The association of cognitive impairment as screened by the Mini-Cog with long term post-hospitalization outcomes

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ABSTRACT

Background: Prior studies have suggested that patients with cognitive impairment are at increased risk for adverse post-hospitalization outcomes. We aimed to determine if cognitive status assessed by the Mini-Cog, a quick bedside screening test, is associated with long-term outcomes.

Methods: In this secondary analysis of data from a prospective cohort study, 668 patients > 65 years of age admitted to a tertiary care academic hospital over a two-year period were screened for cognitive impairment with the Mini-Cog within 24 h of admission. We performed multivariable regression adjusting for demographics, comorbidities, principal diagnoses and functional status to determine association between cognitive impairment and discharge to post-acute care, 90-day readmission and one-year mortality.

Results: Overall 35% screened positive for cognitive impairment. Those with impairment were older (median age 83 versus 78), less likely to be admitted from home and had lower functional independence and self-reported performance scores (p < 0.001 for all). Patients with cognitive impairment were more likely to be discharged to post-acute care facilities (54% versus 39%, p < 0.001). 90-day readmission rate of patients with and without cognitive impairment was 35% versus 27%; one-year survival 77% versus 84% and median length-of-stay was 4 days for both groups. Differences in readmission and mortality were not statistically significant after adjusting for covariates.

Conclusion: Cognitive impairment as screened for by the Mini-Cog was not associated with readmission, length-of-stay, or 1-year mortality but was associated with discharge to post-acute care. Other tools such as frailty assessment may be more useful in predicting these outcomes in hospitalized older adults.

1. Introduction

Cognitive impairment is common in elderly patients (Daiello, Gardner, Epstein-Lubow, Butterfield, & Gravenstein, 2014). In the US population in 2010, the estimated rate of dementia was 14.7% for those over 70 years of age with an attributable total cost of 157–215 billion USD (Hurd, Martorell, & Langa, 2013). Although several screening tools for cognitive impairment exist, studies have shown that clinicians often fail to identify cognitive impairment (Borson, Scanlan, Watanabe, Tu, & Lessig, 2006; Raymont, Bingley, & Buchanan, 2004). These tools include the Montreal Cognitive Assessment test (MOCA), the Saint Louis University Mental Status exam (SLUMS) and the Folstein Mini Mental Status Examination (MMSE) among others. The simplest assessment

tool for cognitive impairment is the Mini-Cog screening test which consists of a three-item recall test and clock draw; it is a validated tool which is readily accessible to clinicians and can be performed quickly at bedside (Borson, Scanlan, Chen, & Ganguli, 2003, 2006; Scanlan & Borson, 2001). The maximum score is five, with a score of two or less suggesting cognitive impairment. It screens accurately for mild to severe dementia and may also predict functional abilities in terms of self-management tasks at home (Anderson, Jue, & Madaras-Kelly, 2008). Given its simplicity some studies have assessed its value as a predictor for hospital readmission or mortality. In a recent study of 720 patients hospitalized with congestive heart failure, patients with poor Mini-Cog performance had almost twice the risk for readmission (Patel et al., 2015). In surgical elderly patients, cognitive impairment was associated

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with longer length of stay, greater rates of post-surgical complications and increased hospital mortality (Culley, Flaherty, & Fahey, 2017; Heng et al., 2016; Ketterer, Chawa, & Paone, 2017). However, limited data exist on the relationship between cognitive impairment and long-term outcomes post hospitalization in a broad range of diagnoses of medical or surgical patients. In the present study, we aimed to determine whether cognitive impairment as identified using the Mini-Cog test is associated with readmission, length of stay or one-year mortality for older adults. Based on the prior literature we hypothesized that patients with cognitive impairment will have worse outcomes. If this assumption was true, then including the Mini-Cog in the electronic medical record as a recommended assessment could help discussing risks and planning appropriately for this group of patients.

2. Methods

2.1. Setting and subjects

This was a secondary analysis of the data from a two-year prospective study examining frailty in elderly adults ($\geq$ 65 years of age) who were admitted for a non-elective medical or surgical diagnosis from June 2014 to August 2016 at a 716 bed academic tertiary medical center in Western Massachusetts. Frailty was assessed using the Reported Edmonton Frailty scale, a validated tool to assess frailty which examines nine geriatric domains including functionality (Hilmer, Perera, & Mitchell, 2009; Rolfson, Majumdar, Tsuyuki, Tahir, & Rockwood, 2006).

Patients were excluded if they had existing diagnosis of advanced dementia, if they did not speak English and if they were admitted to the intensive care unit. Observations with missing cognitive assessment or outcomes data were excluded. Patients who expired during the index admission (as we report on post-discharge outcomes) or were discharged to hospice were also excluded. We extracted patient characteristics including age, sex, comorbidities, principal admission diagnosis (ICD-9 diagnosis code), length of stay, discharge disposition, and readmission dates from the hospital's billing database (McKesson Performance Analytics version 18.0 [2014]). To determine the co-morbidity burden we calculated the Elixhauser comorbidity score (Healthcare Cost & Utilization Project, 2017). Of note, the Elixhauser score does not include dementia as one of the comorbidities. Principal diagnoses were grouped in categories as best described by their active condition in categories such as cardiac, gastrointestinal, infectious, pulmonary, renal, hematological, and primary surgical admissions. We also included patient characteristics collected as part of the Reported Edmonton Frail Scale assessment (Hilmer et al., 2009; Rolfson et al., 2006), including: 1) functional independence which is grouped in 3 categories based on number of tasks requiring assistance out of eight daily tasks (excellent = 0–1, fair = 2–4, poor = 5–8); and 2) self-reported performance score (score 0–3, lower is better). We recorded discharge status as post-acute care when patient was discharged to any of the following: skilled nursing facility, intermediate care facility, long term care hospital, rehab facility, or short term hospital. Mortality data was obtained from the National Death Index (NDI) maintained by the Center for Disease Control (CDC - National Center for Health Statistics, 2017).

2.2. Mini-Cog testing

Trained research assistants (RAs) interviewed patients and/or caregivers within 24 h of admission and administered Mini-Cog together with frailty assessment, collected information on the patient's living situation (Ramdass, Brennan, & Starr, 2018). The RAs were trained by a geriatrician and one of the authors (MS) of the study using the hospital elderly life program delirium training manual and coding guide for short confusion assessment method (Inouye, 2014). For each of the instruments, as specified in our protocol, after the training the PI supervised the RAs for the first 10 patients, and randomly thereafter for at least 4 times a month.

We used the Mini-Cog test as described by Borson, et al. to screen for cognitive impairment (three-item recall test and clock drawing) with a score $\leq$ 2 indicating cognitive impairment (Borson et al., 2003). The recall task contributes 1 point for each of the three items accurately remembered and the clock-draw contributes a total of 2 possible points to the overall score (depending on accuracy) for a total of 5 possible points on the overall test. Although data for both the recall and clock draw sections were collected for all patients in the study, as per the defined scoring system by Borson only those patients correctly recalling 1–2 words have the clock draw scored. The stricter cutoff of $\leq$ 2 is often used to screen for dementia although scores of $\leq$ 3 have previously been used in other studies to target patients with mild cognitive impairment (MCI) as well (Borson et al., 2003).

2.3. Outcomes

Our primary outcomes were 30-, 60-, 90-day readmission. Secondary outcomes included length of stay, discharge disposition, time to first readmission and 1-year post-discharge mortality.

2.4. Statistical analysis

Characteristics of the study cohort were reported as means, medians and inter-quartile range for continuous variables and as counts and percentages for categorical variables. We compared the characteristics and outcomes of patients with and without cognitive impairment, as determined using the Mini-Cog assessment, using Chi-square, Wilcoxon and Kruskal–Wallis tests. A p-value < 0.05 was considered statistically significant and all tests were two-sided. To calculate readmission at 30, 60 and 90 days we excluded admissions where the patient expired. We performed multivariable logistic regression to assess the association between cognitive impairment and readmission rates, discharge disposition, time to readmission, and 1-year survival. An adjusted Cox proportional hazards model was used to assess the relationship between cognitive impairment and time to first readmission. Due to the right-skew of length-of-stay data, its relationship with cognitive impairment was modeled using Poisson regression. We adjusted for age, sex, race, admission source (home or not), and comorbidities (Elixhauser score). We also adjusted for the functional independent score and the self-reported Edmonton performance score as noted above. Because prior studies have shown an association between cognitive impairment and outcomes in patients with heart failure and some surgical specialties, we also investigated the potential for interaction between cognitive impairment and patient type (medical versus surgery), and between those with and without a principal diagnosis of heart failure. Of note, this exploratory analysis of potential heterogeneity was not accounted for in the original sample size calculations.

Results are reported as point estimates and 95% confidence intervals (CI). All data management and statistical analyses were performed using R version 3.5 (R Core Team, 2014).

The study was approved by the Baystate Medical Center Institutional Review Board.

3. Results

3.1. Patient characteristics

Among the 668 patients enrolled in the study, median age was 80 (IQR 74–86), 88% were of white race and 58% were female. The baseline characteristics are summarized in Table 1. There were 482 (72%) patients admitted for medical diagnosis and 186 (28%) were admitted for urgent surgical diagnoses.

Overall, 232 (34.7%) patients screened positive for cognitive impairment based on the Mini-Cog test. The cognitive screen results are

Table 1
Baseline Characteristics of subjects in the study.

| | | Overall | Cognitive Impairment | | P-value |
			Negative	Positive	
Number		668	436	232	
Age (median [IQR])		80.00 [74.00, 86.00]	78.00 [72.00, 84.00]	83.00 [77.00, 88.00]	< 0.001
Age Category (%)	65-74	189 (28.3)	149 (34.2)	40 (17.2)	< 0.001
	75-84	275 (41.2)	186 (42.7)	89 (38.4)	
	85+	204 (30.5)	101 (23.2)	103 (44.4)	
Sex (%)	Female	385 (57.6)	258 (59.2)	127 (54.7)	0.30
Race (%)	White	586 (87.7)	387 (88.8)	199 (85.8)	0.08
	Black	39 (5.8)	19 (4.4)	20 (8.6)	
	Hispanic	35 (5.2)	23 (5.3)	12 (5.2)	
	Other	8 (1.2)	7 (1.6)	1 (0.4)	
Hospitalization Prior Year (%)	None	228 (34.2)	169 (38.8)	59 (25.5)	< 0.001
	1 or 2	293 (43.9)	189 (43.3)	104 (45.0)	
	3+	146 (21.9)	78 (17.9)	68 (29.4)	
Encounter Type (%)	Surgery	186 (27.8)	140 (32.1)	46 (19.8)	0.001
	Medical	482 (72.2)	296 (67.9)	186 (80.2)	
Payor Category (%)	Medicare	597 (89.4)	387 (88.8)	210 (90.5)	0.57
History of Dementia (%)		67 (10.0)	19 (4.4)	48 (20.7)	< 0.001
Elixhauser Score (median [IQR])		4.50 [3.00, 6.00]	4.00 [3.00, 6.00]	5.00 [3.00, 7.00]	0.12
Falls Prior Year (%)	None	450 (68.0)	300 (69.3)	150 (65.5)	0.61
	1 or 2	155 (23.4)	97 (22.4)	58 (25.3)	
	3+	57 (8.6)	36 (8.3)	21 (9.2)	
Live at Home (%)		579 (86.7)	392 (89.9)	187 (80.6)	0.001
Functional Independence (%)	Excellent	308 (46.1)	236 (54.1)	72 (31.0)	< 0.001
	Fair	176 (26.3)	118 (27.1)	58 (25.0)	
	Poor	184 (27.5)	82 (18.8)	102 (44.0)	
Performance Score (mean and standard difference)		1.46 (1.23)	1.32 (1.22)	1.72 (1.20)	< 0.001

Table 2
Results of Mini-Cog testing in all subjects.

| | | Overall | Cognitive Impairment | | P-value |
			Negative	Positive	
		N = 668	N = 436	N = 232	
Mini-Cog Words Recalled (%)	All 3	165 (24.7)	165 (37.8)	0 (0.0)	< 0.001
	1 or 2	398 (59.6)	271 (62.2)	127 (54.7)	
	None	105 (15.7)	0 (0.0)	105 (45.3)	
Mini-Cog Clock Draw (%)	No Errors	386 (57.8)	343 (78.7)	43 (18.5)	< 0.001
	Any Error	282 (42.2)	93 (21.3)	189 (81.5)	

summarized in Table 2. Out of the 668 patients tested, 165 patients (25%) were able to recall all 3 words in the item recall task. Performance on clock draw showed large differences between those who eventually tested positive for cognitive impairment compared with cognitively intact patients, with 82% making errors on the clock draw versus 21% respectively (p < 0.001). Those screening positive were significantly older with median age of 83 (IQR 77–88) compared with 78 (IQR 72–84) in those without. Medical patients were more likely than surgical patients to be cognitively impaired (39% vs. 25%; p < 0.001). Two hundred thirty-two patients (34.7%) had a Mini-Cog score suggesting cognitive impairment but only 20.7% of those identified with cognitive impairment had a diagnosis of dementia. The median Elixhauser score was 5 (IQR 3–7) for those screening positive, and 4 (IQR 3–6) for those screening negative for cognitive impairment. In addition, patients with cognitive impairment were more likely to have at least one hospitalization in the prior year (74.8% vs 61.2%), to have poor functional independence with only 31% rating their independence as "excellent" versus 54% in those without cognitive impairment (p < 0.001). Similarly, mean performance score was significantly lower (1.7 versus 1.3, p < 0.001). Those screening in for cognitive impairment were significantly less likely to be admitted from home rather than other facility (81% versus 90%, p < 0.001).

3.2. Outcomes

3.2.1. Unadjusted analysis

When we compared patients with and without cognitive impairment we did not find any significant statistical differences in the proportion with a readmission at 30- or 60-day. Readmission rate at 90 days was 35% for those with cognitive impairment and 27% for those without (p = 0.03), while one year survival rate was 77% for those with cognitive impairment and 84% for those without (p = 0.02). Time to readmission was 6 days shorter (95% CI: -1.9 days, 8.0 days) for those with cognitive impairment compared to those without. The readmission-free survival curve is shown in Fig. 1. Notably, patients with cognitive impairment were more likely than those without to be discharged to a post-acute care facility (54% versus 39%, p < 0.001). Median length of stay was 4 days in both groups; though due to difference in IQR (3–7 in those with CI, verses, 3–6 in those without) a statistically significant difference was obtained (p = 0.007). These results are summarized in Table 3.

3.2.2. Adjusted analyses

In the multivariable regression model which adjusted for demographics, principal diagnosis, admission from home, functional capacity, self-reported general health and comorbidities, only discharge disposition was significantly different between the two groups. There was no evidence of statistical interaction between cognitive impairment and patient type (medical versus surgery patients), and between cognitive impairment and those with and without a principal diagnosis of heart failure. These results showed lack of heterogeneity of effect of cognitive impairment on the outcomes among those groups. Our adjusted primary outcome results are summarized in Table 4.

4. Discussion

In this study of almost 700 elderly patients admitted with a medical diagnosis or for urgent surgery at our tertiary center we found that cognitive impairment as screened for by the Mini-Cog test was not a predictor of post-hospitalization outcomes including one-year survival,
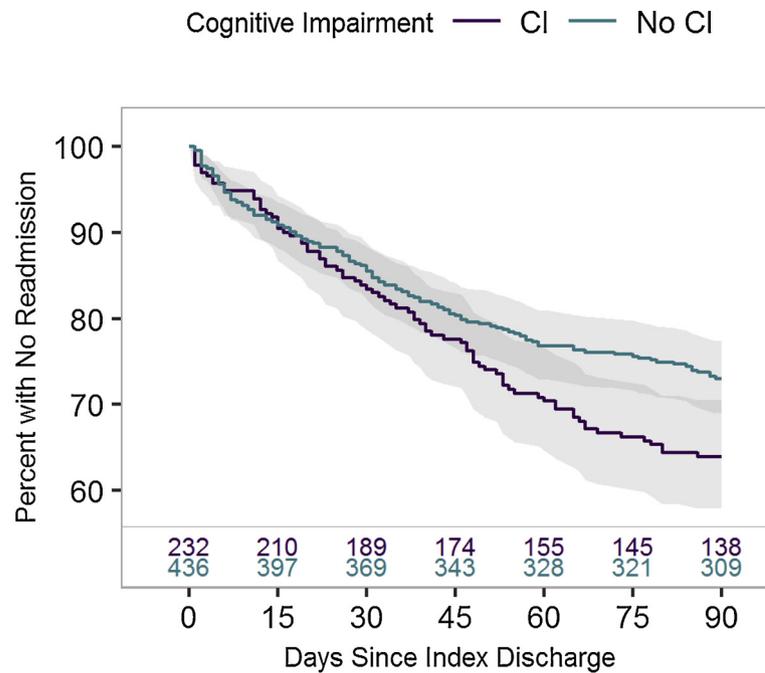
Fig. 1. Kaplan-Meier survival curve of time to all cause readmission for subjects screening positive for cognitive impairment (CI) versus negative (no CI).

readmission or hospital length-of-stay, but was associated with discharge to post-acute care facilities.

The Mini-Cog test offers a quick, validated tool to screen for the presence of cognitive impairment. The benefit of the Mini-Cog is the ease of administration, requiring less than 5 min to administer, yet maintaining a high specificity (76–99%) and sensitivity (89–93%) for the detection of dementia (Borson et al., 2003, 2006; Scanlan & Borson, 2001). If this test was predictive for our outcomes, then performing a quick Mini-Cog assessment at admission could help providers in discussion of risks with patient's families and allow planning appropriately for this group of patients.

To our knowledge, our study is one of the few that has examined the association of the Mini-Cog as a screening tool for cognitive impairment with post-hospitalization outcomes in a broad range of medical and surgical patients admitted to a large tertiary-care hospital. Although this is a largely negative study it provides valuable information to inform future work; negative results also advance the field. We now need studies testing other screening tools and additional factors such as social support at home, clinician awareness of cognitive impairment and subsequent development of delirium and other hazards of hospitalization. Prior to this, a few studies have used the Mini-Cog to identify patients at increased risk for hospital adverse events but focused on specific diagnoses such as heart failure or certain surgical procedures (Benedetti, Ginex, & Mariani, 2015; Culley et al., 2017; Patel et al.,

2015). For example in a study of 720 patients hospitalized with heart failure, the 6-month readmission rate was 46% in those with cognitive impairment versus 22% in those without. In this group of patients, cognitive impairment (as defined by Mini-Cog screening) was the most important predictor for readmission (Patel et al., 2015). Likewise, studies focused on surgical patients undergoing procedures in cardiothoracic and orthopedic settings have also found strong association between early post-operative readmission rates in patients with cognitive impairment (Benedetti et al., 2015; Heng et al., 2016; Ketterer et al., 2017).

Intuitively, patients with dementia will be more likely to have worse outcomes including readmissions to the hospital and post-discharge mortality. In our study, there was a trend for worse outcomes in patients with cognitive impairment (90-days readmission was 8.1

Table 4
Adjusted and Unadjusted Odds ratios for included Outcome Measures.

	Unadjusted			Adjusted*		
	Odds Ratio	95% CI		Odds Ratio	95% CI	
30-Day Readmission	1.16	0.75	1.80	1.02	0.64	1.64
60-Day Readmission	1.33	0.92	1.92	1.18	0.79	1.75
90-Day Readmission	1.46	1.02	2.08	1.39	0.94	2.06
1-year survival	0.62	0.42	0.92	0.82	0.53	1.27

Table 3
Unadjusted outcomes of readmission, length of stay, 1-year survival, and discharge location based on cognitive screening result.

	Total	Cognitive Screening		P-value
		Negative	Positive	
N	668	436	232	
30 Day Readmission (%)	101 (15.1)	63 (14.4)	38 (16.4)	0.58
60 Day Readmission (%)	167 (25.0)	100 (22.9)	67 (28.9)	0.11
90 Day Readmission (%)	197 (29.5)	116 (26.6)	81 (34.9)	0.03
Length of Stay (median [IQR])	4.00 [3.00, 6.00]	4.00 [3.00, 6.00]	4.00 [3.00, 7.00]	0.007
1 Year Survival (%)	545 (81.6)	367 (84.2)	178 (76.7)	0.02
Discharge Location (% discharged to home)	375 (56.1)	268 (61.5)	107 (46.1)	< 0.001
Discharge location (% discharged to post-acute care)	293 (43.9)	168 (38.5)	125 (53.9)	

percentage points higher and one-year survival was 7.2 percentage points lower) but the results were not statistically significant after adjusting for other confounders. The differences in findings in our study could be due to several factors: first, only heart failure patients were included in the Patel study with much higher readmission rates and nonspecific principal diagnoses in our study (Patel et al., 2015); second, exclusion of patients with advanced dementia in our study could have resulted in a less sick population; third, the hospital-culture and processes seeking to optimize care of hospitalized older adults may well have differed among the institutions. For example, some of the patients in this medical cohort were patients in its Acute Care for Elders program (ACE). This may well have affected the outcomes by mitigating excess risk. The lack of interaction between heart failure diagnosis and cognitive impairment could also be due to our limited sample size. Large retrospective studies in Medicare populations have also reported rather conflicting results. A retrospective study of more than 3000 Medicare beneficiaries with dementia in Rhode Island by Daiello et al found that patients carrying an ICD-9 dementia diagnosis had higher 30-day readmission rates (17.8% vs. 14.5%; p < 0.001) (Daiello et al., 2014). However, in another study of nearly 1 million Medicare patients, those with Alzheimer dementia diagnosis were less likely to be admitted to hospital for a diagnosis of heart failure (OR = 0.80; 95% CI 0.50–1.26) but more likely to be admitted for diabetes (OR = 3.61; OR = 2.60) (Lin, Fillit, Cohen, & Neumann, 2013). A recently- large retrospective cohort study of elders in Japan (N = 1,834,378) found that risk of hospital readmission in dementia patients showed substantial variation according to the primary admitting diagnoses (Sakata, Okumura, Fushimi, Nakanishi, & Ogawa, 2018). For instance, the authors highlight that a diagnosis of hip fracture was associated with an increased risk for 30-day hospital readmission (relative risk 1.46; 95% CI: 1.28–1.68), compared to a negligible adjusted relative risk for a diagnosis of cholecystitis (1.03; 95% CI:0.90–1.18) (Sakata et al., 2018). The readmission rates for cognitive impairment patients in our study are comparable with those reported in these studies (16.4% vs 14.4%) and the lack of significance could be due to the smaller sample. Lastly in a recent systematic review, the impact of diagnosed dementia on readmission was only found to be modest as four of five cohort studies in this review showed only small increase in readmission rates (Pickens, Naik, Catic, & Kunik, 2017).

Although we did not find an association between a positive Mini-Cog test and our primary outcomes, we believe that establishing the prevalence of cognitive impairment at admission remains valuable in and of itself. It may be that different screening tools should be employed or that cutoffs need to be adjusted to provide better discrimination of patients at highest risk for poor outcomes. Further studies are needed to assess the best ways to assess for a potential role of cognitive screening in hospitalization outcomes and optimize communication about newly detected cognitive impairment across settings of care.

Our data confirm the high prevalence of cognitive impairment in hospitalized patients with one in three hospitalized elders screening positive. This, in fact, is an underestimate of the extent of more subtle impairment. It is worth noting that only 1 in 4 patients was able to recall all 3 words and for that minority with perfect recall an additional 21% had some errors on the clock-drawing task. Depending on the method of case identification, the prevalence of cognitive impairment among hospitalized elders has been reported as high 30–45% and importantly, at least half of those with significant cognitive deficits may go unrecognized without systematic screening (Naylor, Stephens, Bowles, & Bixby, 2005). In our study, 79% of the patients with cognitive impairment based on Mini-Cog screening did not have a prior diagnosis of dementia or cognitive impairment, supporting the idea that without structured screening cognitive impairment may not be noticed by the patient's healthcare providers. Notably, we found that patients on the surgical service were less likely to test positive with cognitive screening (25% vs 39%; p < 0.001). This may be attributed to

decreased likelihood of planning urgent surgical intervention in those with significant cognitive impairment or altered mentation, opting instead for medical management or admission to a medical service with surgery consultation when possible in these cases.

Our study has several limitations. First, the result of the Mini-Cog can be confounded by the occurrence of delirium in hospitalized elders. Delirium is associated with in-hospital and post-discharge negative outcomes and can contribute to outcomes independently and in presence of existing dementia. A large cohort study of over 10,000 patients in the United Kingdom used a structured geriatric assessment within 24 h to assess the association of a spectrum of cognitive disorders including dementia, delirium and delirium superimposed on dementia with outcomes of readmission, length of stay, and 1 year mortality. Significantly increased risk for adverse outcomes including length of stay, 1 year mortality and one year death or readmission were seen in those with both delirium as well as other forms of cognitive impairment (Reynish et al., 2017). In our study, research assistants performed the confusion assessment and enroll only patients without overt delirium at the time of initial assessment. Some of the prior studies did not specify how they controlled for this situation. However, we should note our purpose in this study was to use the Mini-Cog to assess for cognitive impairment upon admission hypothesizing that impairment predisposes patients to adverse outcomes post discharge. Although we excluded patients with delirium based on the admission CAM, some patients who were not delirious at presentation could have developed delirium subsequently. Since we are unable to identify and control for subsequent delirium this may have contributed to our negative results.

Second, this was a single-center study and hospital wide-specific interventions for elderly adults may differ from other hospitals and could have influence the outcomes. Third, we did not have information on the level of home support, anesthesia or surgical type, the standards of nursing care for ambulation, all of which could impact the outcomes. Fourth, due to limitations in practicality with applying the test in patients speaking other languages, we only included English-speaking patients. Fifth, the population was heterogeneous and although the statistical testing for heterogeneity was negative, our study was not powered to detect this association so this relationship could still exist. Lastly, the results of the Mini-Cog screening were not known to the supervising physician, and therefore we are unable to assess what impact the knowledge of cognitive impairment would have had on their care or management once applied to general hospital care.

5. Conclusion

We found that Mini-Cog test as a screening tool for cognitive impairment was not associated with readmission, length of stay, or 1-year mortality rates but was associated with discharge to post-acute care facilities. The addition of other tools such as frailty assessment may be more useful in predicting these outcomes.

CRediT authorship contribution statement

Ali Shami: Conceptualization, Methodology, Writing - original draft, Writing - review & editing. **Maura Brennan:** Conceptualization, Methodology, Writing - original draft, Writing - review & editing. **Peter St. Marie:** Methodology, Software, Validation, Formal analysis, Data curation, Writing - original draft. **Peter K. Lindenauer:** Writing - review & editing, Supervision. **Mihaela S. Stefan:** Conceptualization, Methodology, Writing - original draft, Writing - review & editing, Supervision, Project administration.

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Declaration of Competing Interest

All authors declare no conflict of interest in the current work.

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