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Running head: Predicting outcome in delirium

Key words: delirium, aged, prognosis, mortality, predictor, systematic review

Key points:

- Delirium is associated with poor outcomes
- Hypoactive delirium and duration of delirium predict worse outcomes
- Psychiatric co-morbidity with dementia and depression predict worse outcomes
- Further identification of factors predicting worse outcomes in delirium is needed and will help inform delirium pathophysiology

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Conflict of Interest

There are no disclosures to report.

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Description of Author's Roles

TJ devised the protocol and planned the organisation of the review. All authors contributed to reviewing articles, data extraction and contributed to data analysis. TJ wrote the first draft and all authors contributed to revision of the manuscript and provided final edits. TJ is guarantor

Abstract

Objective

Delirium is a serious neuropsychiatric syndrome common in older hospitalised adults. It is associated with poor outcomes, however not all people with delirium have poor outcomes and the risk factors for adverse outcomes within this group are not well described. The objective was to report which predictors of outcome had been reported in the literature.

Methods

We performed a systematic review by an initial electronic database search of MEDLINE, Embase and PsycINFO using four key search criteria. These were: (1) participants with a diagnosis of delirium, (2) clearly defined outcome measures, (3) a clearly defined variable as predictor of outcomes and (4) participants in the general hospital, rehabilitation and care home settings, excluding intensive care. Studies were then selected in a systematic fashion using specific predetermined criteria by three reviewers.

Results

559 articles were screened and 57 full text articles assessed for eligibility. 27 studies describing 18 different predictors of poor outcome were reported. The studies were rated by the Newcastle-Ottawa Score and were generally at low risk of bias. Four broad themes of predictor were identified; five delirium related predictors, two co-morbid psychiatric illness related predictors, eight patient related predictors, and three biomarker related predictors. The most numerously described and clinically important appear to be the duration of the delirium episode, a hypoactive motor subtype, delirium severity and pre-existing psychiatric morbidity with dementia or depression. These are all associated with poorer delirium outcomes.

Conclusion

Important predictors of poor outcomes in patients with delirium have been demonstrated. These could be used in clinical practice to focus direct management and guide discussions regarding prognosis. These results also demonstrate a number of key unknowns, where further research to explore delirium prognosis is recommended and is vital to improve understanding and management of this condition.

Key words: delirium, aged, prognosis, mortality, predictor, systematic review

Introduction

Delirium is a serious and common syndrome affecting mainly older people(Inouye et al., 2014). It is an acute neuropsychiatric condition affecting global cognitive function, typically attention and working memory, as well as consciousness. Delirium is often undiagnosed, yet affects between 14-24% of hospital admissions and develops in between 29-64% of patients on general medical and geriatric medicine wards (Inouye et al., 2014). The clinical presentation of patients with delirium is varied and specific motor sub-types, hyperactive and hypoactive, have been described (Inouye et al., 2014).

Delirium is associated with adverse clinical outcomes including increased mortality, increased length of hospital stay, more hospital-acquired complications, such as falls and pressure sores, and increased rates of institutionalisation, re-admission and dementia(Siddiqi et al., 2006, Witlox et al., 2010). These outcomes have significant morbidity both for the patient and their carers, causing considerable short and long-term distress (Partridge et al., 2013). They also lead to additional healthcare costs, estimated at an extra £13,000 per admission (Akunne et al., 2012).

In studies of older people in general, it has been possible to identify predictors of poor outcomes such as death, increased length of stay, reduced function and institutionalisation (Drame et al., 2008, Campbell et al., 2004). Identifying predictors of poor outcomes specific to delirium would allow clinicians to risk stratify patients in order to focus immediate and follow-up management strategies according to baseline risk with the aim of improving outcomes. Exploration of the factors behind the heterogeneity of delirium presentation and outcome may also inform future research into its pathophysiology and treatment.

Objectives

To identify published predictors of poor outcome in hospitalised patients with delirium.

Method, Search Criteria and Strategy

We undertook a comprehensive literature review of the following databases: MEDLINE, Embase and PsycINFO. The primary search terms were delirium, acute confusional state and confusion. These were searched for together with recognised terms for prognosis, mortality and outcomes (Wilczynski et al., 2004). The full search strategy is given in supplementary data (see supplemental appendix). The databases were accessed on 02/11/14 and databases searched from 1980 onwards. Abstracts were reviewed to determine which papers to extract by two reviewers (TJ + DW). Inclusion criteria at that stage were studies that evaluated variables with recognised outcomes in patients with delirium. A further search of the references of selected papers was completed to find additional papers. A forward citation search of selected papers was also carried out.

The studies selected by these processes were obtained in full and reviewed independently by three reviewers (TJ, DW, and SR) against the following inclusion criteria:

1. Included patients with delirium, diagnosed using a recognised and validated method
2. Included clearly defined outcomes; death, institutionalisation, length of stay and cognitive change;
3. Variables used as predictors were clearly defined with appropriate statistical analysis.
4. Included patients in the general hospital, rehabilitation facilities or care homes, but not in the intensive care setting or community;

Exclusion criteria were non-English language papers and non-human studies.

Once included, the following information was recorded on a standardised proforma: reference, setting, study group size, diagnostic tool, outcomes, covariates used, predictors identified with associated hazard ratio (HR) or odds ratio (OR) if quoted. The included studies were reviewed by a fourth reviewer (JL) who also discussed any disagreement on inclusion.

We used the Newcastle-Ottawa Quality Assessment Scale (Wells et al., 2012) to assess selected studies for risk of bias. We followed the Guidelines for Meta-Analyses and Systematic Reviews of Observational Studies (MOOSE) when reporting findings (Stroup et al., 2000).

Results

The initial search returned 843 articles of which 88 were not in English. Fifty-seven articles were selected having met the criteria. Two further articles were identified from the reference lists of selected articles. Of those 59, 27 met the inclusion criteria. No further studies were identified by a forward citation search. Figure 1 illustrates the study selection. The individual studies with relevant extracted data and Newcastle-Ottawa scores (NOS) are available as supplementary data (see supplementary table 1 and 2). NOS scores ranged from six to nine (maximum nine) suggesting a low risk of bias across all studies selected.

Patients

Mean age of participants ranged from 70 to 89 years and the majority of studies included more women than men.

Setting

Thirteen studies were set in acute and general medical admission wards, six in hip fracture patients, four in post-acute and rehabilitation units, two in palliative care units and a single study in the emergency department. Ten studies were based in the United States of America, four in Canada,

three in Italy, two in the United Kingdom, two in Finland, two in Ireland and a single study was based in Chile, South Korea, Netherlands and Taiwan.

Diagnosis of delirium

To diagnose delirium, eight studies used the gold standard of the Diagnostic and Statistical Manual of Mental Disorders (DSM), and 19 used the Confusion Assessment Method (CAM)

Outcomes

In the 27 studies, mortality as an outcome was described 25 times (outcome mortality ranged from one month to 40 months), new institutionalisation five times, length of hospital stay once and a single study used a combined outcome of death, new institutionalisation or functional decline. There were no studies describing cognitive outcomes.

Predictors of poor outcomes

In the 27 studies, eighteen main predictors of these outcomes are described.

Four broad themes were identified when analysing the predictors identified; delirium related predictors, co-morbid psychiatric illness related predictors, patient related predictors, and biomarker related predictors. Figure 2 illustrates the five most frequently reported predictors.

Delirium related predictors

Motor subtype

Seven studies (N=1260 with delirium) examined the effect of motor subtype of delirium on outcomes. Three studies suggest the hypoactive subtype has worse outcome, with association with mortality being shown in a palliative care population (Meagher et al., 2011). Two studies in a post-acute care facility showed a HR for mortality over 12 months of 1.62 (95%CI 1.11-2.37) for

hypoactive delirium(Kiely et al., 2007) and a HR of 3.98 (95% CI 1.76-8.98) for mortality over six months in patients with hypoactive delirium and dementia (Yang et al., 2009) when compared with patients with hyperactive delirium. In a hip fracture population, hyperactive delirium was associated with a six fold (OR 5.9 95% CI 1.3-29.0) increased risk of mortality or new nursing home placement (Marcantonio et al., 2002). However, three studies demonstrated no relationship between motor subtype and outcomes (DeCrane et al., 2011, Slor et al., 2013, Kelly et al., 2001).

Duration

The prognostic importance of the duration of delirium was examined in eight studies (n=871 with delirium). Every day of delirium was associated with a HR of 1.17 (95% CI 1.07-1.28) for death over a six month period (Bellelli et al., 2014), and delirium longer than 48 hours carried a HR of 1.16 for mortality over three months, in comparison to the population whose delirium resolved within that period (Gonzalez et al., 2009). Persistent delirium at discharge was associated with greater mortality or new nursing home placement at twelve months (McAvay et al., 2006), and persistent delirium at six months had a HR of 2.9 (95% CI 1.9-4.4) for mortality over the subsequent six months (Kiely et al., 2009). In a hip fracture group, persistent delirium at one month was associated with mortality, new nursing home placement and reduced functional outcomes at six months (Marcantonio et al., 2000). Conversely, in a hip fracture population prolonged delirium (lasting greater than four weeks) was not associated with worse outcomes (Lee et al., 2011) and recovery from delirium was not associated with length of stay (Adamis et al., 2006)

Delirium severity

In three studies (N=465 with delirium), severity of delirium was assessed using the Memorial Delirium Assessment Scale (MDAS). A rise by two points on the scale was associated with an OR of 1.16 (95% CI 1.06-1.26) of poor outcome (Dasgupta and Brymer, 2014), an MDAS score of greater than 24 was associated with increased mortality at 3 months (Kelly et al., 2001), and an MDAS of

greater than 12.44 was associated with a relative risk (RR) of 3.1 (95% CI 1.2-8.2) for nursing home placement at six months in a hip fracture population (Marcantonio et al., 2002). Caution is warranted here given the classifications of severe delirium using different MDAS scores.

Missed diagnosis

Missed diagnosis of delirium in an emergency department population had a HR of 8.22 (95% CI 1.69-39.98) for mortality at six months (N=107 with delirium), opposed to a non-significant HR of 5.63 (95% CI 0.53–19.09) in a diagnosed group (Kakuma et al., 2003). However, caution is needed when interpreting this study given the low numbers of actual deaths in this group, leading to wide confidence intervals.

Co-morbid psychiatric illness as predictors

The association of delirium with other psychiatric illness was investigated in six studies (N=789 with delirium). Three studies showed that co-morbid dementia was associated with worse outcomes. In medical patients a diagnosis of delirium alone carried a HR of death at 12 months of 1.6 (95% CI 1.06-1.26), but in patients with delirium and dementia this was increased to a HR of 2.3 (95% CI 1.1-5.5) (Bellelli et al., 2007). Delirium superimposed on dementia (DSD) was associated with increased mortality and new institutionalisation at one month (Givens et al., 2008) and one year (Morandi et al., 2014). Conversely, a single study showed prior cognitive impairment or dementia was protective for mortality at one year (McCusker et al., 2002).

In a general medical cohort, delirium with depression was associated with a HR for death or new nursing home placement at 1 month of 5.38 (Givens et al., 2009). The cumulative addition of dementia and/or depression superimposed with delirium was associated with an increasing adjusted OR of 3.90 for death or new nursing home placement at 1 month (Givens et al., 2008).

Patient related predictors

Patient related predictors of poor outcome were investigated in five studies (N=1073 with delirium). Increased age predicted worse outcomes in three studies (Dasgupta and Brymer, 2014, Tsai et al., 2012, Leonard et al., 2008) and frailty (defined as a frailty index of >0.25) was associated with shorter survival times in a cohort of medical patients with delirium (Eeles et al., 2012). The presence of organ failure and lower initial cognitive test score was associated with shorter survival times (Leonard et al., 2008) as was anaesthetic risk score (Morandi et al., 2014). Hypoxia, acute kidney injury and worse baseline function were associated with poor recovery at 3 months (Dasgupta and Brymer, 2014). However, these factors are also known predictors of outcome in all older patients, so these studies may simply represent the underlying illness severity rather than a factor of the delirium itself.

Biomarkers as predictors

Biomarkers as predictors of poor outcome were investigated in three studies (N=126 with delirium). A set of cerebrospinal fluid (CSF) studies performed in delirium patients showed that raised cerebrospinal fluid (CSF) 5-Hydroxyindoleacetic acid (5-HIAA)(Koponen et al., 1994a) and reduced CSF acetylcholinesterase activity were associated with reduced time to death over a four year period (Koponen et al., 1994b). Reduced albumin was associated with increased 6-month mortality (Bellelli et al., 2014)

Figure 3 shows each outcome grouped with each predictor identified:

We did not attempt meta-analysis of the selected study outcomes due to the heterogeneity of the studies in terms of populations, statistical methods used and varied outcome measures.

Discussion

Nine predictors of clinically important outcomes in patients with delirium have been identified from 27 studies. The main predictors in patients with delirium were across four broad themes. The most frequently reported predictors were increased duration of delirium, the hypoactive subtype, delirium severity assessed by MDAS, and co-morbid dementia and depression.

A limitation of this review is publication bias, whereby some studies that may show negative results have not been published. Selection bias in the systematic review process has been minimised by having a strict protocol and solving selection disagreements by consensus. The exclusion of non-English language studies also has potential for bias, but the number of abstracts excluded was relatively low. The selected studies themselves all had a low risk of bias when assessed using the Newcastle-Ottawa Scale (NOS). However, 10 of the 27 studies were at risk of bias when assessed for comparability by the NOS indicating that appropriate controlling for known confounders was not done.

There was some differences in how delirium was defined and diagnosed, with the majority of studies using the CAM, based on criteria taken from the DSM-III. A true reference criterion, for example DSM-IV or ICD-10, was used in eight studies. The duration of delirium is an important predictor. An explanation for this observation may be that the stimulus causing the delirium is more severe or prolonged, but it may also be due to impaired negative feedback from the stress response, thus causing on-going inflammatory brain pathology; a reduced 'switch off'. This is hypothesised to occur in older brains with pre-existing neuropathology (Maclullich et al., 2008).

Hypoactive delirium is also associated with poor outcomes. Hypoactive delirium is more commonly missed as a diagnosis than in hyperactive patients so a delay in recognition and treatment may be a cause for this (Inouye et al., 2001). However, given the heterogeneity of delirium phenomenology, it may be that hypoactive patients have a more severe global pathology, akin to severe illness

behaviour. This in turn may lead to a risk of increased complications of inactivity, including dehydration, pressure damage, hypoventilation and venous thrombosis.

The relationship between dementia and delirium outcomes is conflicting. Delirium is more common in people with dementia and this is thought to be due to pre-existing neuropathology causing the brain to be at higher risk, mainly through an increase in a 'primed' microglial population (Cunningham, 2013). Microglia are the principal macrophage population in the brain and have an important role in initiating and managing the inflammatory cascade in response to a peripheral or direct brain insult. The poorer outcomes seen may be representative of this underlying pathology, and it is also important to note that delirium itself would appear to worsen cognitive decline in those both with and without pre-existing dementia (Davis et al., 2012). A single study demonstrates dementia as protective, and this may be an illustration of a less severe systemic insult being required to cause a delirium in dementia patients. In this case the insult is more benign and thus the outcomes better. As dementia itself is a risk factor for poor long term outcome a study which adjusts for both illness severity and baseline cognition would be of help.

Other potential confounders in observational studies of delirium include the disease severity of the underlying precipitant that prompted the episode of delirium, as well as the complex co-morbidity and frailty of patients who are at higher risk of developing delirium. Although most studies attempted to correct for these using recognised scales, these are still difficult to control for reliably.

The use of biomarkers for prediction of outcome is less well researched. A set of data on CSF biomarkers is interesting, suggesting a role for serotonin in the pathophysiology of delirium, as well as confirming previous views about acetylcholine being a primary neurotransmitter in the development of delirium (Hshieh et al., 2008). Although not necessarily practical in routine clinical practice, studies of this kind provide an important insight into the neuropathological mechanisms underlying delirium and as such, further work is justified

Conclusions

In conclusion, a number of important predictors of poor outcomes in patients with delirium have been demonstrated. The most numerously described and clinically important would appear to be the duration of the delirium episode, delirium severity, a hypoactive motor subtype and pre-existing psychiatric morbidity with dementia or depression. In general, these are easily recordable variables which could be used in clinical practice to focus direct management and guide discussions regarding prognosis. The review has also further demonstrated the broad clinical phenotype of delirium seen in practice.

These results also demonstrate a number of key unknowns, where further research to explore the relationship between delirium phenomenology and its outcome is recommended and is vital to improve management and understanding of this condition and potentially improve outcomes.

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Figure 1: Flow chart of study selection

Figure 2: Flowchart of the most frequently reported predictors and the reported outcomes. The number of studies reporting the predictor and outcome is represented on the arrow. New institution = new institutionalisation

Figure 3: Outcomes listed with associated predictors identified

Supplemental Digital Content

Supplemental Digital Content 1, data table: MS Word file

Supplemental Digital Content 2, data table: MS Word file

Supplemental Digital Content 3, supplementary appendix: MS word file

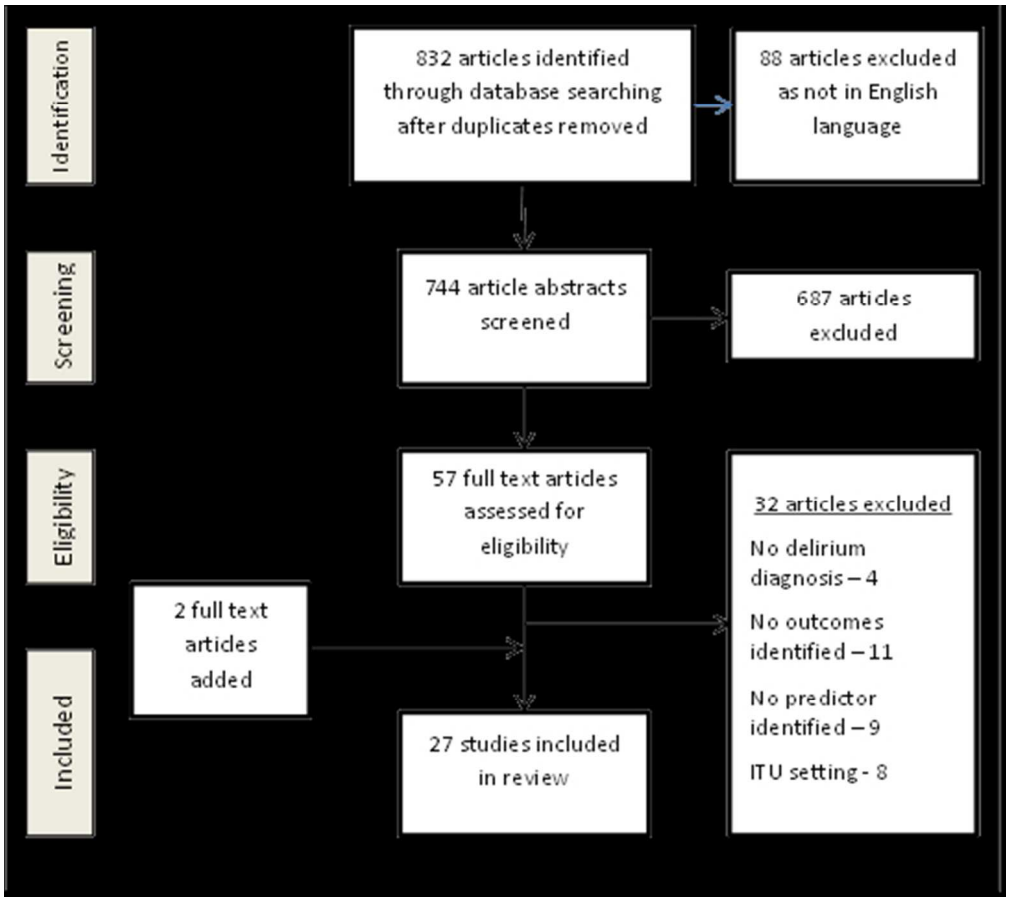

Figure 1: Flow chart of study selection
143x127mm (96 x 96 DPI)

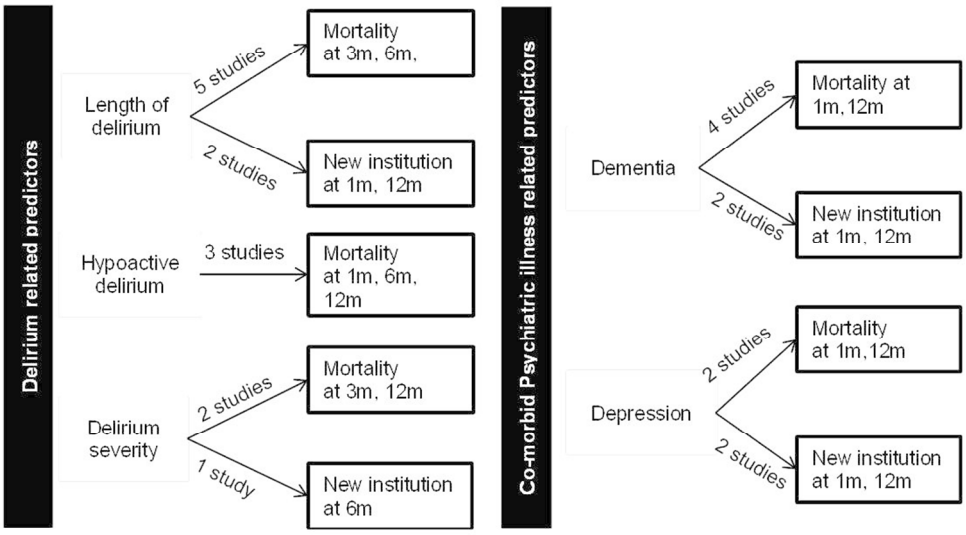

Figure 2: Flowchart of the most frequently reported predictors and the reported outcomes. The number of studies reporting the predictor and outcome is represented on the arrow. New institution = new institutionalisation
194x129mm (150 x 150 DPI)

Outcome		Predictors identified, in order of frequency
Mortality	1 month	Hypoactive subtype, length of delirium, delirium and depression
	1-6 months	Hypoactive subtype, severity of delirium, dementia, length of delirium, hyperactive subtype, age, ↓serum Alb, missed diagnosis
	=>1 year	Length of delirium, hypoactive subtype, dementia, no dementia, illness severity, age, hospital length of stay
	Reduced survival time	Length of delirium, frailty, age, ↑CSF 5-HIAA, ↑CSF AcHE activity
New Institutionalisation		Persistent delirium, delirium and depression, delirium severity, hyperactive subtype

Figure 3: Outcomes listed with associated predictors identified
204x141mm (150 x 150 DPI)