Persistent delirium in older hospital patients: a systematic review of frequency and prognosis

MARTIN G. COLE1,2, ANTONIO CIAMPI3,4, ERIC BELZILE3, LIHONG ZHONG3

1Department of Psychiatry, St. Mary’s Hospital Center, Montreal, Quebec, Canada
2Department of Psychiatry, McGill University, Montreal, Quebec, Canada
3Department of Clinical Epidemiology and Community Studies, St. Mary’s Hospital Center, Montreal, Quebec, Canada
4Department of Epidemiology and Biostatistics, McGill University, Montreal, Quebec, Canada

Address correspondence to: Martin G. Cole. Tel: (+1) 5143453511, Ext. 5060; Fax: (+1) 5147342652.
Email: martin.cole@ssss.gouv.qc.ca

Abstract

Background: one explanation for the poor prognosis of delirium among older hospital patients may be that many of these patients do not recover from delirium. We sought to determine the frequency and prognosis of persistent delirium (PerD) in older hospital patients by systematically reviewing original research on this topic.

Methods: MEDLINE, EMBASE, PsycINFO and the Cochrane Database of Systematic Reviews were searched for potentially relevant articles. The bibliographies of relevant articles were searched for additional references. Eighteen reports (involving 1,322 patients with delirium) met the following seven inclusion criteria: original research published in English or French, prospective study design, study population of at least 20 hospital patients, patients aged 50 years or more, follow-up of at least 1 week, acceptable definition of delirium at enrolment and included at least one assessment for PerD at discharge or later. The methods of each study were assessed according to the six criteria for prognostic studies described by the Evidence-Based Medicine Working Group. Information about the sample origin and size, age, proportion with dementia, criteria for delirium, timing of follow-up assessments, criteria for PerD, proportion with PerD and prognosis of PerD was systematically abstracted from each report, tabulated and combined using standard meta-analysis techniques.

Results: the combined proportions with PerD at discharge, 1, 3 and 6 months were 44.7% (95% CI 26.8%, 63.7%), 32.8% (95% CI 18.4%, 47.2%), 25.6% (95% CI 7.9%, 43.4%) and 21% (95% CI 1.4%, 40.6%), respectively. The outcomes (mortality, nursing home placement, function, cognition) of patients with PerD were consistently worse than the outcomes of patients who had recovered from delirium.

Conclusion: PerD in older hospital patients is frequent, appears to be associated with adverse outcomes and may account for the poor prognosis of delirium in this population. These findings have potentially important implications for clinical practice and research.

Keywords: persistent delirium, aged, frequency, prognosis, elderly

Introduction

Delirium is a cognitive disorder defined by acute onset, fluctuating course and disturbances of consciousness, attention, orientation, memory, thought, perception and behaviour [1]. It occurs in hyperactive, hypoactive or mixed forms in up to 50% of older hospital patients [2,3], many with pre-existing dementia [4].

Traditionally, the course of delirium has been described as transient [5], in which recovery is likely to be complete if the underlying etiological factor is promptly corrected or self-limited [1]. Among older hospital patients, however, the prognosis is poor [3,6]. In this population, delirium is associated with significant increases in cognitive impairment and functional disability [7–9], length of hospital stay [10,11], rates of institutionalisation [7,9] and rates of death [12–14], independent of many socio-demographic (e.g. age, gender, marital status, living arrangements) and clinical (e.g. presence of dementia, co-morbidity, illness severity) variables.
One explanation for the poor prognosis of delirium among older hospital patients may be that many of these patients do not recover from delirium [15,16] and that the persistence of delirium, rather than the occurrence of an episode of delirium per se, accounts for many of the adverse outcomes. Because this issue has potentially important implications for clinical practice and research, the primary objectives of this study were to determine the frequency and prognosis of persistent delirium (PerD) in older hospital patients by systematically reviewing original research on this topic. For the purpose of this review, persistent delirium was defined as a cognitive disorder that met accepted diagnostic criteria for delirium at admission (or shortly after admission) and continued to meet criteria for delirium at the time of discharge or beyond. The review process, modified from the one described by Oxman et al. [17], involved systematic selection of articles, assessment of validity, abstraction of data and qualitative and quantitative synthesis of results.

Methods
Selection of articles
The selection process involved four steps. First, four computer databases, MEDLINE, EMBASE, PsycINFO and the Cochrane Database of Systematic Reviews, were searched for potentially relevant articles published from January 1966 to September 2007, January 1996 to September 2007, January 1985 to September 2007 and to the third quarter of 2007, respectively. The key words (title, abstract, text, key words, subject headings, identifiers) used for all databases were ‘delirium’, ‘prognosis’, ‘outcome’ and ‘aged’. Second, relevant articles (based on the title and abstract) were retrieved for more detailed evaluation. Third, the bibliographies of relevant articles were searched for additional references. Finally, all retrieved articles were screened to meet the following seven inclusion criteria: (i) original research published in English or French; (ii) study population of at least 20 (current or recent) hospital patients; (iii) patients aged 50 years or more; (iv) prospective study; (v) follow-up of at least 1 week; (vi) acceptable definition of delirium at enrolment; (vii) included at least one assessment for PerD at discharge or later.

Assessment of validity
To determine validity, the methods of each study were assessed according to the six criteria for prognostic studies described by the Evidence-Based Medicine Working Group [18]: (i) representative and well-defined sample of patients at a similar point in the course of the disease; (ii) follow-up that was sufficiently long (i.e. 3 months); (iii) follow-up that was complete (i.e. 80% of the inception cohort); (iv) use of objective outcome criteria; (v) unbiased outcome assessment (i.e. blind to inception diagnosis of delirium); (vi) adjustment for potentially confounding prognostic factors (e.g. dementia, severity of medical illness). Each study was scored with respect to meeting (+) or not meeting (−) each of the above criteria.

Abstraction of data
Information about the sample origin and size, age, proportion with dementia, criteria for delirium, timing of follow-up assessments, criteria for PerD, proportion with PerD and prognosis of PerD was systematically abstracted from each report and tabulated.

Data synthesis
(a) Qualitative: a qualitative meta-analysis was conducted by summarising, comparing and contrasting abstracted data.
(b) Quantitative: standard meta-analysis techniques were applied to different groups of studies. Meta-analysis was used to calculate the combined estimate of prevalence of PerD at different time points. According to usual practice we used a fixed effect model first, followed by a test of homogeneity. If the test of homogeneity was rejected, the random effect model was used [19]. All analyses were performed using STATA software 10.0.

Results
Selection of articles
The search strategy yielded 250 potentially relevant studies; 46 were retrieved for more detailed evaluation. Eighteen studies met the inclusion criteria (Table 1) [10,15,20–35]. The other 28 studies were excluded for the following reasons: 25 did not include at least one assessment for PerD at discharge or later and 3 did not meet two or more of the inclusion criteria.

Assessment of validity
The results of the validity assessment are presented in Table 2. Three studies met all of the criteria. Many studies did not have a follow-up that was sufficiently long, conduct unbiased outcome assessments or adjust for potentially confounding prognostic factors.

Data synthesis
(a) Qualitative: the 18 studies enrolled 1,322 patients with delirium (Table 1). One study [35] included two cohorts, development and validation cohorts, but the results of the validation cohort were reported in an earlier publication [33]; consequently, we used only data from the development cohort.

Patients were enrolled from hospital medical units in 13 studies, hospital medical and surgical units in 2 studies, hospital surgical units in 2 studies and post-acute care facilities in 1 study. Four studies enrolled only patients with prevalent delirium (delirium present on admission), 4 studies enrolled only patients with incident delirium (delirium developing after admission) and 10 studies enrolled patients with prevalent and incident delirium. Subjects’ mean ages were 72–89 years, median 82 years. The mean length of hospital stay ranged from 7 to 43 days, median 18 days. The length of reported follow-up ranged from discharge to 12 months, median...
<table>
<thead>
<tr>
<th>Author/year</th>
<th>Patient population</th>
<th>Mean age</th>
<th>Frequency of persistent delirium</th>
<th>Criteria for delirium</th>
<th>Criteria for persistent delirium</th>
<th>Frequency of persistent delirium</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Discharge</td>
<td>1 month</td>
<td>3 months</td>
<td>6 months</td>
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<tr>
<td>Hodkinson/1973</td>
<td>M</td>
<td>82</td>
<td>0</td>
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<td>0</td>
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<tr>
<td>Rockwood/1989</td>
<td>M</td>
<td>82</td>
<td>0</td>
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<tr>
<td>Lev koff et al./1992</td>
<td>M-S</td>
<td>82</td>
<td>0</td>
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<tr>
<td>Williams et al./1992</td>
<td>S</td>
<td>83</td>
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<td>Jitapunkul et al./1992</td>
<td>M (20)</td>
<td>83</td>
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<td>Gaudet et al./1993</td>
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<td>82</td>
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<td>Rudberg et al./1997</td>
<td>M-S</td>
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<td>O'Keeffe et al./1997</td>
<td>M</td>
<td>82</td>
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<tr>
<td>Treloar et al./1997</td>
<td>M</td>
<td>82</td>
<td>0</td>
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<tr>
<td>Marcantonio et al./2006</td>
<td>S</td>
<td>82</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Kelly et al./2001</td>
<td>M</td>
<td>82</td>
<td>0</td>
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<tr>
<td>McCusker et al./2003</td>
<td>M</td>
<td>82</td>
<td>0</td>
<td>0</td>
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<td>0</td>
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<tr>
<td>Kiely et al./2004</td>
<td>PAC</td>
<td>82</td>
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<td>Lundstrom et al./2005</td>
<td>M</td>
<td>82</td>
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<td>McAvay et al./2006</td>
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<tr>
<td>Pitkala et al./2006</td>
<td>M</td>
<td>82</td>
<td>0</td>
<td>0</td>
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<td>0</td>
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<tr>
<td>Inouye et al./2007</td>
<td>M</td>
<td>82</td>
<td>0</td>
<td>0</td>
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</table>

M, medical units; S, surgical units; PAC, post-acute care facility; CT, clinical trial; est, estimated; DSM, Diagnostic and Statistical Manual of the American Psychiatric Association; ICD, International Classification of Diseases; CAMDEX, Cambridge Examination for Mental Disorders of the Elderly; OBS, organic brain syndrome; CAM, Confusion Assessment Method; MMSE, Mini-Mental State Exam; DI, delirium Index; MDAS, Memorial Delirium Assessment scale.

*Criteria for dementia. 1Criteria for dementia. 2Clinical impression. 3DSM. 4Chart review. 5MMSE < 21–24. 6IQCODE > 3.5. 7Blessed Dementia Scale = 4.
4 weeks. Criteria for dementia varied from one study to the next (see Table 1); the proportion of patients with dementia ranged from 0% to 75%, median 44%. Only three studies measured depressive symptoms at baseline [23,34,35]. Ten studies used DSM criteria to diagnose delirium at enrolment, five used the Confusion Assessment Method (CAM) algorithm, one used the Organic Brain Syndrome (OBS) scale, one used the criterion of ‘acute onset of confusion’ and one study used three different sets of criteria. Nine studies used validated diagnostic criteria for delirium to determine the presence of PD: five used the CAM algorithm, three used DSM criteria and one used the OBS scale. The other nine studies used non-validated criteria: four used change scores on cognitive or delirium rating scales, two used a clinical impression, two used the presence of any DSM symptom of delirium (i.e. 58–60%) and lowest of any DSM symptom of delirium (i.e. 0%).

Even though all included studies were studies of the prognosis of delirium, only three studies (involving 288 patients with delirium) determined the outcomes of patients with PerD (Table 3). The first study [29] reported that PerD at 1 month (compared to patients whose delirium had resolved by 1 month) was associated with increased mortality and nursing home placement and decreased function at 1 month, although the differences between groups failed to reach levels of clinical or statistical significance. The second study [15] reported that PerD at 24 h (compared to delirium recovered by 24 h) was independently associated with a clinically significant increase in mortality at 12 months and a clinically and statistically significant decline in function at 12 months; similarly, PerD at discharge (compared to delirium recovered by 24 h) was independently associated with a clinically significant increase in mortality at 12 months and clinically and statistically significant declines in both cognition and function at 12 months. The third study [33] reported that PerD at discharge (compared to delirium recovered by discharge) was independently associated with a clinically, but not statistically, significant increase in mortality and nursing home placement at 12 months.

(b) Quantitative: Estimates of the proportions and combined proportions of PerD are presented in Figure 1. Combined proportions were 17.4% (95% CI 15.3%, 19.4%) at discharge, 32.8% (95% CI 18.4%, 47.2%) at 1 month, 25.6% (95% CI 7.9%, 43.4%) at 3 months and 21% (95% CI 1.4%, 40.6%) at 6 months; one study reported a proportion of 41% (95% CI 33.8%, 48.2%) at 12 months. Notably, when two studies with 0 values (and very narrow confidence intervals) at discharge were excluded from the analysis, there was a
### Table 3. Summary of studies of the prognosis of patients with persistent delirium

<table>
<thead>
<tr>
<th>Author/year</th>
<th>N</th>
<th>PerD determined at</th>
<th>Proportion with PerD (%)</th>
<th>Outcomes determined at</th>
<th>Mortality [OR (95% CI)]</th>
<th>NH placement</th>
<th>ADL decline [Adjusted odds ratio]</th>
<th>Cognitive decline [Adjusted mean difference on Mini-Mental State Exam]</th>
<th>Ambulation decline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marcantonio et al. /2000</td>
<td>52</td>
<td>1 month</td>
<td>32</td>
<td>1 month</td>
<td>1.5 (0.45, 5.0) (^{a,c} )</td>
<td>3.05 (0.74, 12.64)</td>
<td>5.73 (1.51, 21.78) (^{a} )</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>McCusker et al. /2003</td>
<td>181</td>
<td>24 h after enrolment</td>
<td>61</td>
<td>12 months</td>
<td>1.62 (0.79, 3.34) (^{b} )</td>
<td>-10.7 (-19.8, 1.6)</td>
<td>0.87 (-1.1, 2.8) (^{d} )</td>
<td>-121.9 (-31.1, -7.5) (^{c} )</td>
<td>-21.9 (-31.1, -12.7) (^{d} )</td>
</tr>
<tr>
<td>McAvay et al. /2006</td>
<td>55</td>
<td>Discharge</td>
<td>44</td>
<td>12 months</td>
<td>1.63 (0.77, 3.44) (^{b} )</td>
<td>-21.9 (-31.1, -5.3)</td>
<td>-5.3 (-7.5, -3.1) (^{d} )</td>
<td>-127 (-7.5, -3.1) (^{d} )</td>
<td>-5.3 (-7.5, -3.1) (^{d} )</td>
</tr>
</tbody>
</table>

NH, nursing home; ADL, activities of daily living; PerD, persistent delirium.

\(^{a} \)Unadjusted odds ratio (95% confidence interval), \(^{b} \)adjusted odds ratio, \(^{c} \)adjusted mean difference on Barthel Index, \(^{d} \)adjusted mean difference on Mini-Mental State Exam, \(^{e} \)combined OR for death/Nursing Home placement = 1.85 (0.76, 4.5).

**Figure 1.** Individual and combined proportions (and 95% confidence intervals) for persistent delirium at discharge and 1, 3, 6 months after enrolment. \(^{*} \)Combined estimate after excluding two studies with 0 values.
striking difference in the combined proportion at discharge, 44.7% (95% CI 25.8%, 63.7%). This latter proportion was considered to be a better summary of the discharge data presented in the studies. The estimate of one combined outcome OR, death or nursing home placement, was 1.85 (95% CI 0.76, 4.50). Estimates of the other combined ORs could not be calculated because of the differences in outcome measures from one study to the next.

Discussion

This study proposed to determine the frequency and prognosis of PerD in older hospital patients by systematically reviewing original research on this topic. The combined proportions with PerD at discharge, 1, 3 and 6 months were 44.7, 32.8, 25.6 and 21%, respectively; one study reported a proportion of 41% at 12 months. In three studies, the longer term outcomes (mortality, nursing home placement, cognition, function) of patients with PerD were consistently worse than the outcomes of patients who had recovered from delirium, although the clinically significant differences between groups in many studies often failed to reach levels of statistical significance, perhaps because of the small numbers of subjects.

It appears that many older hospital patients do not recover from delirium and that the persistence of delirium is associated with adverse outcomes. Thus, the inclusion of many patients with PerD in previous studies of prognosis [3,6–14] may account, at least in part, for many of the adverse outcomes reported to be associated with delirium in this population. This possibility is supported by the findings of two recent studies. The first study [36] reported that the 6 and 12 month outcomes of patients with persistent sub-syndromal delirium (SSD) were poorer than the outcomes of patients who recovered from SSD. The second study [37] reported that most of the 6- and 12-month outcomes of patients who recovered from delirium by 8 weeks and survived were similar to the outcomes of patients who did not have an index episode.

The findings of this systematic review have five potentially important implications for clinical practice and research. First, the course and outcome of delirium in older hospital patients must be re-examined in original studies that determine the outcomes of patients with recovered delirium or PerD separately.

Second, it appears that half of the patients with PerD at discharge had recovered by 3 months. It is unknown whether this delayed recovery has adverse prognostic implications although one study included in the review [15] reported that faster recovery from delirium was associated with better outcomes.

Third, it is unknown whether most of the patients with PerD at 3 months can ever recover, even with intervention. There should be efforts to identify patients with PerD at 3 months in order to explore the usefulness of different types of interventions. The presence of persistent symptoms of delirium suggests that these interventions might involve protocols to detect and manage putative causes of PerD such as unresolved medical illness or unrecognised drug toxicity. To date, the results of intervention trials that have targeted all patients with delirium on admission to hospital or shortly after admission have been modest [32,34,38] or negative [39], possibly because these trials included many patients with transient delirium who recovered with usual care, irrespective of any intervention effect. Alternatively, these trials may have included many patients with PerD. Trials that target patients with PerD at discharge or 3 months and use interventions specific to PerD may demonstrate a greater impact on outcomes.

Fourth, the persistence of delirium and associated cognitive impairment may interfere with the patient's self-management of chronic medical conditions (e.g. poor compliance with medication). This impaired self-management may, in turn, contribute to adverse outcomes.

Finally, possible relationships between PerD and functional decline, mild cognitive impairment and new-onset dementia should be explored. Dementia is the strongest risk factor for delirium among older patients [40]; delirium appears to increase the risk of dementia [13]. Four studies included in the review reported that the presence of dementia was the strongest risk factor for PerD [15,31,33,35] Many patients with dementia appear to have some symptoms of delirium such as inattention and fluctuation [41]. Both delirium and dementia are characterised by reduced metabolic rates and impaired cholinergic function [42]. Many conditions that cause delirium can also cause dementia if they are prolonged and severe (e.g. hypoxia, hypoglycaemia), presumably related to excitotoxic damage and death of neurons [43]. Interestingly, prior to the twentieth century, persistence of symptoms and possible progression to dementia were considered common features of delirium [44].

The studies of PerD included in this systematic review have three potential limitations. First, many studies used non-validated criteria to determine proportions with PerD; however, the proportions with PerD were similar in studies using validated or non-validated criteria (Table 1). Second, most of the studies enrolled patients with prevalent delirium (delirium present on admission). Many patients may have had PerD long before admission and represent prevalent PerD rather than incident PerD; however, the frequency and prognosis of PerD did not seem to be related to enrolment of patients with prevalent as opposed to incident delirium (Table 1). Third, the high proportions of delirium after discharge (i.e. at 1, 3, 6 and 12 months) suggest that PerD persists well beyond discharge; however, because the reported proportions after discharge were group proportions derived from assessments repeated after intervals of weeks or months, it was not possible to determine if the high proportions of delirium after discharge reflect PerD in the same patients or episodes of recurrent delirium in different patients. Consequently, it is not possible to determine whether the adverse outcomes associated
with PerD at discharge are related to the presence of an ongoing delirium process or to recurrent episodes of delirium.

This systematic review has three potential limitations. First, the literature search was limited to articles published in English and French because resources to translate articles written in other languages were not available. Second, publication bias was not assessed, although it is unlikely that this bias influences publication of studies of frequency or prognosis. Third, relatively few studies determined the prognosis of PerD and the examination of prognosis was complicated by the small numbers of subjects and differences in the criteria for PerD, length of follow-up and outcome measures from one study to the next.

**Conclusion**

PerD in older hospital patients is frequent, appears to be associated with adverse outcomes and may account for the poor prognosis of delirium in this population. Despite the limitations of the studies of PerD and this systematic review, these findings suggest that PerD warrants increased attention from clinicians and researchers.

**Recommendations**

The following recommendations should be considered in the design of new studies to characterise the phenomenology, predictors, course and outcome of PerD.

- Selection criteria should include explicit diagnostic criteria for delirium and PerD; criteria for PerD should include the time of assessment for PerD; patients with imminently terminal illnesses should be excluded.
- Proportions and outcomes of PerD in cohorts of patients with prevalent and incident delirium should be determined separately.
- Patients should be assessed at least every few days throughout the follow-up period to determine the evolution of PerD and whether these disorders are recurrent rather than persistent or a combination of both.
- Phenomenology (including good measures of cognition and mood) should be assessed using one or more widely accepted instruments. It is especially important to develop and use better clinical measures of level of consciousness, attention and psychomotor activity.
- Important characteristics of subjects, potential risk factors and possible confounding factors (e.g. dementia, type and severity of physical illnesses, functional status, pre-admission institutional status and medication use) should be assessed using reliable and valid measures. Subjects could be categorised by the presence or absence of dementia, and the prognosis of each category could be reported separately.
- The minimum follow-up period should be 6 months, and the follow-up period should begin at enrolment.

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- Outcome categories should include cognition, activities of daily living and rates of new-onset dementia, institutional care and mortality. The longer term outcomes of patients with PerD at different time points (e.g. discharge and 1, 3 and 6 months after discharge) should be compared to both the outcomes of patients who recover from delirium at different time points and the outcomes of patients who did not have an index episode of delirium.
- The assessment of outcomes should be independent of the assessments for PerD and the prognostic factors for PerD.
- Outcomes should be adjusted for potential confounders (e.g. dementia, severity of medical illness).
- Comparison groups should include patients with recovered prevalent and incident delirium and no delirium.
- Procedures to detect and manage delirium should be recorded in detail and related to frequency of PerD; similarly, procedures to detect and manage PerD should be recorded in detail and related to outcomes.
- All phases of the study (e.g. selection of cases, diagnosis and outcome measures) should have demonstrated reliability.

**Key points**

- Persistent delirium is frequent in older hospital patients.
- Patients with persistent delirium appear to have worse outcomes than patients who recover from delirium.
- Inclusion of patients with persistent delirium in previous studies of the prognosis of delirium may account, at least in part, for the adverse outcomes reported to be associated with delirium in older hospital patients.
- Use of protocols to detect and treat delirium that persists at discharge or later may improve the longer term outcomes of delirium in older hospital patients.

**Conflicts of interest**

None declared.

**References**


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