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Is anemia associated with cognitive impairment and delirium among older acute surgical patients?

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Aim: The determinants of cognitive impairment and delirium during acute illness are poorly understood, despite being common among older people. Anemia is common in older people, and there is ongoing debate regarding the association between anemia, cognitive impairment and delirium, primarily in non-surgical patients.

Methods: Using data from the Older Persons Surgical Outcomes Collaboration 2013 and 2014 audit cycles, we examined the association between anemia and cognitive outcomes in patients aged ≥65 years admitted to five UK acute surgical units. On admission, the Confusion Assessment Method was carried out to detect delirium. Cognition was assessed using the Montreal Cognitive Assessment, and two levels of impairment were defined as Montreal Cognitive Assessment <26 and <20. Logistic regression models were constructed to examine these associations in all participants, and individuals aged ≥75 years only.

Results: A total of 653 patients, with a median age of 76.5 years (interquartile range 73.0–80.0 years) and 53% women, were included. Statistically significant associations were found between anemia and age; polypharmacy; hyperglycemia; and hypoalbuminemia. There was no association between anemia and cognitive impairment or delirium. The adjusted odds ratios of cognitive impairment were 0.95 (95% CI 0.56–1.61) and 1.00 (95% CI 0.61–1.64) for the Montreal Cognitive Assessment <26 and <20, respectively. The adjusted odds ratio of delirium was 1.00 (95% CI 0.48–2.10) in patients with anemia compared with those without. Similar results were observed for the ≥75 years age group.

Conclusions: There was no association between anemia and cognitive outcomes among older people in this acute surgical setting. Considering the retrospective nature of the study and possible lack of power, findings should be taken with caution. **Geriatr Gerontol Int 2018; 18: 1025–1030.**

Keywords: anemia, cognitive impairment, delirium, older surgical patients.

Introduction

An increasing number of older people are being admitted to hospital for surgical management.[1,2] Cognitive impairment with or without delirium, an acute clinical syndrome characterized by a fluctuating course, disturbed consciousness, and reduced ability to focus, sustain or shift attention,[3,4] is prevalent in older people, especially in the acute surgical setting. Our recent work suggests that the prevalence of cognitive impairment in this patient population is extremely common;[5] up to 70% of older people have cognitive impairment in the acute surgical setting.[6] Delirium is also estimated to be present in up to 30% of older patients during their hospital admission.[7]

Anemia is another common condition in older age. According to The Third National Health and Nutrition Examination Survey, the prevalence of World Health Organization-defined anemia among community-dwelling adults aged ≥65 years in the USA was 11.0%

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and 10.2% in men and women, respectively,[8] rising to >20% in those >85 years.[9] Contemporary literature in hospitalized patient populations mirrors these figures; in patients admitted with stroke (mean age ~78.0 years), anemia was present in ~25% of patients and indeed associated with high mortality.[10]

There has been growing interest in the role of anemia in cognition among older adults. A recent systematic review and meta-analysis showed a significant positive association between anemia and global cognitive decline, reduced executive function, and the incidence of dementia.[11] A recent report suggested anemia as an independent risk factor for delirium in hospitalized older patients along with dementia in a small cohort of 190 patients.[12] However, there is still a dearth of information on the link between anemia and delirium in acutely unwell older patients, especially in the acute surgical setting.

We were interested to examine the association between anemia and cognitive impairment as well as delirium in a cohort of older acute surgical patients. The existence of such an association would provide the potential to identify older people who are at risk of delirium from the outset, and raise the intriguing possibility of hemoglobin as a potential therapeutic target in managing delirium both pre- and postoperatively. Indeed, the current National Institute for Health and Care Excellence preoperative guidelines for transfusion accept a level of preoperative anemia, and therefore any potential link between anemia and delirium could significantly modify guidelines and, subsequently, the clinical approach.[13] Secondarily, we also aimed to examine the link between anemia and cognitive impairment among older acute surgical emergency admissions, as little is known about this link in this patient population with a high prevalence of cognitive impairment.

Methods

As part of the Older Persons Surgical Collaboration (OPSOC), the present observational study was carried out across five UK hospitals. Data were collected for consecutive patients aged ≥65 years who presented to the acute general surgical unit of each study site during May to June in 2013 and 2014. The data collection methods have been previously reported for each audit cycle.[14–16] In brief, baseline demographics and comorbidities were recorded, and multimorbidity was defined as the presence of two or more comorbid conditions (Table S1), anemia was defined as hemoglobin <129 g/L, hypoalbuminemia as albumin <35 g/L, and polypharmacy as five or more medications on admission.[17,18]

Within 24 h of admission, and before any surgical intervention, participants received two cognitive function tests, the Confusion Assessment Method (CAM) and the Montreal Cognitive Assessment (MoCA). The CAM is a simple to use, validated, 4-point score used to detect delirium (Fig. S1). The MoCA is a validated 30-point questionnaire with a sensitivity of 90% for detecting mild cognitive impairment (Fig. S2).[19] Scores ≥26 were considered normal. Scores <20 were used to characterize moderate/severe impairment, as previously used within the literature.[20–22] For participants who were unable to complete the MoCA, the reason was recorded. Data collectors were trained in carrying out the CAM and MoCA before study commencement.

Frailty was assessed using the validated 7-point Canadian Study of Health and Aging Clinical Frailty Score (Table S2) and categorized into five groups (1-2, 3, 4, 5 and 6-7).[23] Length of stay was calculated from admission and discharge dates. Data were recorded and stored in conjunction with local data management standard operating procedures. All participants were service users, and both the MoCA and the CAM are freely available for routine use. As such, the present study was deemed a service evaluation, and did not require ethical approval and was registered at each participating site as per the local guidelines. Respective Institutional Approvals were obtained for each audit cycle. A separate unique ID was assigned for anonymization purposes before pooling of the data.

Statistical analysis was carried out following an a priori protocol using STATA 13.0 (StataCorp, College Station, TX, USA) using anonymized combined audit data. Characteristics and outcomes were compared between those with and without anemia. The prevalence of cognitive impairment at two levels (using two cut-off points of MoCA <26 and MoCA <20) and delirium were estimated and compared between patients with and without anemia. We set two thresholds for MoCA analysis, as it is a sensitive measure with lower specificity for clinical dementia and MoCA values close to 20 are more comparable with moderate cognitive impairment. Univariable and multivariable logistic regression models were constructed to examine these associations in all patients and then confined to those aged ≥75 years. Linear regression models were also constructed for every 10-g/L decrease in hemoglobin levels in a subset with hemoglobin data (data from 2014 audit cycle only). *P*-values were reported from χ^2-tests of association, and *P*-values and 95% confidence intervals were reported from the logistic regression models. Because of multiplicity, evidence of a difference was determined at the 1% statistical significance level (two-sided $P < 0.01$).

Results

A total of 653 older acute surgical patients were included in this report across five UK sites during two audit cycles (2013 and 2014 cycles). Women made up 53% (346/653) of the patients, and the cohort had a median age of 76.5 years (IQR 73–80). The number of

patients with data on covariates varied, as data on multimorbidity, diabetes, albumin and hyperglycemia were collected only in one out of two cycles, depending on the focus of the audit.

Table 1 shows the sample characteristics compared between those with and without anemia. Evidence of statistically significant associations was found between anemia at the time of acute surgical admission and polypharmacy ($P < 0.001$), and hyperglycemia ($P = 0.009$) and hypoalbuminemia ($P < 0.001$). There was limited evidence that multimorbidity ($P = 0.02$) and length of stay ($P = 0.04$) were also associated with anemia.

Using univariable or multivariable logistic regression models, no evidence was found to suggest that anemia was associated with either cognitive decline or delirium (Table 2). In models adjusted by age, sex, polypharmacy, multimorbidity, frailty and diabetes mellitus for cognitive impairment, and adjusted by age, sex, polypharmacy, multimorbidity, frailty and hyperglycemia for delirium, the adjusted odds ratios of cognitive impairment were 0.95 (95% CI 0.56–1.61) and 1.00 (95% CI 0.61–1.64) for having MoCA <26 and <20, respectively, and the odds of delirium at presentation was 1.00 (95% CI 0.48–2.10) in patients with anemia compared with those with no anemia. Similar results were observed for the ≥75 years age group.

For every 10-g/L decrease in hemoglobin, it was estimated that there was a reduction in MoCA of 0.25 (95% CI −0.1 to 0.6; $P = 0.21$).

Discussion

In the present study of 653 older acute surgical patients, anemia on admission was associated with polypharmacy, hyperglycemia and hypoalbuminemia on admission. Anemia was not associated with cognitive impairment or delirium. There is some evidence to suggest that anemia is associated with multimorbidity and increased length of hospital stay. To our knowledge, the present study is the largest study to date that has assessed the association between anemia in older acute surgical patients and the presence of delirium and cognitive impairment.

The multicenter nature of this current study allowed us to capture acute surgical admissions among older people in both rural and urban populations, allowing for good generalizability to the UK population of older acute surgical patients. Both the MoCA and the CAM are validated tools for detecting the presence of cognitive impairment and delirium respectively, meaning that we can be confident in the detection of these clinical variables.[24,25] In addition, all data collectors were trained in using these screening tools, limiting interobserver bias.

The main weakness of the present study was the fact that the analysis was carried out retrospectively using existing audit data. Although we had an a priori statistical analysis plan, we did not power this study to detect this specific hypothesis, so it cannot be assumed that the negative findings observed in this study prove that no difference exists, merely that a difference was not detected. In addition, multimorbidity, diabetes, albumin and hyperglycemia data were not collected consistently in both audit cycles. This was primarily due to the focus of the audit in each audit cycle. This makes it difficult to make any firm conclusions regarding the relationship amongst these variables, the presence of anemia and the clinical outcomes being investigated. A hemoglobin cut off level of <129 g/L was used to define anemia as per audit standards of OPSOC 2013 and 2014 cycles. The actual hemoglobin values were available only in one out of two audit cycles. Given the cut-off value of 129 g/L, anemia defined in the present study might fail to detect any threshold relationship between low hemoglobin and the outcomes of interest.

The number of older people undergoing emergency surgical intervention is rising,[1] and as such increasing efforts are being made to identify characteristics that predict adverse outcomes in this group.[26] The association between anemia and poor clinical outcome is well recognized within the literature. Preoperative anemia is known to be associated with both postoperative mortality (odds ratio 1.42, 95% CI 1.31–1.54), and postoperative morbidity (adjusted odds ratio 1.35, 95% CI 1.30–1.40) at 30 days in surgical patients.[27] The presence of anemia, delirium and cognitive impairment, and the role they play in determining outcomes for older patients has also been investigated.

A recent systematic review by Andro *et al.* aimed to examine the relationship between anemia on cognitive functions in an older community-dwelling population.[11] Findings suggest that low hemoglobin levels might be considered as a potential contributing factor to cognitive impairment, particularly in executive functions, inducing cognitive decline and conversion from mild cognitive impairment to dementia. Furthermore, anemia as a risk factor for the development of delirium has been studied in an older population. Joosten *et al.* investigated 190 older patients admitted to an acute geriatric ward for the presence of anemia (hemoglobin level <12 g/L in women and <13 g/L in men) and delirium.[12] The authors reported that anemia, male sex, age >82 years, dehydration and a clinical diagnosis of dementia were independent risk factors for delirium in the total group. After adjustment for these variables, anemia remained significantly associated with delirium (odds ratio 2.4, 95% CI 1.02–5.5).

Aside from the relatively large sample size, to the best of our knowledge, this is the first study to investigate the association between anemia, cognitive impairment and delirium specifically within an older acute

Table 1 Characteristics and outcome comparison between those with or without anemia in Older Persons Surgical Collaboration (2013–2014)

Covariate	Total (*n*)	Anemia *n* = 320	No anemia *n* = 333	*P*-value*
Age (years)				
65–74	653	133 (44%)	164 (47%)	0.11
75–84		111 (37%)	130 (37%)	
≥85		58 (19%)	57 (16%)	
Sex				
Female	653	176 (55%)	170 (51%)	0.31
Male		144, (45%)	163 (49%)	
Multimorbidity				
No	411	37 (20%)	70 (31%)	0.016
Yes		146 (80%)	158 (69%)	
Polypharmacy				
No	653	91 (28%)	155 (47%)	<0.001
Yes		229 (72%)	178 (53%)	
Diabetes mellitus				
No	411	147 (81%)	183 (81%)	0.97
Yes		35 (19%)	44 (19%)	
Frailty				
1–2	644	176 (56%)	185 (56%)	0.06
3		34 (11%)	55 (17%)	
4		40 (13%)	41 (12%)	
5		29 (9%)	27 (8%)	
6–7		36 (11%)	21 (6%)	
Hyperglycemia				
Under 7	293	83 (65%)	88 (53%)	0.009
7 to 11		37 (29%)	62 (37%)	
Over 11		7 (6%)	16 (10%)	
Albumin				
No	411	76 (42%)	164 (72%)	<0.001
Yes		107 (58%)	64 (28%)	
Length of stay				
1 Day	653	47 (15%)	66 (20%)	0.04
Up to 1 week		106 (33%)	129 (39%)	
Up to 2 weeks		66 (21%)	58 (17%)	
Longer		101 (32%)	80 (24%)	
MoCA				
26–30	556	59 (23%)	78 (27%)	0.27
1–25		203 (77%)	216 (73%)	
MoCA				
20–30	556	172 (66%)	194 (66%)	0.93
1–19		90 (34%)	100 (34%)	
Delirium				
Not delirious	403	161 (90%)	206 (92%)	0.48
Delirious		18 (10%)	18 (8%)	
Operation				
No	403	140 (78%)	184 (83%)	0.32
Yes		40 (22%)	39 (17%)	

*The χ^2-test of association. MoCA, Montreal Cognitive Assessment.

surgical population. Therefore, it is difficult to compare previous studies' results directly with the present study because of the differences in anemia definitions used, and the fact that the proportions of surgical and medical inpatients within the previous cohorts are not known.

Table 2 Odds ratios and 95% confidence intervals for outcomes of Montreal Cognitive Assessment <26, Montreal Cognitive Assessment <20 and Delirium for anemic patients compared with patients with no anemia by age in the Older Persons Surgical Collaboration 2013–2014

Age (years)	Outcomes	Anemia (*n*)	No anemia (*n*)	Crude OR (95% CI)	*P*-value	aOR_1 (95% CI)	*P*-value	aOR_2 (95% CI)	*P*-value
MoCA									
≥65	<26	203	216	1.24 (0.84–1.83)	0.27	1.16 (0.77–1.73)	0.48	0.95 (0.56–1.61)	0.85
	≥26	59	78	Reference		Reference		Reference	
≥75	<26	130	122	1.28 (0.67–2.43)	0.45	1.32 (0.69–2.52)	0.40	1.11 (0.50–2.50)	0.80
	≥26	20	24	Reference		Reference		Reference	
≥65	<20	90	100	1.02 (0.71–1.44)	0.93	1.02 (0.71–1.44)	0.93	1.00 (0.61–1.64)	0.99
	≥20	172	194	Reference		Reference		Reference	
≥75	<20	63	65	0.90 (0.57–1.43)	0.66	0.89 (0.56–1.42)	0.64	1.02 (0.53–1.97)	0.95
	≥20	87	81	Reference		Reference		Reference	
Delirium									
≥65	Delirious	18	18	1.28 (0.64–2.54)	0.48	0.28 (0.64–2.54)	0.48	1.00 (0.48–2.10)	0.98
	Not delirious	161	206	Reference		Reference		Reference	
≥75	Delirious	16	11	1.43 (0.63–3.23)	0.40	1.18 (0.58–2.38)	0.65	1.22 (0.49–3.01)	0.67
	Not delirious	100	98	Reference		Reference		Reference	

Adjusted odds ratios $(aOR)_1$ are adjusted for age and sex. aOR_2, Covariates for Montreal Cognitive Assessment (MoCA) outcomes are: age, sex, polypharmacy, multimorbidity, frailty and diabetes mellitus. Covariates for delirium outcome are: age, sex, polypharmacy, multimorbidity, frailty and hyperglycemia.

Delirium is still a major problem affecting older patients and their clinical outcomes. Although there is a growing body of research on the pathophysiology, diagnosis and management of delirium, few studies have been carried out with the view of identifying biomarkers of delirium that can easily be assessed at the point of care, and that might serve as a therapeutic biomarker. Our point estimates suggest a potential usefulness of hemoglobin level as a biomarker of the risk of delirium and cognitive impairment in the surgical patient population, and this requires further investigation using larger samples at various hemoglobin thresholds.

In summary, no evidence of association was found between anemia and cognitive outcomes among older people in this acute surgical setting. Considering the retrospective nature of the study and possible lack of power, these findings should be taken with caution. The clinical and cost-effectiveness of correcting anemia pre- or postsurgery as an intervention to improve cognitive outcomes in the acute surgical setting, with the view of improving overall surgical outcome, should be thoroughly examined in a clinical trial setting.

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Disclosure statement

The authors declare no conflict of interest.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website: .

Table S1 Information box of the criteria used to quantify conditions to define multimorbidity in the current study.
Table S2 The Canadian Study of Health and Aging (CSHA) frailty scale used to define the level of frailty of each patient during hospital admission.
Figure S1 The Confusion Assessment Method Diagnostic Algorithm used to define the presence of delirium on admission.
Figure S2 The Montreal Cognitive Assessment Test (MoCA) used to define the presence of cognitive impairment on admission.