Author/s:
Canet, E;Amjad, S;Robbins, R;Lewis, J;Matalanis, M;Jones, D;Bellomo, R

Title:
Differential clinical characteristics, management and outcome of delirium among ward compared with intensive care unit patients

Date:
2019-12-01

Citation:
Canet, E., Amjad, S., Robbins, R., Lewis, J., Matalanis, M., Jones, D. & Bellomo, R. (2019). Differential clinical characteristics, management and outcome of delirium among ward compared with intensive care unit patients. Internal Medicine Journal, 49 (12), pp.1496-1504. https://doi.org/10.1111/imj.14287.

Canet Emmanuel (Orcid ID: 0000-0002-2143-8082)

Differential Clinical Characteristics, Management, and Outcome of Delirium among Ward Compared with ICU Patients

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/imj.14287

ABBREVIATIONS

AKI: Acute Kidney Injury

CAM: Confusion Assessment Method

CAM-ICU: Confusion Assessment Method - Intensive Care Unit

CI: Confidence interval

DSM-5: Diagnostic and Statistical manual of Mental disorders 5th edition

ESRD: End Stage Renal Disease

ICD-10: International Classification of Diseases system 10th revision

ICU: Intensive Care Unit

IQR: Interquartile range

IV: Intravenous

OR: Odds ratio

RRT: Renal Replacement Therapy

Acknowledgements: none

INTRODUCTION

Delirium is increasingly recognized as a common condition in hospitalized patients. It is associated with significant adverse outcomes such as mortality, institutionalization, and long term cognitive impairment (1,2). Its definition was updated in 2013 by the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and includes acute disturbances in cognition and attention not fully explained by an underlying neurocognitive disorder (3).

Although common, delirium appears frequently unrecognized, and its incidence varies widely across different settings from 10% in the emergency department to 50% after major surgery, and to over 80% in mechanically ventilated ICU patients (4–6). These discrepancies are partly explained by the lack of a robust "gold standard" for its clinical diagnosis, and therefore, the use of numerous diagnostic tools developed for specific environments. Moreover, delirium appears to be a syndrome with at least two major clinical phenotypes, variable duration, etiology, prognosis, and likelihood of recovery (7–9). Finally, the global burden and the epidemiology of delirium at a hospital level are poorly characterized, its optimal management remains unclear, and current empirical treatment largely unknown. Yet, a better understanding of such aspects of delirium epidemiology, phenotype, treatment and outcome in ward patients compared with ICU patients may help guide clinical practice and further research (10).

Accordingly, we conducted an epidemiological study with a trans-sectional approach in an Australian University-affiliated hospital, by using the International Classification of

Diseases 10th Revision (ICD-10) coding system to identify hospitalized patients with delirium. We aimed to test the hypothesis that ward and ICU patients would have different demographics, predisposing factors, phenotypes, treatments, outcomes and predictors of recovery.

METHODS

This retrospective study was approved by the Human Research Ethics Committee of the Austin Hospital with a waiver for informed consent. The STROBE recommendations were followed for the reporting of observational studies (11).

Study Design, Setting, and Population

All adult patients (≥ 18 years old) admitted to the Austin Hospital, Melbourne, Australia, for a minimum of 24 hours between 01 March 2013 and 30 April 2017 were assessed for delirium coding. For patients who had multiple admissions during the study period, only the first admission was considered. Patients who developed delirium were identified from the hospital electronic database using the code for delirium (R41.0) from the International Classification of Diseases system (ICD-10) coding system. In our institution, coders from the administrative staff use the patients' formal discharge summary to identify patients with delirium (the word "delirium" must be mentioned in the summary to be coded). For ICU patients, delirium first developed in the ICU. We used a random sequence generator (website: https://www.random.org) to create a sample of 200 patients (100 ICU patients and 100 ward patients) from the base population coded for delirium (n=2,864) for a detailed analysis of demographics, predisposing factors, phenotypes, treatments, outcomes and predictors of delirium recovery using the electronic medical records (EMR) (Figure 1).

Data Collection and Outcomes

We obtained data for baseline patient characteristics, including demographics, comorbidities, and risk factors for delirium (12). The clinical features of delirium were identified according to the nurses and doctors' notes written in the medical charts. The onset of delirium was the date when delirium was mentioned for the first time. The date of resolution was the date either where the episode of delirium was stated to have resolved in the EMR, or the last date where delirium was mentioned if it was followed by no further signs or symptoms of delirium for a period of at least 48 hours and no delirious state was reported at the time of discharge. If none of these 2 conditions were reported, the episode of delirium was considered as persistent. The delirium phenotype was classified into 2 categories (hypoactive delirium or agitated delirium) according to daily progress notes. Delirium was defined as agitated if at least one of the following words were used in the notes to describe the patient's condition during the episode of delirium: "agitated", "combative", "aggressive", "violent", or "endangering himself or staff". In the absence of signs and symptoms of acute agitation, the episode of delirium was classified as hypoactive. Patients who fluctuated between episodes of agitation and hypoactive symptoms were classified as having agitated delirium. When patients had underlying dementia or other neurocognitive disorders, a worsening of the clinical state during hospitalization had to be mentioned in the patients' EMR. The following drugs administered intravenously or orally during the episode of delirium were extracted from the electronic prescription database of the hospital and verified with the patients' EMR: benzodiazepines, opioid analgesics, serotonin uptake receptors inhibitors, quetiapine, haloperidol, olanzapine, clonidine, dexmedetomidine, and droperidol.

Objectives

The primary objective of the study was to test the hypothesis that ward and ICU patients have different demographics, predisposing factors, phenotypes, treatments, outcomes and predictors of recovery.

Statistical Analysis

Quantitative variables are described as median and interquartile range (IQR) and compared using Mann-Whitney tests; qualitative variables are shown as counts (percent) and compared using chi-square tests. The admission type (ICU versus ward) as well as the persistence of delirium at hospital discharge was analyzed as binary variables. Logistic regression analyses were performed to identify variables that were associated with the persistence of delirium at hospital discharge. The multivariable model selected to identify factors independently associated with the persistence of delirium at hospital discharge was also a logistic regression model. Factors which were significant at the 0.2 level on univariate analysis were candidates for the multivariable analysis. The measures of associations are presented with odds ratios and confidence intervals at 95%. All tests were two-sided and p-values lower than 5% were considered to indicate significant associations. Statistical tests were conducted using the SAS 5.0.1 software package (SAS Institute Inc., Cary, CA, USA).

RESULTS

Study population

Among 61,032 patients admitted to hospital during the study period, 2,864 (4.7%) were coded as having delirium. Of these, 2,095 were treated in the wards and 769 in the ICU, with an ICU incidence which was six-fold higher than in ward patients (Figure 1). From such patients a sample of 200 patients (100 ward patients and 100 ICU patients) was randomly selected for analysis. Overall median age was 77 [64-85] years and 112 (56%) were male (Table 1). Ward patients were older than ICU patients, three-quarters had hypertension, and almost 40% had pre-existing dementia. In addition, they were also more likely to be receiving psychotropic drugs at hospital admission (Table 2). In contrast, ICU patients were more likely to have cirrhosis and/or a history of intravenous drug use and/or alcohol abuse (Table 1). A recent surgical procedure was much more frequent in ICU patients, while the incidence of sepsis and laboratory abnormalities (Table S2) was similar.

Clinical features of delirium and drug management

Delirium was typically diagnosed 1 [1-2] day after hospital admission with significant differences in clinical phenotype and pharmacological management between ICU and ward patients (Table 2). Almost three-quarters of ward patients had hypoactive delirium, while two-thirds of ICU patients had agitated delirium. Approximately half of the ICU patients were intubated at the time of delirium diagnosis. Differences in drug management between ICU patients treated by mechanical ventilation and non-intubated patients are displayed in Table S3. Differences in drug management according to delirium phenotype are reported in Table S4. Quetiapine, haloperidol, clonidine, and dexmedetomidine were significantly more frequently used in the ICU setting than in the wards. Benzodiazepines and opioid analgesics

were commonly prescribed (27.5% and 29% in each cohort, respectively). However, more than a third of ward patients and more than one-fifth of ICU patients did not receive any of these medications during the delirium episode.

Outcomes

Overall, 41.5% of study patients had a persistent delirium at hospital discharge. Ward patients were markedly more likely to have persistent delirium than ICU patients (66% versus 17%, $p<0.0001$) (Table 3). Among the 117 patients who recovered before hospital discharge, the median duration of delirium was 4 [2-6] days, without a difference between ICU and ward patients. ICU patients had longer hospital length of stay but similar hospital mortality (10%). However, the destination at hospital discharge differed. Seventy-one percent of ICU patients returned home compared to 56% of ward patients. Moreover, while one-third of ward patients required nursing home care or were transferred to another hospital, only16% of ICU patients experienced such outcomes. Finally, 32 (18%) patients had a hospital discharge prescription for an antipsychotic drug (23% of ward patients vs. 12% of ICU patients, $p=0.05$).

Factors associated with persistent delirium

Patient characteristics according to delirium status at hospital discharge are reported in Table S1. By univariate analysis, older age, dementia, hypoactive delirium, and treatment with selective serotonin uptake inhibitors (SSRI) were associated with increased risk of persistent delirium at hospital discharge. In contrast, haloperidol, clonidine, ICU setting, and

surgery were more common in patients who recovered. On multivariable analysis, only two factors were independently associated with a persistent delirium at hospital discharge: age and dementia. In contrast, having received a surgical procedure was associated with a lower risk of persistent delirium.

DISCUSSION

Key findings

We used ICD-10 criteria and a large electronic hospital database and random sampling with detailed analysis to study the demographics, predisposing factors, phenotypes, treatments, outcomes and predictors of recovery of in-hospital patients coded for delirium and to compare ward with ICU patients. We found that such patients represented approximately 5% of all hospitalized patients. Moreover, we found that compared with ward patients with delirium, ICU patients were younger, had fewer dementia, were more likely to have agitated delirium, more likely to receive quetiapine, haloperidol, clonidine and dexmedetomidine, to develop delirium after major surgery, and to recover at hospital discharge. Finally, although most patients received some form of medication for the management of delirium, the likelihood of recovery was associated with the type of precipitating factor (surgery) or the presence of predisposing factors (age and dementia) but not with the characteristics of medical treatment or the ICU or ward environment.

Relationship to previous studies

Knowledge on delirium in hospitalized patients is limited to specific populations (geriatric wards, palliative care units, ICUs, and major surgery wards) all reporting a high incidence (1,5,6,13). However, various diagnostic tools were used which are not sufficiently versatile to be applied to every setting (2,14), making comparisons difficult and large-scale investigations of delirium difficult. In contrast, the ICD-10 criteria enable a cross-sectional approach and have shown the highest specificity so far for the diagnosis of delirium compared with the DSM classifications (15–17). Thus, we report for the first time the burden of ICD-10 coded delirium at a hospital level and describe differences in predisposing factors, pre-admission use of psychotropic drugs, clinical phenotype, treatment, and outcomes of delirious ward patients compared with delirious ICU patients.

Older age, dementia, alcohol misuse, major surgery, comorbidities and severity of illness have been reported as strong risk factors for delirium (1,12,13,18,19). We also found that ward patients with delirium were older, more likely to have dementia and close to ten times more likely to be receiving chronic psychotropic drugs supporting the need for a multicomponent approach to delirium (20,21).

Delirium appears to have at least two major clinical phenotypes. Geriatric patients are commonly diagnosed with the hypoactive form (1,13) while the hyperactive form is more frequent in ICU patients (22,23). Our findings expand this notion to all non-ICU patients. However, the relevance of such phenotypes to outcomes is controversial (24). Three studies showed a higher mortality in patients with hypoactive delirium (8,9,25), one reported an increased mortality after hyperactive delirium in surgical patients (26), and three others failed to demonstrate any association between delirium phenotypes and outcomes (27–29). Our

study did not find any association of delirium phenotype with hospital mortality or on delirium recovery.

The optimal management of established delirium in hospital patients has yet to be determined (30), although surveys suggest that antipsychotics are considered as the first line treatment (31–33). However, knowledge on actual practice is limited to two studies conducted in geriatric ward patients (34,35). One reported that 86% of 401 elderly patients with delirium were treated with drugs, with haloperidol being the first choice regardless the phenotype (34). Another study reported that half of 156 ward patients with delirium received antipsychotics, and a quarter had benzodiazepines or antidepressants (35). In contrast, in our study, among ward patients with delirium, haloperidol use was rare; antipsychotics were administered to only a third of patients, benzodiazepines to one fourth and antidepressants to one in six patients. Such treatment was markedly different from that of ICU patients. Both our cohorts clearly differed with regard to treatment from geriatric patients, highlighting the fact that different groups of patients (those from acute wards, ICU, and geriatric wards) appear to be treated differently.

Delirium is an acute syndrome and yet, 45% of elderly patients may experience a persistent delirium-like state associated with pre-existing neurological disease and not present before hospital admission (36). Only two studies investigated factors associated with delirium recovery but focused on geriatric wards (37,38). One studied 85 patients and reported that age, pre-existing cognitive impairment, and delirium features (number of symptoms) were independent predictors of non-recovery (37). Another found that dementia, visual and functional impairment, comorbidities, and the use of physical restraints were associated with

a higher risk of persistent delirium (38). We found that the type of precipitating factor was by itself a predictor of recovery, in addition to pre-existing patient-related factors. In particular, surgical patients (a quarter of ward patients and the majority of ICU patients) had a better chance of recovery.

Study implications

The findings of our study imply that, despite a degree of overlap, delirium in ward patients has different demographics, predisposing factors and clinical phenotype compared to ICU patients and may have a different pathophysiological substrate .They imply that, in ICU patients, delirium is more often a form of acute organ dysfunction triggered by a major precipitating factor, while in the wards this syndrome has features more consistent with acute on chronic organ dysfunction in older and vulnerable patients, precipitated by limited or no definable trigger. Moreover, delirium has different subtypes in terms of symptoms and duration. Thus, our study implies that drawing inferences on the effectiveness of specific treatments in ward patients from studies performed in the ICU or vice versa may be misleading. Finally, the identification of major surgery as a predictor of delirium recovery implies that trials focused on surgical patients (in contrast to geriatric or chronic medical patients) are a priority.

Strengths and limitations

This study has a number of strengths. First, we used a cross disciplinary approach to delirium at a hospital level, which allowed us to compare its incidence, predisposing factors,

clinical phenotype, management, and outcomes across two major and different settings. Second, we used specific and independently documented criteria to identify patients with delirium, thus minimizing selection bias (17). Third, we obtained detailed information on the use of psychotropic drugs prior to hospital admission, an area not systematically explored in previous studies. Fourth, we obtained information on the use of all drugs, which might affect brain function after the onset to delirium documenting major differences in the management of ICU vs. non-ICU patients. Finally, we provide information on delirium persistence and continued treatment at hospital discharge in both ICU and ward patients, an area previously only explored in selected geriatric populations.

This study carries certain limitations. First, although ICD-10 discharge coding has strong specificity for the diagnosis of delirium (between 91% to 100%), it suffers from low sensitivity (ranging from 53% to 61%) (15,17,39). Moreover, patients were not screened for delirium by a specific tool on a daily basis. Thus, we are likely to have underestimated the true incidence of delirium and to have studied a particular cohort of patients, who may have had a more easily diagnosed and perhaps more severe and prolonged phenotype. However, there is no consensus on a reference method for delirium assessment at the bedside (2,10) and our approach, by relying on independent coding, diminishes the consequences of investigator-dependent selection, confirmation, ascertainment, and performance bias. Second, patients in the wards and in the ICU have different characteristics and obviously represent two different populations. Thus, the differences in predisposing factors and clinical phenotype reflects such differences. Third, the study was conducted in a single institution. Therefore, case mix may have significantly influenced our findings. Nonetheless, we

conducted this study at a hospital level in a large university-affiliated centre and thus, our results should apply to other similar settings in high-income countries. Finally, we retrospectively assessed the date of resolution of delirium using pragmatic but non-validated criteria and may have identified patients with symptomatic improvement rather than true delirium recovery. Nevertheless, symptomatic improvement as assessed by treating clinicians can be considered a relevant outcome. Moreover, there is no gold standard for the definition of delirium recovery (40).

CONCLUSION

In conclusion, delirium in hospitalized patients is a heterogeneous syndrome with respect to its demographics, predisposing factors, clinical phenotype, management, and outcomes when comparing ICU and ward patients. The likelihood of recovery is influenced by the patient's age, the presence of dementia, and the type of precipitating factor. These findings imply that, in ICU patients, delirium may mostly be a form of acute organ dysfunction triggered by a major precipitating factor, while, in the wards, it may mostly be a form of acute on chronic brain dysfunction in older and vulnerable patients, precipitated by a small or unidentifiable trigger. Moreover, they imply that a treatment which is effective in ward patients may fail in ICU patients or vice versa. Finally, the identification that major surgery patients are more likely to recover suggests the need to focus on these patients in future studies.

REFERENCES

1. Marcantonio ER. Delirium in Hospitalized Older Adults. *N Engl J Med* 2017; **377**: 1456 -66.

2. Oh ES, Fong TG, Hshieh TT, Inouye SK. Delirium in Older Persons: Advances in Diagnosis and Treatment. *JAMA* 2017; **318**: 1161-74.

3. European Delirium Association, American Delirium Society. The DSM-5 criteria, level of arousal and delirium diagnosis: inclusiveness is safer. *BMC Med* 2014; **12**: 141.

4. Kennedy M, Enander RA, Tadiri SP, Wolfe RE, Shapiro NI, Marcantonio ER. Delirium risk prediction, healthcare use and mortality of elderly adults in the emergency department. *J Am Geriatr Soc* 2014; **62**: 462 -9.

5. Marcantonio ER. Postoperative delirium: a 76-year-old woman with delirium following surgery. *JAMA* 2012; **308**: 73 -81.

6. Ely EW, Inouye SK, Bernard GR, Gordon S, Francis J, May L, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA* 2001; **286**: 2703 -10.

7. Marcantonio ER. In the clinic. Delirium. *Ann Intern Med* 2011; **154**: ITC6-1, ITC6-2, ITC6-3, ITC6-4, ITC6-5, ITC6-6, ITC6-7, ITC6-8, ITC6-9, ITC6-10, ITC6-11, ITC6-12, ITC6-13, ITC6-14, ITC6-15; quiz ITC6-16.

8. Kiely DK, Jones RN, Bergmann MA, Marcantonio ER. Association between psychomotor activity delirium subtypes and mortality among newly admitted post-acute facility patients. *J Gerontol A Biol Sci Med Sci* 2007; **62**: 174 -9.

9. Yang FM, Marcantonio ER, Inouye SK, Kiely DK, Rudolph JL, Fearing MA, et al. Phenomenological subtypes of delirium in older persons: patterns, prevalence, and prognosis. *Psychosomatics* 2009; **50**: 248 -54.

10. Harwood RH, Teale E. Where next for delirium research? *Int J Geriatr Psychiatry* 2018; **33**: 1512-20.

11. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *PLoS Med* 2007; **4**: e296.

12. Zaal IJ, Devlin JW, Peelen LM, Slooter AJC. A Systematic Review of Risk Factors for Delirium in the ICU*: *Crit Care Med* 2015; **43**: 40 -7.

13. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. *The Lancet* 2014; **383**: 911–922.

14. Reade MC, Eastwood GM, Peck L, Bellomo R, Baldwin I. Routine use of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) by bedside nurses may underdiagnose delirium. *Crit Care Resusc* 2011; **13**: 217 -24.

15. Trzepacz PT, Meagher DJ, Franco JG. Comparison of diagnostic classification systems for delirium with new research criteria that incorporate the three core domains. *J Psychosom Res* 2016; **84**: 60 -8.

16. Kazmierski J, Kowman M, Banach M, Fendler W, Okonski P, Banys A, et al. The use of DSM-IV and ICD-10 criteria and diagnostic scales for delirium among cardiac surgery patients: results from the IPDACS study. *J Neuropsychiatry Clin Neurosci* 2010; **22**: 426 -32.

17. Sepulveda E, Franco JG, Trzepacz PT, Gaviria AM, Meagher DJ, Palma J, et al. Delirium diagnosis defined by cluster analysis of symptoms versus diagnosis by DSM and ICD criteria: diagnostic accuracy study. *BMC Psychiatry* 2016; **16**: 167.

18. Inouye SK, Viscoli CM, Horwitz RI, Hurst LD, Tinetti ME. A predictive model for delirium in hospitalized elderly medical patients based on admission characteristics. *Ann Intern Med* 1993; **119**: 474 -81.

19. Inouye SK, Charpentier PA. Precipitating factors for delirium in hospitalized elderly persons. Predictive model and interrelationship with baseline vulnerability. *JAMA* 1996; **275**: 852 -7.

20. Inouye SK, Bogardus ST, Charpentier PA, Leo-Summers L, Acampora D, Holford TR, et al. A multicomponent intervention to prevent delirium in hospitalized older patients. *N Engl J Med* 1999; **340**: 669 -76.

21. Siddiqi N, Harrison JK, Clegg A, Teale EA, Young J, Taylor J, et al. Interventions for preventing delirium in hospitalised non-ICU patients. *Cochrane Database Syst Rev* 2016; **3**: CD005563.

22. Peterson JF, Pun BT, Dittus RS, Thomason JWW, Jackson JC, Shintani AK, et al. Delirium and Its Motoric Subtypes: A Study of 614 Critically Ill Patients: DELIRIUM SUBTYPES IN THE CRITICALLY ILL. *J Am Geriatr Soc* 2006; **54**: 479 -84.

23. Hayhurst CJ, Pandharipande PP, Hughes CG. Intensive Care Unit Delirium: A Review of Diagnosis, Prevention, and Treatment. *Anesthesiology* 2016; **125**: 1229 -41.

24. Jackson TA, Wilson D, Richardson S, Lord JM. Predicting outcome in older hospital patients with delirium: a systematic literature review. *Int J Geriatr Psychiatry* 2016; **31**: 392 -9.

25. Meagher DJ, Leonard M, Donnelly S, Conroy M, Adamis D, Trzepacz PT. A longitudinal study of motor subtypes in delirium: relationship with other phenomenology, etiology, medication exposure and prognosis. *J Psychosom Res* 2011; **71**: 395 -403.

26. Marcantonio E, Ta T, Duthie E, Resnick NM. Delirium severity and psychomotor types: their relationship with outcomes after hip fracture repair. *J Am Geriatr Soc* 2002; **50**: 850 -7.

27. Kelly KG, Zisselman M, Cutillo-Schmitter T, Reichard R, Payne D, Denman SJ. Severity and course of delirium in medically hospitalized nursing facility residents. *Am J Geriatr Psychiatry* 2001; **9**: 72 -7.

28. DeCrane SK, Culp KR, Wakefield B. Twelve-month mortality among delirium subtypes. *Clin Nurs Res* 2011; **20**: 404 -21.

29. Slor CJ, Adamis D, Jansen RWMM, Meagher DJ, Witlox J, Houdijk APJ, et al. Delirium motor subtypes in elderly hip fracture patients: risk factors, outcomes and longitudinal stability. *J Psychosom Res* 2013; **74**: 444 -9.

30. Meagher D, Agar MR, Teodorczuk A. Debate article: Antipsychotic medications are clinically useful for the treatment of delirium: Antipsychotic prescribing in delirium. *Int J Geriatr Psychiatry* 2018; **33**: 1420-27.

31. Mac Sweeney R, Barber V, Page V, Ely EW, Perkins GD, Young JD, et al. A national survey of the management of delirium in UK intensive care units. *QJM* 2010; **103**: 243 -51.

32. Morandi A, Davis D, Taylor JK, Bellelli G, Olofsson B, Kreisel S, et al. Consensus and variations in opinions on delirium care: a survey of European delirium specialists. *Int Psychogeriatr* 2013; **25**: 2067 -75.

33. Krotsetis S, Nydahl P, Dubb R, Hermes C, Kaltwasser A, von Haken R. Status quo of delirium management in German-speaking countries: comparison between intensive care units and wards. *Intensive Care Med* 2018; **44**: 252 -3.

34. van Velthuijsen EL, Zwakhalen SMG, Mulder WJ, Verhey FRJ, Kempen GIJM. Detection and management of hyperactive and hypoactive delirium in older patients during hospitalization: a retrospective cohort study evaluating daily practice: Detection and management of delirium subtypes. *Int J Geriatr Psychiatry* 2018; **33**: 1521-29

35. Rooney S, Qadir M, Adamis D, McCarthy G. Diagnostic and treatment practices of delirium in a general hospital. *Aging Clin Exp Res* 2014; **26**: 625 -33.

36. Cole MG, Ciampi A, Belzile E, Zhong L. Persistent delirium in older hospital patients: a systematic review of frequency and prognosis. *Age Ageing* 2008; **38**: 19 -26.

37. Kiely DK, Bergmann MA, Jones RN, Murphy KM, Orav EJ, Marcantonio ER. Characteristics associated with delirium persistence among newly admitted post-acute facility patients. *J Gerontol A Biol Sci Med Sci* 2004; **59**: 344 -9.

38. Inouye SK, Zhang Y, Jones RN, Kiely DK, Yang F, Marcantonio ER. Risk factors for delirium at discharge: development and validation of a predictive model. *Arch Intern Med* 2007; **167**: 1406–1413.

39. Cole MG, Dendukuri N, McCusker J, Han L. An empirical study of different diagnostic criteria for delirium among elderly medical inpatients. *J Neuropsychiatry Clin Neurosci* 2003; **15**: 200 -7.

40. Adamis D, Devaney A, Shanahan E, McCarthy G, Meagher D. Defining « recovery » for delirium research: a systematic review. *Age Ageing* 2015; **44**: 318 -21.

FIGURE LEGENDS AND TABLES

Figure 1: Flowchart of the study

ICU: Intensive Care Unit; LOS: Length Of Stay

Table 1: Baseline characteristics of study participants

Variable	All patients N=200	Ward patients N=100	ICU patients N=100	P-value
Demographics				
Age, median [IQR], years	77 [64-85]	84 [78-90]	65 [52-76]	<0.0001
Male gender, n (%)	112 (56)	46 (46)	66 (66)	<0.004
Co-morbidities				
Diabetes on insulin, n (%)	18 (9)	7 (7)	11 (11)	0.32
Metastatic cancer, n (%)	12 (6)	9 (9)	3 (3)	0.07
Cirrhosis, n (%)	7 (3.5)	0 (0)	7 (7)	0.007
ESRD on RRT, n (%)	3 (1.5)	1 (1)	2 (2)	0.56
IV drug user, n (%)	6 (3)	0 (0)	6 (6)	0.01
Risk factors for Delirium				
Hypertension, n (%)	126 (63)	75 (75)	51 (51)	0.0004
Alcohol, n (%)	25 (12.5)	4 (4)	21 (21)	0.0003
Dementia, n (%)	40 (20)	38 (38)	2 (2)	<0.0001
Pre-existing neurological disease [a], n (%)	26 (13)	15 (15)	11 (11)	0.53
Psychosis, n (%)	6 (3)	4 (4)	2 (2)	
Parkinson disease, n (%)	12 (6)	10 (10)	2 (2)	
Stroke, n (%)	22 (11)	15 (15)	7 (7)	
Other neurodegenerative disease, n (%)	3 (1.5)	2 (2)	1 (1)	
Depression, n (%)	31 (15.5)	18 (18)	13 (13)	0.32
Surgical procedure, n (%)	86 (43)	24 (24)	62 (62)	<0.0001
Sepsis treated by antibiotics, n (%)	85 (42.5)	45 (45)	40 (40)	0.43
Laboratory abnormalities [b], n (%)	94 (47)	44 (44)	50 (50)	0.39

ESRD: End Stage Renal Disease; ICU: Intensive Care Unit; IQR: InterQuartile Range [25th-75th percentiles]; IV: intravenous; RRT: Renal Replacement Therapy.

[a] Patients having at least one the following diseases: psychosis, Parkinson disease, stroke, and other neurodegenerative disease. [b] Patients having at least one the following laboratory abnormalities: hyponatremia (<135mmol/L), hypernatremia (>145mmol/L), hypoglycemia (<3mmol/L), hypercapnia (>45mmHg), hypoxia (PaO_2<60mmHg or SpO_2<90mmHg), and AKI (KDIGO stage 2 or 3).

Table 2: Clinical features of Delirium and pharmacological management

Variable	**All patients N=200**	**Ward patients N=100**	**ICU patients N=100**	**P-value**
Chronic medications				
SSRIs n (%)	34 (17)	24 (24)	10 (10)	0.008
Benzodiazepines, n (%)	30 (15)	21 (21)	9 (9)	0.01
Antipsychotic drugs, n (%)	29 (14.5)	26 (26)	3 (3)	<0.0001
Opioid analgesics, n (%)	16 (8)	11 (11)	5 (5)	0.11
Steroids, n (%)	6 (3)	4 (4)	2 (2)	0.40
Clinical features of Delirium				
Time from hospital admission to onset of delirium, median [IQR], days	1 [1-2]	1 [1-1]	1 [0-3]	<0.0001
Time from surgery to onset of delirium, median [IQR], days (n=86)	2 [1-4]	2 [1-2]	2 [1-4]	0.04
Delirium phenotype				<0.0001
Hypoactive delirium, n (%)	110 (55)	74 (74)	36 (36)	
Agitated delirium, n (%)	90 (45)	26 (26)	64 (64)	
Drugs administered at the time of Delirium				
Benzodiazepines, n (%)	55 (27.5)	27 (27)	28 (28)	0.87
Opioid analgesics, n (%)	58 (29)	30 (30)	28 (28)	0.75
SSRIs, n (%)	19 (9.5)	17 (17)	2 (2)	0.0003
Quetiapine, n (%)	73 (36.5)	15 (15)	58 (58)	<0.0001
Haloperidol, n (%)	38 (19)	2 (2)	36 (36)	<0.0001

Olanzapine, n (%)	30 (15)	15 (15)	15 (15)	1.0
Clonidine, n (%)	20 (10)	0 (0)	20 (20)	<0.0001
Dexmedetomidine, n (%)	14 (7)	0 (0)	14 (14)	<0.0001
Droperidol, n (%)	3 (1.5)	1 (1)	2 (2)	0.56
No antidelirium drugs [a], n (%)	57 (28.5)	36 (36)	21 (21)	0.02

ICU: Intensive Care Unit; IQR: InterQuartile Range [25^{th}-75^{th} percentiles].
SSRI=selective serotonin reuptake inhibitors
[a] Patients did not receive any of the following drugs: benzodiazepines, opioid analgesics, serotonin uptake receptors inhibitors, quetiapine, haloperidol, olanzapine, clonidine, dexmedetomidine, and droperidol.

Table 3: Outcomes

Variable	All patients N=200	Ward patients N=100	ICU patients N=100	P-value
Delirium outcome				
Persistent at ICU discharge, n (%)	na	na	50 (50)	
Persistent at hospital discharge, n (%)	83 (41.5)	66 (66)	17 (17)	<0.0001
Duration of delirium [a], median [IQR], days (n=117)	4 [2-6]	4 [2-6]	4 [2-6]	0.98
Medications at hospital discharge [b]				
Serotonin uptake receptors inhibitors, n (%)	21 (12)	16 (18)	5 (6)	0.01
Benzodiazepines, n (%)	17 (9)	11 (12)	6 (7)	0.20
Antipsychotic drugs, n (%)	32 (18)	21 (23)	11 (12)	0.05
Length of stay				
ICU LOS, median [IQR], days	na	na	5 [2-11]	
Hospital LOS, median [IQR], days	13 [7-24]	7.5 [4-13]	17 [11-31]	<0.0001
Destination at hospital discharge				<0.0001
Home, n (%)	127 (63.5)	56 (56)	71 (71)	
Nursing home, n (%)	24 (12)	23 (23)	1 (1)	
Transfer to another hospital, n (%)	24 (12)	9 (9)	15 (15)	
Transition care, n (%)	2 (1)	0 (0)	2 (2)	
Left against medical advice, n (%)	3 (1.5)	2 (2)	1 (1)	
Mortality				
ICU mortality, n (%)	na	na	7 (7)	
Hospital mortality, n (%)	20 (10)	10 (10)	10 (10)	1.0

ICU: Intensive Care Unit; IQR: InterQuartile Range [25th-75th percentiles]; LOS: Length Of Stay; na: not applicable.

[a] Data restricted to the 117 patients who recovered from the episode of delirium before hospital discharge.

[b] Data restricted to the 180 patients alive at hospital discharge.

Table 4: Logistic regression analyses for factors associated with persistence of delirium at hospital discharge.

Factors	Univariate analysis		Multivariable analysis [†]	
	OR (95% CI)	p value	OR (95% CI)	p value
Demographics				
Age (per year)	1.08 (1.05-1.19)	<0.0001	1.06 (1.02-1.11)	0.002
Male gender	0.63 (0.35-1.11)	0.11	0.72 (0.32-1.63)	0.43
Dementia	21.64 (7.30-64.21)	<0.0001	12.46 (3.38-45.98)	0.0002
Pre-existing neurological disease [a]	1.04 (0.45-2.40)	0.93		
Depression	1.89 (0.87-4.10)	0.10	2.34 (0.74-7.45)	0.15
Clinical features of Delirium				
Surgical procedure	0.16 (0.08-0.31)	<0.0001	0.14 (0.06-0.34)	<0.0001
Sepsis treated by antibiotics	1.40 (0.79-2.47)	0.24		
Laboratory abnormalities [b], n (%)	0.84 (0.48-1.48)	0.56		
ICU patients (versus ward patients)	0.10 (0.05-0.20)	<0.0001	0.75 (0.23-2.47)	0.64
Hypoactive delirium (versus agitated)	1.86 (1.04-3.30)	0.03	0.61 (0.24-1.54)	0.30
Drugs administered at the time of Delirium				
Benzodiazepines	0.91 (0.48-1.72)	0.79		
Opioid analgesics	0.99 (0.53-1.84)	0.98		
Serotonin uptake receptors inhibitors	3.43 (1.24-9.45)	0.01	1.61 (0.41-6.26)	0.49
Quetiapine	0.74 (0.41-1.34)	0.32		
Haloperidol	0.30 (0.13-0.71)	0.006	0.68 (0.20-2.33)	0.54
Olanzapine	1.28 (0.58-2.79)	0.53		
Clonidine	0.22 (0.06-0.77)	0.01	0.81 (0.17-3.86)	0.79
Dexmedetomidine	0.36 (0.09-1.33)	0.12	2.62 (0.54-12.71)	0.23
Droperidol	0.70 (0.06-7.86)	0.77		

Any drugs [c]	1.14 (0.61-2.13)	0.66		

ESRD: End Stage Renal Disease; ICU: Intensive Care Unit; IQR: InterQuartile Range [25th-75th percentiles]; IV: intravenous; RRT: Renal Replacement Therapy.

[a] Patients having at least one the following diseases: psychosis, Parkinson disease, stroke, and other neurodegenerative disease.

[b] Patients having at least one the following laboratory abnormalities: hyponatremia (<135mmol/L), hypernatremia (>145mmol/L), hypoglycemia (<3mmol/L), hypercapnia (>45mmHg), hypoxia (PaO_2<60mmHg or SpO_2<90mmHg), and AKI (KDIGO stage 2 or 3).

[c] Patients did not receive any of the following drugs: benzodiazepines, opioid analgesics, serotonin uptake receptors inhibitors, quetiapine, haloperidol, olanzapine, clonidine, dexmedetomidine, and droperidol.

[†] Candidate predictors were: age, male gender, dementia, depression, surgical procedure, ICU patients (versus ward patients), hypoactive delirium (versus agitated delirium), serotonin uptake receptors inhibitors, haloperidol, clonidine, and dexmedetomidine.

ABSTRACT

Background: Delirium is common in hospitalized patients but its epidemiology remains poorly characterized.

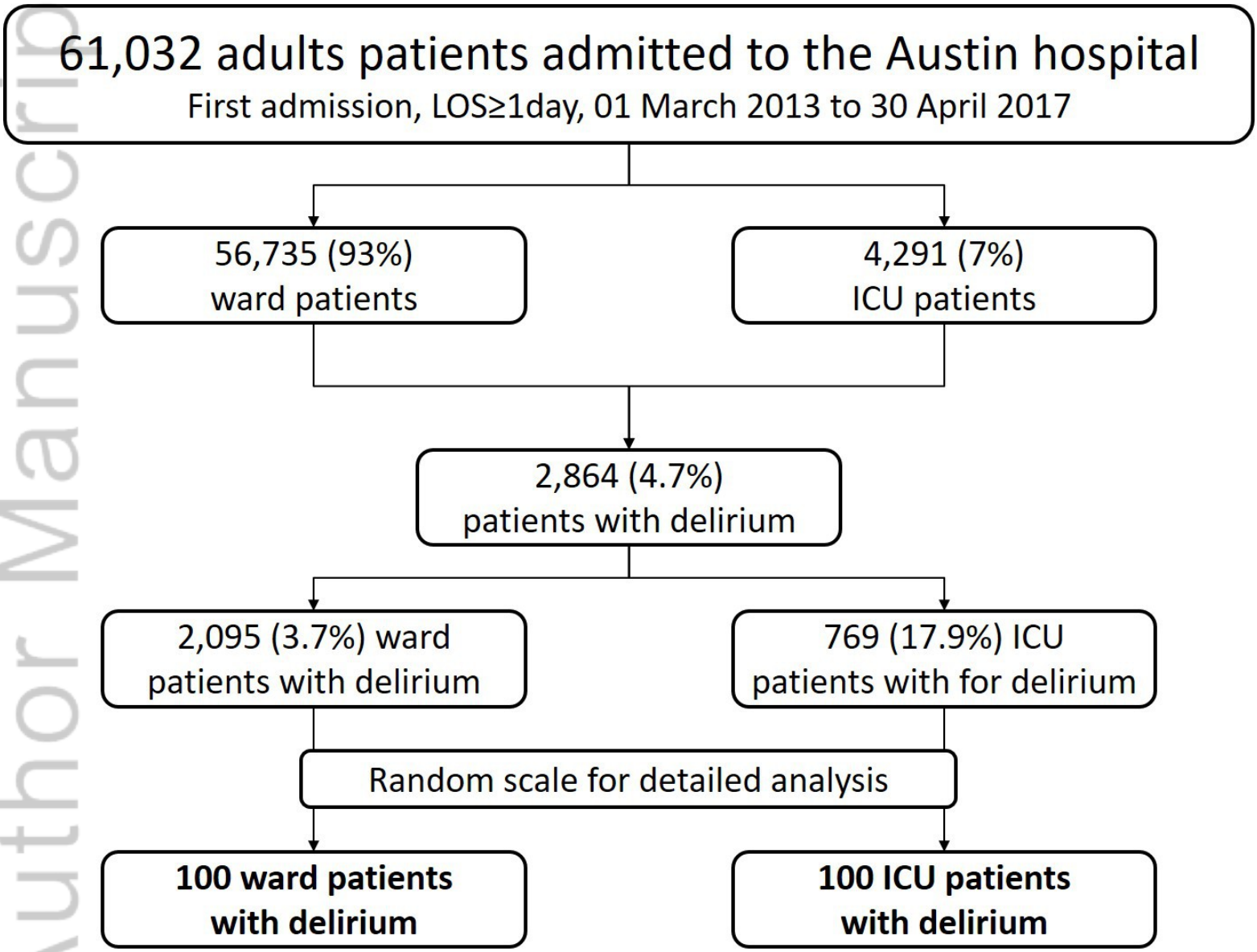
Aims: To test the hypothesis that patient demographics, clinical phenotype, management, and outcomes of patient with delirium in hospital ward patients differ from ICU patients.

Methods: Retrospective cohort of patients admitted to an Australian university-affiliated hospital between March 2013 and April 2017 and coded for delirium at discharge using the ICD-10 criteria.

Results: Among 61,032 hospitalized patients, 2,864 (4.7%) were coded for delirium. From these, we studied a random sample of 100 ward patients and 100 ICU patients. Ward patients were older (median age: 84 vs. 65 years; P<0.0001), more likely to have dementia (38% vs. 2% for ICU patients; P<0.0001) and less likely to have had surgery (24 vs. 62%; P<0.0001). Of ward patients, 74% had hypoactive delirium, while 64% of ICU patients had agitated delirium (P<0.0001). Persistent delirium at hospital discharge was more common among ward patients (66% vs 17%, p<0.0001). On multivariable analysis, age and dementia predicted persistent delirium, while surgery predicted recovery.

Conclusions: Delirium in ward patients is profoundly different from delirium in ICU patients. It has a dominant hypoactive clinical phenotype, is preceded by dementia, and is less likely to recover at hospital discharge. Therefore, delirium prevention, detection, and goals of care should be adapted to the environment in which it occurs.

Keywords: Agitation; Antipsychotics; Delirium; ICU; Ward.



IMJ_14287_Figure 1.jpg

Differential Clinical Characteristics, Management, and Outcome of Delirium among Ward Compared with ICU Patients

Authors: Emmanuel Canet[1], Sobia Amjad[2], Raymond Robbins[3], Jane Lewis[1], Michelle Matalanis[4], Daryl Jones[1,5], Rinaldo Bellomo[1,6,7,8]

1. Department of Intensive Care, Austin Hospital, Heidelberg, Melbourne, Victoria, Australia
2. School of Computing and Information Systems, The University of Melbourne, Parkville, Melbourne, Victoria, Australia
3. Business Intelligence Unit, Austin Hospital, Heidelberg, Melbourne, Victoria, Australia
4. Pharmacy Department, Austin Hospital, Heidelberg, Melbourne, Victoria, Australia
5. School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia
6. School of Medicine, The University of Melbourne, Parkville, Melbourne, Victoria, Australia
7. Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia
8. Data Analytics Research & Evaluation Centre, The University of Melbourne and Austin Hospital, Melbourne, Australia.

Corresponding author:

Rinaldo Bellomo

Department of Intensive Care, Austin Hospital,

145 Studley Rd, Heidelberg, Victoria, Australia

Tel: +61-3-9496 5992

Fax: + 61-3-9496 3932

Email: Rinaldo.bellomo@austin.org.au

Acknowledgements: None

Financial support: Supported by an educational grant from the Austin Intensive Care Trust Fund

Conflict of interest: The authors declare they have no conflict of interest.

Abstract word count: 220

Body manuscript word count: 2931

Number of tables: 4

Number of figures: 1

Short title: Comparing delirium in ICU and hospital wards.

This manuscript has an online supplementary appendix.