-defined delirium. The top 2 cutpoints were selected to distribute the delirium-positive cases evenly across the 2 groups, an approach preferred when the sample distribution is imbalanced across the range of scores[36].

Hospital outcomes, including major post-operative complications, hospital length of stay, and discharge to a post-acute nursing facility, were determined by chart review. A major post-operative complication was defined as a life-altering or life-threatening event (i.e., unstable arrhythmia or heart block requiring pacemaker, myocardial infarction, respiratory failure, pulmonary embolism, pneumonia, sepsis, new renal failure requiring dialysis, stroke, surgical wound infection, or unplanned return to surgery)[37]. Major postoperative complications[37] were adjudicated and validated by an expert panel, which included a surgeon, hospitalist, and internist.

The following outcomes were evaluated during the one-month follow-up interview: hospital readmission, change in physical function, new impairment in cognitive IADLs, and new or ongoing stay in a nursing facility. Physical function was measured using a composite physical functioning score based on activities of daily living (ADL), overall IADLs, and the physical function sub-score of the 12-item Short Form Health Survey, scaled to the normative sample from Patient Reported Outcomes Measurement Information System (PROMIS). Lower scores on the physical composite indicate worse physical functioning and have been shown to be associated with adverse clinical outcomes[38]. A clinically significant decline was conservatively defined as a decrease of 5 points or more (0.5 SD for the cohort) on the composite score at one month, as our prior work identified 2 points as the minimal clinically important difference[39]. New impairment in cognitive IADLs was indicated by any new assistance required at one month for handling money, managing medications, using the telephone, or cooking[40, 41].

Demographic data, including sex, race, ethnicity, education, marital status, and surgery type were obtained from interviews and medical record review. The Modified Mini-Mental State Examination (3MS) was used as a global cognitive measure at baseline. Depression was assessed at the baseline interview using the 15-item Geriatric Depression Scale (GDS). The Charlson comorbidity score[42] was calculated based on diagnoses abstracted from medical records.

2.5. Statistical analysis

Assuming, conservatively, a baseline sample prevalence of MCI of 0.10 and a population rate of each clinical outcome of 10% among individuals without MCI, the study sample provides 80% power to detect relative risks (quantifying the multiplicative increase in risk of the clinical outcome in MCI) of at least 2.4 in unadjusted analysis. The analytic design was prospective and used a ‘modified’ Poisson regression approach[43] to estimate the relative risk (RR) of events in the presence (vs. absence) of MCI along with robust standard errors. Separate models evaluated the relative risks (RR) of delirium, delirium severity group, and dichotomized clinical outcomes during hospitalization and at one-month follow-up (described above), controlling for age, sex, race, Charlson comorbidity, education, and

surgery type. To account for multiple comparisons, results were evaluated using false discovery rate (FDR) correction ($\alpha=0.05$, two-tailed).

The differential risk conferred by MCI in the presence of delirium was investigated by inclusion of an interaction term between MCI and delirium (MCI $\times$ delirium) in models examining hospital and one-month outcomes. To empirically test whether the RR for each outcome was greater than would be expected if both MCI and delirium contributed independent and additive effects, a *post hoc* synergism analysis was conducted using Rothman's Synergy Index.[44]

All analyses were conducted using Stata software version 14.2 (College Station, TX).

2.6. Role of the Funding source

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3. RESULTS

3.1. Sample characteristics and rate of MCI

Characteristics of the sample are described in Table 1. The cohort included older adults (mean age 77 years), of whom 326 (58%) were women. The cohort was generally healthy, with 29% (n=164) having a Charlson score ≤ 2 . Incident postoperative delirium developed in 24% (n=134). Thirty-three patients met criteria for consensus-MCI, 54 met criteria for psychometric-MCI, and 26 patients met criteria for both, yielding a total of 11% (n=61) with MCI in this cohort (Supplementary Table A1). The MCI group was slightly older, less educated, and more likely to be non-white, have subjective cognitive complaints (based on IQCODE), be depressed, or have any IADL impairment. Groups did not differ on rates of surgical type, surgical duration, or anesthesia type, but the MCI group had greater estimated blood loss during surgery. As expected, the MCI group also had a lower average 3MS performance compared to the non-MCI group.

3.2. Association between MCI with hospital and one-month outcomes

MCI was associated with an increased risk for incident delirium following surgery (adjusted RR=1.9, 95% C.I. [1.3, 2.7], Table 2). Delirium severity as measured by mean peak CAM-S score was higher in the MCI versus non-MCI group (5.7 vs. 3.7 points), with an adjusted mean difference of 1.6 points ($p < .001$). Those with MCI had an increased risk of developing the most severe delirium (peak CAM-S scores 8–19; RR=4.6 95% C.I. [2.0, 10.8]) and moderate delirium (CAM-S peak scores 3–7; RR=2.3, 95% C.I. [1.1–4.6]) compared to the group without MCI or delirium. MCI was not associated with any other adverse hospital or one-month outcomes (Table 3).

3.3. Association between MCI and delirium with hospital and one-month outcomes

Table 4 shows the hospital and one-month clinical outcomes for patients with MCI only (n=34), delirium only (n=107), and MCI and delirium combined (n=27) groups. All relative risks in this table are adjusted for age, sex, race, education, Charlson score, and surgery type. The reference group for all comparisons is the group without MCI or delirium (n=392). Patients in the delirium only group had increased risk for all hospital and one-month adverse outcomes except functional decline and new cognitive IADL impairment, which did not survive FDR-correction for multiple comparisons. Patients in the MCI only group did not have increased risk for any outcomes. Patients with both MCI and delirium had increased risk for discharge to a post-acute facility; and, at one month, increased risk for a new cognitive IADL impairment, for which the RR was greater than for either delirium or MCI alone. On *post hoc* analysis, there was a synergistic effect for MCI and delirium on the risk of developing new cognitive IADL impairment (Rothman's Synergy Index = 4.3, 95% C.I. 1.7–11).

3.4. Supplementary analysis

Analysis by either consensus-MCI or psychometric-MCI criteria did not differ from the results presented here. However, to evaluate whether our findings were robust to alternative definitions of MCI, we conducted a supplementary analysis using the 3MS with accepted cutpoints indicating possible MCI of 80 points (for participants with 8 years of education) and 88 points or lower (for participants with 9 years of education)[45]. By this alternative definition of MCI, the findings are highly consistent with those utilizing the psychometric and consensus criteria used in this study (Supplementary Tables A2–5, Figure A1).

4. DISCUSSION

As rates of major surgery increase in older adults, more persons with MCI will be exposed to the effects of surgery and/or delirium. This study supports previous findings that MCI at baseline is an important risk factor for delirium following surgery[18, 46], and extends previous work by demonstrating the effect of MCI on delirium severity (peak CAM-S score) and adverse clinical outcomes. Patients with co-occurring MCI and delirium showed synergistically increased risk of future functional impairment on cognitive IADLs, which holds substantial clinical implications for older adults and their families.

MCI in the absence of delirium was not associated with increased risk of adverse outcomes after surgery, but increased risks were observed in patients with MCI who also had delirium. Our findings suggest that while MCI is associated with increased risk of delirium, it is the delirium—rather than MCI—that appears to be associated with most adverse outcomes following surgery, at least in the short-term. Interestingly, we found that the group with delirium but no MCI had greater risk of several outcomes compared to the group with both MCI and delirium. It is possible that there are important unmeasured differences between groups that account for this finding, but it is also possible that we were underpowered to detect some associations. For some outcomes (e.g. length of stay), the effect size may still be clinically meaningful despite not reaching statistical significance in the group with both MCI and delirium. Supportive findings were found in our supplementary analysis using the 3MS

definition of MCI, which yielded larger sample sizes in the MCI and delirium group, and showed significant associations with multiple clinical outcomes with effect sizes that were more similar to the delirium only group. This is one of the first studies to examine the interaction of MCI and delirium on post-operative outcomes, but replication in even larger studies will be necessary to confirm and expand on the present findings.

Cognitive impairment is well established as a strong predictor of delirium[9, 15–20]. While we hypothesized that MCI and delirium would act synergistically to predict the worst clinical outcomes, the combined effect was demonstrated only for new impairment in cognitive IADLs. It appears possible that the synergistic relationship between MCI and delirium could only be detected among cognitive outcomes, whereas more medical complications, such as prolonged hospitalization, admission to nursing facility, and post-operative complications, are affected more by delirium. Prior studies have shown certain IADL activities such as handling finances, taking care of medication, shopping for groceries, managing the telephone and using public transportation to be sensitive to early cognitive decline and to predict dementia[40]. These findings suggest not only an acceleration of cognitive decline following delirium, but also that patients with MCI who develop delirium are particularly vulnerable.

About 1/3 of patients with MCI will convert to AD within 10 years [47], and this rate is even higher in individuals with high amyloid deposition, with at least one study suggesting a conversion rate of 82% over 3 years[48]. Our finding of increased rates of new cognitive impairments in patients with MCI even just one month after delirium suggests that delirium could also accelerate conversion from MCI to dementia. Longitudinal studies examining conversion to dementia as well as biomarkers for molecular evidence of AD in the present cohort will be an important extension of the current work.

Prior studies of MCI and post-operative cognitive dysfunction (POCD) have not always examined delirium as a covariable[49, 50], thus, our results raise the intriguing possibility that outcomes attributed to baseline cognitive impairment may have actually been, at least in part, due to the effects of unrecognized postoperative delirium. It is possible that while delirium is more predictive of adverse short-term outcomes demonstrated in the present study, MCI may be more predictive of long-term outcomes. We have reported previously that patients with delirium demonstrate more cognitive impairment both in the short-term (up to one month) and in the long-term, with greater cognitive decline over the subsequent 3 years[51]. Examining the association of delirium with the development of MCI after surgery and whether presence of MCI at baseline moderates the association between delirium and long-term cognitive decline are important priorities for future research.

Our study has important strengths, including exclusion of dementia at baseline, careful measurement of delirium incidence and severity, and near-complete prospective follow-up at one month. However, several caveats about this study are worthy of comment. First, our definition of MCI for this study was based on two accepted sets of criteria derived from epidemiologic studies, psychometric-MCI[27] and consensus-MCI based on AA-NIA criteria[5]. However, given feasibility constraints, our study did not include a reference standard clinical neurologic evaluation. Notably, there is significant variation in the literature

on how to define MCI, and at least one study has found that using different criteria can affect the results[46]. While we chose two accepted approaches intended to capture the majority of persons with MCI, it is possible that our findings may have differed with alternative criteria. However, our supplemental analyses using a 3MS definition for MCI lends support for the robustness of our findings to alternative definitions, and further demonstrate that the effect of MCI on delirium is not necessarily specific to the amnesic variant of MCI. An important next step may be to more thoroughly investigate potentially important clinical differences between amnesic and non-amnesic MCI on post-operative outcomes as well as in empirically-derived MCI subgroups based on pathology[52, 53].

Second, our sample was relatively homogenous in terms of race/ethnicity and educational attainment. However, we did control for confounding effects of race and education in our analyses, along with multiple other covariates. Differences in intraoperative and postoperative factors may have contributed to differences in the outcomes between the MCI groups. However, exploration of these potential mediators was beyond the scope of the present study. This will be an important area for future investigation. We selected confounders that we expected to be predictive of both our predictor (MCI) and the clinical outcomes, and excluded those thought to be along the causal pathway between primary exposure and outcome. To assess for the possibility of overfitting, given our limited number of outcomes, we repeated our analysis using only age and sex as covariates and found that although the magnitude of the effect was generally increased with fewer covariates, the general pattern was the same and no new outcomes reached statistical significance nor became non-significant. Model fit statistics (Akaike Information Criterion, AIC) were also highly stable across the full covariate-adjusted model, a model adjusting only for age and sex, as well as an unadjusted model (Supplementary Table A6).

Third, the prevalence of MCI in our surgical cohort (11%) is slightly lower than MCI prevalence rates of 16–35% in large population observational studies[26, 54]. Given this prevalence, our study was adequately powered to detect strong associations between MCI and other events and conditions (see Methods, Section 2.5) but would have been unlikely to provide statistically significant evidence of association between MCI and some outcomes where the associations were more modest in magnitude, as our data suggests was the case, for instance, with IADL impairment. For these reasons, it will be especially important to replicate these findings in more diverse and larger cohorts of MCI patients.

Fourth, we used a combination of validated interview-based and chart-based methods to identify delirium which has previously been shown to capture the largest number and broadest range of delirium cases[33], but it is possible episodes of delirium occurred which were not captured by our approach. Last, our study was unable to determine which aspects of the operation or perioperative period may have been most relevant for the adverse outcomes examined. For instance, anesthesia always accompanies surgery and all our patients received either general and/or spinal anesthesia. Importantly, there were no differences in rates of anesthesia types between the MCI and No MCI groups, but it is possible that anesthesia or other perioperative factors may be important contributors to some of the observed outcomes[55].

Two important clinical messages emanate from these results. First, screening in older persons prior to surgery is important to recognize preexisting MCI and to identify persons who are at increased risk for postoperative delirium and its complications. Screening could be achieved using a test such as the Mini-Cog[56, 57] which requires only 3-minutes for administration and thus would not add excessive burden to the preoperative assessment. The Vulnerable Elders Surgical Pathways and Outcomes Assessment (VESPA) trial includes the Mini-Cog in its preoperative risk assessment tool, and has demonstrated the feasibility of this approach[58]. Second, given the substantial impact of delirium on adverse clinical outcomes, these results suggest the need to redouble efforts for prevention of delirium, and screening for MCI could be beneficial to target high-risk patients for these efforts. Previous work[59] has demonstrated that delirium is preventable in about 40% of cases, and thus, preventive strategies will likely play an important role to improve postoperative outcomes and advance clinical care of older adults.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

ADL	Activities of daily living
BNT	Boston Naming Test
CAM	Confusion Assessment Method
CAM-S	Confusion Assessment Method-Severity
DSI	Delirium Symptom Interview
FDR	False discovery rate
GDS	Geriatric Depression Scale
HVLT	Hopkins Verbal Learning Test-Revised
IQCODE	Informant Questionnaire on Cognitive Decline in the Elderly
IADLs	Instrumental activities of daily living
3MS	Modified Mini-Mental State Examination

NIA-AA	National Institute on Aging-Alzheimer's Association
PROMIS	Patient Reported Outcomes Measurement Information System
POCD	Post-operative cognitive dysfunction
RR	Relative risks
SAGES	Successful Aging after Elective Surgery
TMT	Trail Making Test
VSAT	Visual Search and Attention Test

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Figure 1. Racine et al

Relative Risk of Clinical Outcomes Associated with Mild Cognitive Impairment and/or Delirium.

CI = Confidence Interval; IADL = Instrumental Activities of Daily Living; RR = Relative Risk.

- Relative risk is referent to the cognitively normal group without delirium (N=392).

Relative risk axis is displayed on a logarithmic scale. All models adjusted for age, sex, race, Charlson comorbidity score, education, and surgery type.

- New impairment in cognitive IADL is impairment at one month not present at baseline in ability to use money, manage medications, use the telephone, or prepare meals

-Decline in physical function was defined as a decline of 5 or more points (0.5 population SD) on a composite physical functioning score based on ADLs, IADLs, and the physical function sub-score of the 12-Item Short Form Health Survey. See text for complete variable definitions.

Table 1**Baseline Description of Study Sample**

	Full Sample	MCI	No MCI
Baseline Characteristic	(N = 560)	(N = 61)	(N = 499)
Age – mean (SD) *	76.7 (5.2)	79.1 (6.7)	76.4 (4.9)
Sex – n (% male, self-reported)	234 (42)	29 (48)	205 (41)
Nonwhite – n (%) *	42 (8)	11 (18)	31 (6)
Education – mean years (SD) *	15.0 (2.9)	14.1 (3.1)	15.1 (2.9)
Married – n (%)	332 (59)	32 (52)	300 (60)
Charlson score 2 – n (%)	164 (29)	19 (31)	145 (29)
Vascular Comorbidity – n (%)	214 (38)	28 (46)	186 (37)
Ever a Smoker – n (%)	338 (60)	36 (59)	302 (61)
SF-12 physical variables – mean (SD)	31.6 (7.4)	30.6 (7.4)	31.7 (7.4)
3MS score – mean score (SD) *	93.5 (5.4)	87.6 (5.6)	94.2 (4.9)
Proxy IQCODE > 3.2 – n (%)	118 (22)	29 (30)	89 (20)
Patient IQCODE > 3.2 – n (%)	101 (18)	21 (22)	80 (17)
GDS 15 score 6 – n (%) *	69 (12)	13 (21)	56 (11)
Any ADL impairment – n (%)	42 (8)	5 (8)	37 (7)
Any IADL impairment – n (%) *	152 (27)	25 (41)	127 (25)
Any Cognitive IADL impairment – n (%)	27 (5)	6 (10)	21 (4)
Surgery type - n (%)			
Orthopedic	454 (81)	51 (84)	403 (81)
Total Hip Replacement	116 (21)	6 (10)	110 (22)
Total Knee Replacement	204 (36)	28 (46)	176 (35)
Laminectomy	134 (24)	17 (28)	117 (23)
Vascular	35 (6)	5 (8)	30 (6)
Abdominal Aortic Aneurysm Repair	12 (2)	1 (2)	11 (2)
Low Extremity Revascularization	23 (4)	4 (7)	19 (4)
General (Colectomy)	71 (13)	5 (8)	66 (13)
Anesthesia type – n (%)			
General alone	476 (85)	55 (90)	421 (84)
Spinal alone	75 (13)	5 (8)	70 (14)
General and spinal	4 (1)	1 (2)	3 (1)
Regional	5 (1)	0 (0)	5 (1)

ADL= activities of daily living; GDS 15=Geriatric Depression Scale; IADL=Instrumental Activities of Daily Living; IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly 3MS= modified mini-mental state examination; SD=standard deviation. Charlson comorbidity score was calculated based on diagnoses abstracted from medical record review, scored from 0–35 with higher scores indicating more comorbidity. Vascular comorbidity was defined as presence or absence of at least one of the following pathological conditions: confirmed or history of myocardial infarction, congestive heart failure, peripheral vascular disease, diabetes (with or without end organ damage), cerebrovascular disease (carotid stenosis, history of stroke or transient ischemic attack), or hemiplegia. Geriatric Depression Scale, scored 0–15, with higher scores indicating more depressive symptoms. GDS scores were missing in two participants; no missing data for any other variables.

* Indicates significant difference ($p < .05$) between MCI and No MCI groups. Comparison between the MCI and No MCI groups were performed using t-tests for continuous variables and chi square tests for dichotomous variables.

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Table 2

Delirium Incidence and Severity by Mild Cognitive Impairment Status

Outcome	Overall N=560	MCI N=61	No MCI N=499	Adjusted Relative Risk* (95% CI)	P-value
Delirium Incidence – N (%)	134 (24)	27 (44)	107 (21)	1.9 (1.3 – 2.7)	<0.001 [‡]
Delirium Severity, CAM-S peak					
Score – mean (SD)	3.9 (3.2)	5.7 (3.8)	3.7 (3.1)	N/A	<0.001 [‡]
Score level – N (%)					
0–2 points	244 (44)	12 (20)	232 (46)	referent	N/A
3–7 points	248 (44)	34 (56)	214 (43)	2.3 (1.1 – 4.6)	0.03
8–19 points	68 (12)	15 (25)	53 (11)	4.6 (2.0 – 10.8)	<0.001 [‡]

CAM-S = Confusion Assessment Method-Severity; CI = Confidence Intervals; IADL = Instrumental Activities of Daily Living; MCI = Mild Cognitive Impairment.

* Relative Risks are for the MCI group (N=61) relative to the no MCI group without delirium (N=392). All models adjusted for age, sex, race, Charlson comorbidity, education, and surgery type. Relative risk axis is displayed on a logarithmic scale.

[‡] Significant with false discovery rate (FDR) correction for multiple comparison

[‡] Based on adjusted difference (1.57 points) between MCI and no-MCI groups.

Variance inflation factor was in the normal range (<10), indicating low collinearity amongst covariables.

Table 3

Clinical Outcomes by Mild Cognitive Impairment Status

Outcome, n (%)	Overall N=560	MCI N=61	No MCI N=499	Adjusted Relative Risk* (95% Confidence Interval)	P-value
Hospital Outcomes					
Delirium	134 (24)	27 (44)	107 (21)	1.9 (1.34 – 2.65)	<0.001 [‡]
Major post-operative complication(s)	47 (8)	4 (7)	43 (9)	0.6 (0.22 – 1.43)	0.22
Length of stay >5 days	148 (26)	16 (26)	132 (26)	1.0 (0.62 – 1.48)	0.84
Discharge to post-acute facility	318 (57)	43 (70)	275 (55)	1.1 (0.91 – 1.28)	0.40
One-month Outcomes[‡]					
Decline in Physical Function [‡]	205 (37)	24 (42)	181 (37)	1.2 (0.8 – 1.6)	0.41
New impairment in Cognitive IADL [‡]	49 (9)	9 (17)	40 (8)	1.6 (0.8 – 3.1)	0.16
Readmission	67 (12)	7 (12)	60 (12)	0.9 (0.4 – 1.8)	0.68
New or continued nursing facility	58 (11)	6 (11)	52 (11)	0.7 (0.3 – 1.7)	0.42

IADL = Instrumental Activities of Daily Living; MCI = Mild Cognitive Impairment.

* Relative risks calculated for MCI group relative to No MCI group. All models adjusted for age, sex, race, Charlson comorbidity score, education, and surgery type. Relative risk axis is displayed on a logarithmic scale.

[‡] Significant with false discovery rate (FDR) correction for multiple comparisons.

[‡] New impairment in cognitive IADL is impairment at one month not present at baseline in ability to use money, manage medications, use the telephone, or cooking. Decline in physical function was defined as a decline of 5 or more points (0.5SD) on a composite physical functioning score based on ADLs, IADLs, and the physical function sub-score of the 12-Item Short Form Health Survey. See text for details.

Variance inflation factor was in the normal range (<10), indicating low collinearity amongst covariables.

Table 4

Clinical Outcomes in MCI Only, Delirium Only, and Combined Groups*

Outcome	MCI only (N=34)				Delirium only (N=107)				MCI and Delirium (N=27)			
	n (%)	RR* (95% CI)	p	n (%)	RR* (95% CI)	p	n (%)	RR* (95% CI)	p	n (%)	RR* (95% CI)	p
Hospital Outcomes												
Major post-operative complication(s)	2 (6)	0.8 (0.2 – 3.2)	0.72	18 (17)	2.5 (1.4 – 4.4)	0.002 [‡]	2 (7)	0.8 (0.2 – 2.6)	0.65			
Length of stay >5 days	7 (21)	1.1 (0.6 – 2.1)	0.83	53 (50)	2.2 (1.7 – 2.9)	<0.001 [‡]	9 (33)	1.5 (0.8 – 2.7)	0.18			
Discharge to post-acute facility	20 (59)	1.0 (0.8 – 1.4)	0.79	84 (79)	1.6 (1.4 – 1.8)	<0.001 [‡]	23 (85)	1.4 (1.2 – 1.7)	<0.001 [‡]			
One month Outcomes[‡]												
Decline in Physical Function [‡]	13 (42)	1.2 (0.8 – 1.9)	0.41	47 (45)	1.3 (1.0 – 1.7)	0.04	11 (42)	1.3 (0.8 – 2.1)	0.34			
New impairment in Cognitive IADL [‡]	2 (7)	0.7 (0.2 – 2.8)	0.61	13 (13)	1.9 (1.0 – 3.6)	0.05	7 (32)	3.6 (1.9 – 7.1)	<0.001 [‡]			
Readmission	3 (10)	1.0 (0.3 – 2.6)	0.87	24 (23)	2.4 (1.5 – 3.8)	<0.001 [‡]	4 (15)	1.4 (0.5 – 4.0)	0.54			
New or continued nursing facility	3 (10)	0.9 (0.3 – 2.9)	0.90	24 (23)	2.9 (1.7 – 4.8)	<0.001 [‡]	3 (12)	1.1 (0.3 – 3.8)	0.90			

CI = Confidence Intervals; IADL = Instrumental Activities of Daily Living; MCI = Mild Cognitive Impairment; RR = Relative Risk.

* Relative risks (RR) calculated for MCI group relative to group with neither MCI nor delirium (N=392). All models adjusted for age, sex, race, Charlson comorbidity score, education, and surgery type.

[‡] Statistically significant with false discovery rate (FDR) correction for multiple comparisons[‡] New impairment in cognitive IADL is impairment at one month not present at baseline in ability to use money, manage medications, use/embodied figure relates to the telephone, or cooking. Decline in physical function was defined as a decline of 5 or more points (0.5 population SD) on a composite physical functioning score based on ADLs, IADLs, and numbers in the columns.

Variance inflation factor was in the normal range (<10), indicating low collinearity amongst covariables.