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Biologic correlates associated with poor functional recovery after delirium: A nested prospective cohort study

1 | INTRODUCTION

To the Editor, Delirium is a common disorder among hospitalized older adults associated with devastating consequences.[1–4] Recovery from delirium is unpredictable and delirium can persist in up to 45% of individuals at hospital discharge[4]; conversely individuals with brief delirium do better functionally.[4] Therefore, poor recovery may partially be related to lingering delirium.[4]

The pathophysiology underlying delirium is not well understood.[1,5] Neuroendocrine homeostasis, metabolic factors and increased inflammation have been implicated. Low levels of insulin-like growth factor-1 (IGF-1),[5] B12 deficiency, elevated C-reactive protein (C-RP), and the presence of the Apo-lipoprotein E4 allele (ApoE4) have been associated with delirium.[2,5–8] Diverse biologic mechanisms may predispose to delirium and possibly heterogeneity in associated longer-term outcome.

We hypothesized that certain risk factors for delirium predispose to persistent delirium and subsequent poor recovery. We examined the association between IGF-1, CRP, vitamin B12, and the ApoE4 allele with poor recovery (defined by death, permanent institutionalization, or decreased functional ability), 3 months after hospitalization with delirium, in community dwelling seniors without cognitive impairment, admitted to medical in-patient units.

2 | METHODS

This study was nested within a larger prospective cohort of delirious individuals described elsewhere.[3] In brief, consecutive patients 70 years of age or older, admitted to the general medicine in-patient teaching units at two sites of the London Health Sciences Center, in London, Ontario, who did not meet exclusion criteria were approached within 3 days of admission, by the investigators for possible study inclusion and informed consent. Eligible participants were community dwelling and not dependent for all their activities of daily living (ADLs). Individuals with life expectancy of less than 3 months (e.g., those with known advanced cancer), no substitute decision maker, or who were noncommunicative were excluded from the study. In all cases of questionable ability to consent, and for all delirious patients, consent from the caregiver was required. Participants were screened for delirium every 2 days three times

after enrollment by a trained research assistant. Patients were classified as delirious if they met Confusion Assessment Method criteria for delirium.[9] The delirious participant's caregiver completed the Informant Questionnaire of Cognitive Decline in the Elderly (IQCODE).[10] For this study, only delirious individuals with IQCODE scores <3.5 (indicating normal baseline cognitive function) were enrolled. This study was started after the larger prospective study and included only participants from one site, as a hypothesis generating study. Caregivers also completed the ADL questionnaire from the Older American Resources and Services Project.[11]

Poor recovery was defined by any one of death, new permanent institutionalization (in a residential facility providing 24 h nursing care), or functional decline (decreased ability to perform ADLs), 3 months after discharge. The outcome was assessed from the medical record or by telephone interview with the caregiver 3 months after discharge. Functional decline was defined by either a full decline in an ADL ability or a partial decline in at least two ADLs.

Non fasting blood was drawn once, by unit staff (not research staff) within 1 week after delirium was established, complementing routine bloodwork that was ordered. Blood was analyzed by hospital Laboratory Services; laboratory tests are described in Supporting Information: File 1.

For this hypothesis generating study, simple univariate correlations were calculated between a priori determined variables (a separate sample size calculation was not done). Blood levels of IGF-1, vitamin B12, and CRP were compared between individuals with and those without poor recovery using median two sample test (for differences in medians) and Wilcoxin rank sum tests (for distribution differences). The presence of ApoE4 allele was compared using Fisher's exact test. Two-sided significance was set at <0.05. Baseline characteristics were compared using t-tests or Fisher's exact test. Analyses were performed using SAS 9.3.

This study was approved by the Health Sciences Research Ethics Board of the University of Western Ontario.

3 | RESULTS

Of 343 delirious individuals in the original study, 125 (37%) had IQCODE scores <3.5 and were eligible for inclusion in this study (Figure 1). Eligible patients were less impaired in baseline ADLs ability
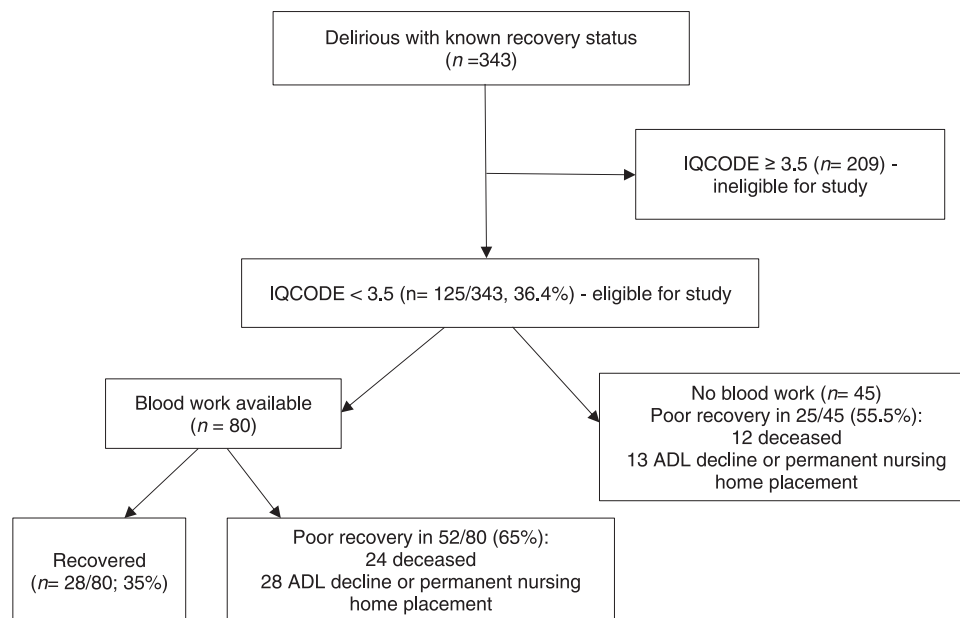
FIGURE 1 Participant enrollment. ADL, activities of daily living.

TABLE 1 Biologic factors and their association with poor recovery after delirium in cognitively intact older medical in-patients.

Biologic factors	Number with blood test done	With poor recovery [n = sample size with blood drawn]	Without poor recovery [n = sample size with blood drawn]	p Value[a]
C-reactive protein, median mg/L (IQR)	67	40.4 (53.8) [n = 46]	51 (95.1) [n = 21]	0.73
Vitamin B12, median pmol/L (IQR)	68	294 (412) [n = 47]	464 (476) [n = 21]	0.02
Insulin like growth factor 1, median μg/ L (IQR)	66	53 (52) [n = 43]	79 (68) [n = 23]	0.02
Number with at least 1 copy of ApoE4 allele (%)	80	18 [52]	13 [28]	0.30

[a]p Values compare those with and without poor recovery (independent samples median test or Fisher's exact test).

and less likely to have poor recovery compared to the entire delirious sample (rate of poor recovery 62% [77/125] vs. 69% [237/343], respectively).

Laboratory results were not available for all eligible participants due to various reasons (such as if participants were enrolled before the present study started, or at the second site, or due to logistic challenges of doing research in an acute environment). Eligible individuals without bloodwork (n = 45) did not differ significantly from those with blood-work (n = 80) in sex (female in 26 and 41 individuals respectively, p = 0.58), baseline ADL dependence (ADL score of 13.4 [SD 2.6] and 13.8, respectively [SD 2.7], p = 0.40), or chance of recovery (poor recovery in 25 and 52, respectively, p = 0.34), although they were older (mean age 86.0 [SD 7.4] vs. 82.4 [SD 7.5], p = 0.01) and trended toward decreased comorbidity (mean cumulative illness rating score[12] of 8.5 [SD 3.7] and 9.8 [SD 3.7], respectively, p = 0.07).

The analysis revealed no statistically significant differences between those with and without poor recovery in the median or distribution of CRP or percentage of individuals carrying at least one ApoE4 allele. Median IGF-1 and B12 levels were significantly lower in those with poor recovery than those without, although the distributions of each did not statistically differ (p = 0.15 and p = 0.08, respectively) (see Table 1).

4 | DISCUSSION

The results of this hypothesis generating study suggests a possible association between low B12 or IGF-1 levels and poor delirium recovery. Biologic plausibility exists supporting IGF-1 and vitamin B12 as enhancing recovery from delirium. IGF-1 has antiapoptotic

and neurotrophic effects, moderates the effect of cytotoxic cytokines and induces neurogenesis.[5,12] Higher vitamin B12 and lower homocysteine concentrations are associated with slower rates of brain volume loss.[13] B12 supplementation may slow the rate of cognitive decline, and brain atrophy; this may apply to the recovering delirious brain as well, though more research is needed to confirm this.[14,15]

This study has several limitations. Individuals with baseline cognitive impairment were excluded; this is because the biologic factors we assayed for are also associated with chronic cognitive disorders (such as Alzheimer's disease), independent of delirium. The study thereby sought to remove the effect of chronic cognitive impairment on recovery. Compared to the larger original delirious sample, current study participants were less functionally compromised at baseline, therefore representing a selected population. Only four biologic risk factors were measured, and we did not use a standardized time point for bloodwork collection. More research is needed to understand the role of biologic risk factors in more cognitively or functionally impaired individuals, at highest risk for delirium and how the role of other biologic risk factors and frailty impact functional recovery from delirium. Heterogenous and complex interactions between biologic factors may lead to delirium and promote recovery, but our study was underpowered to detect these. Lastly the low sample sizes for each factor may have resulted in this study being underpowered to detect significant differences.

Despite these limitations, our study suggests that IGF-1 and B12 are worthy of further study. Understanding delirium and what factors enhance or predict recovery (both symptomatically and functionally) remains an important area to study given its high prevalence, complications, and cost.

KEYWORDS

activities of daily living, aged, delirium, prognosis

AUTHOR CONTRIBUTIONS

Monidipa Dasgupta: Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; writing—original draft; writing—review and editing. **Chris Brymer**: Data curation; writing—original draft; writing—review and editing.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data is available on request due to privacy/ethical restrictions.

TRANSPARENCY STATEMENT

The lead author Monidipa Dasgupta, Monidipa Dasgupta affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.