Clinical outcomes in older surgical patients with mild cognitive impairment

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ABSTRACT

INTRODUCTION: Increasing numbers of older adults are undergoing major surgery, some of whom have mild cognitive impairment (MCI) and/or develop post-operative delirium.

METHODS: MCI and delirium were assessed in 560 non-demented adults ≥70 years old scheduled for major surgery. Relative risks (RR) of adverse outcomes (evaluated during hospitalization and 1 month after surgery) due to MCI or co-occurring MCI and delirium were estimated.

RESULTS: MCI (n=61, 11%) was associated with increased risk of post-operative delirium (RR=1.9, p<.001) and greater delirium severity (RR=4.6, p<.001). Patients with delirium without MCI (n=107) had increased risk for multiple post-operative adverse events, but patients with MCI without delirium (n=34) did not. Concurrent MCI and delirium (n=27) synergistically increased risk for new impairments in cognitive functioning (RR=3.6, p<.001).

DISCUSSION: MCI increases risk of delirium incidence and severity. Patients with both delirium and underlying MCI have elevated risk of developing new difficulties in cognitively demanding tasks.
ABBREVIATIONS

Activities of daily living (ADL)
Boston Naming Test (BNT)
Confusion Assessment Method (CAM)
Confusion Assessment Method-Severity (CAM-S)
Delirium Symptom Interview (DSI)
False discovery rate (FDR)
Geriatric Depression Scale (GDS)
Hopkins Verbal Learning Test-Revised (HVLT)
Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)
Instrumental activities of daily living (IADLs)
Modified Mini-Mental State Examination (3MS)
National Institute on Aging-Alzheimer's Association (NIA-AA)
Patient Reported Outcomes Measurement Information System (PROMIS)
Post-operative cognitive dysfunction (POCD)
Relative risks (RR)
Successful Aging after Elective Surgery (SAGES)
Trail Making Test (TMT)
Visual Search and Attention Test (VSAT)
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 is a syndrome defined by clinical, cognitive, and functional criteria and refers to the symptomatic pre-dementia phase of Alzheimer’s disease (AD)[5]. Previous studies have found that MCI is often present but undiagnosed at time of surgery,[6, 7] and is associated with increased rates of various postoperative complications[6, 8-12] including delirium[7, 10, 13-18]. Postoperative delirium is the most common surgical complication in older adults generally, occurring in 5% to 50% of this population.[19] 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 aims 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[20, 21] 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 cohort study of older adults without dementia undergoing major elective surgery. The study design and methods have been described in detail previously[22, 23]. 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. 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.

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 one test, or greater than one SD on two or more neuropsychological tests[24]. 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[22]. 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[25]. 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 (Table A.1).

2.4. Primary outcomes

Delirium assessment included daily brief cognitive testing,[22, 26] Delirium Symptom Interview (DSI),[27] and family and nurse interviews. Delirium was rated using the Confusion Assessment Method (CAM),[27] a standardized approach with high sensitivity (94-100%), specificity (90-95%)[28, 29], and high reliability (kappa statistic= 0.92 in 71 paired ratings in SAGES). Combined with a validated chart review method,[30, 31] 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.[31]
Delirium severity was rated with the CAM-S long form[32], which is based on 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[32]. 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[33].

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)[34]. Major postoperative complications[34] 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[35]. 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[36]. 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[37, 38].

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[39] was calculated based on diagnoses abstracted from medical records.

2.5. Statistical analysis.

The analytic design was prospective and used a ‘modified’ Poisson regression approach[40] 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 (α=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×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.[41]

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 \( \geq 2 \). Incident postoperative delirium developed in 24%
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. The MCI group was slightly older, less educated and more likely non-white. As expected, they 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)[42]. By this alternative definition of MCI, the findings are highly consistent with those utilizing the psychometric and consensus criteria used in this study (Tables A.2-4, Figure A.1).

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[16, 43], and extends previous work by demonstrating the effect of MCI on delirium severity (peak CAM-S score) and adverse clinical outcomes. Co-occurring MCI and delirium synergistically increase 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 did not increase risk of adverse outcomes after surgery, although increased risks emerged for these patients in the presence of delirium. Our findings suggest that while MCI increases the 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.

Cognitive impairment is well established as a strong predictor of delirium[7, 13-18]. 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[37]. 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 [44], 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[45]. 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[46, 47], 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[48]. Examining the effect of delirium on cognitive impairment over the long-term 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. Our definition of MCI for this study was based on two accepted sets of criteria derived from epidemiologic studies, psychometric-MCI[25] 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[43]. 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. Another limitation of this study is that 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. Lastly, the prevalence of MCI in our surgical cohort (11%) is slightly lower than MCI prevalence rates of 16-35% in large population observational studies[24, 49]. Both the MCI alone and the MCI-Delirium combined group had relatively small sample sizes, which may have led to imprecision in the estimate of hypothesized associations. For these reasons, it will be especially important to replicate these findings in more diverse and larger cohorts of MCI patients.

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. 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[50] 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.
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REFERENCES


Table 1. Baseline Description of Study Sample

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>Full Sample (N = 560)</th>
<th>MCI (N = 61)</th>
<th>No MCI (N = 499)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age – mean (SD)</td>
<td>76.7 (5.2)</td>
<td>79.1 (6.7)</td>
<td>76.4 (4.9)</td>
</tr>
<tr>
<td>Sex – n (% male, self-reported)</td>
<td>234 (42)</td>
<td>29 (48)</td>
<td>205 (41)</td>
</tr>
<tr>
<td>Nonwhite – n (%)</td>
<td>42 (8)</td>
<td>11 (18)</td>
<td>31 (6)</td>
</tr>
<tr>
<td>Education – mean years (SD)</td>
<td>15.0 (2.9)</td>
<td>14.1 (3.1)</td>
<td>15.1 (2.9)</td>
</tr>
<tr>
<td>Married – n (%)</td>
<td>332 (59)</td>
<td>32 (52)</td>
<td>300 (60)</td>
</tr>
<tr>
<td>Charlson score ≥2 – n (%)</td>
<td>164 (29)</td>
<td>19 (31)</td>
<td>145 (29)</td>
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<tr>
<td>3MS score – mean score (SD)</td>
<td>93.5 (5.4)</td>
<td>87.6 (5.6)</td>
<td>94.2 (4.9)</td>
</tr>
<tr>
<td>GDS 15 score ≥6 – n (%)</td>
<td>69 (12)</td>
<td>13 (21)</td>
<td>56 (11)</td>
</tr>
<tr>
<td>Any ADL impairment – n (%)</td>
<td>42 (8)</td>
<td>5 (8)</td>
<td>37 (7)</td>
</tr>
<tr>
<td>Any IADL impairment – n (%)</td>
<td>152 (27)</td>
<td>25 (41)</td>
<td>127 (25)</td>
</tr>
<tr>
<td>Any Cognitive IADL impairment – n (%)</td>
<td>27 (5)</td>
<td>6 (10)</td>
<td>21 (4)</td>
</tr>
<tr>
<td>Surgery type - n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orthopedic</td>
<td>454 (81)</td>
<td>51 (84)</td>
<td>403 (81)</td>
</tr>
<tr>
<td>Vascular</td>
<td>35 (6)</td>
<td>5 (8)</td>
<td>30 (6)</td>
</tr>
<tr>
<td>General</td>
<td>71 (13)</td>
<td>5 (8)</td>
<td>66 (13)</td>
</tr>
</tbody>
</table>

ADL= activities of daily living; GDS 15=Geriatric Depression Scale; IADL=Instrumental Activities of Daily Living; 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. 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.
### Table 2: Delirium Incidence and Severity by Mild Cognitive Impairment Status

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

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

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

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*

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

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 embedded 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.
FIGURE LEGENDS

**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.