



Cognitive Dysfunction and Survival in Hospitalized Patients with Delirium: A 12-Month Prospective Cohort Study

Mousa Kiani Chelmardi¹, Raheleh Rafeaie², Seyed Davood Hosseini Talari³, Nadia Abedi Omali⁴ and Seyed Hamzeh Hosseini^{1,*}

¹Department of Psychiatry, School of Medicine, Mazandaran University of Medical Sciences, Sari, Iran

²Department of Neuroscience, School of Advanced Technologies in Medicine, Mazandaran University of Medical Sciences, Sari, Iran

³Department of Psychiatry, School of Medicine, Babol University of Medical Sciences, Babol, Iran

⁴Psychiatry and Behavioral Sciences Research Center, Addiction Research Institute, Mazandaran University of Medical Sciences, Sari, Iran

*Corresponding author: Department of Psychiatry, School of Medicine, Mazandaran University of Medical Sciences, Sari, Iran. Email: hosseinish20@gmail.com

Received 2020 October 03; Revised 2021 January 26; Accepted 2021 January 29.

Abstract

Background: The effect of delirium of hospitalized inpatients on post-discharge cognitive status and survival of older patients remains unclear, and little is known about the related risk factors of cognitive impairment after delirium.

Objectives: To determine one-year survival of patients with delirium and cognitive dysfunction in elderly inpatients after initial hospital admission.

Methods: This prospective cohort study was conducted on 100 patients with delirium admitted to a general hospital from October 2018 to November 2019. Cognitive dysfunction and death were the primary outcomes. The mini-mental state examination (MMSE) was used to measure cognitive function.

Results: In this study, 12 patients died in hospital and cumulative three-month mortality was 40%. Finally, 60 patients were followed for one year. The one-year survival rate through the Kaplan-Meier approach was 31%. The rate of one-year mortality was found with a significant association with underlying parameters, such as cancer ($P = 0.008$), cirrhosis ($P = 0.04$), trauma ($P = 0.001$), $BUN \geq 50$ mg/dL ($P = 0.02$), $Cr \geq 1.2$ mg/dL ($P = 0.04$), hypocalcemia ($P = 0.0$), and thrombocytopenia ($P = 0.002$). According to the MMSE scores, participants had normal cognition (46.7%), mild dementia (6.7%), moderate dementia (33.3%), and severe dementia (3.3%). The cognitive impairment showed a significant association with underlying parameters, such as pulmonary infections ($P = 0.02$), trauma ($P = 0.02$), and renal failure ($P = 0.04$).

Conclusions: Assessment and screening for delirium is necessary in all older hospitalized inpatients. Cognitive measurement is effective to identify delirium, accelerate proper control, and decrease its negative effects. Family members should be trained and involved in care, particularly for monitoring of risk factors upon discharge.

Keywords: Delirium, Cognitive Dysfunction, Death, Cohort

1. Background

Delirium is commonly observed in the elderly in acute and non-acute care settings and is associated with poor outcomes (1-3). Prevalence estimates typically range from 9 - 32% of older hospitalized inpatients (4). According to studies, around 70% of patients in intensive care units (ICU) are affected by delirium (5) and the hospital mortality rate is 25 - 33% (6). The one-year mortality rate of 35 - 40% is observed for hospitalized seniors with delirium (7), which is similar to the mortality linked to sepsis or acute myocardial infarction (8). The delirium rate in Iran is 21.8%, while its rate in hospitalized cases in ICU and general ward is 24.7% and 17.5%, respectively (9).

Investigating the outcomes after delirium in the el-

derly and providing interventions to improve patient outcomes are of particular interest (10, 11). Although it is an acute disease, it is linked to many long-term complications as well as an increase in healthcare burden and costs (12). Delirium is linked with persistent impairments in brain function, including cognitive decline and increased risk of dementia and death (13, 14). Although numerous studies have documented that persistent cognitive impairment affects 30 - 80% of survivors (15-20), it is necessary to determine the risk factors and predictors of this pernicious complication of critical illness (21).

Despite a high rate of delirium in cases admitted to hospitals in Iran (9), little has been investigated about the future cognitive dysfunction after delirium and related risk factors. Identifying manageable risk factors regarding

the cognitive deterioration in delirium is needed for developing preventive approaches to reduce morbidity (22). Such a decrease in the rate of patients with cognitive dysfunction decreases the possibility of premature nursing home placement as well as the cost of caring for the elderly and increases one's quality of life (QoL) (23).

2. Objectives

This study aimed to follow a cohort of patients with delirium at the time of hospital admission over one year for mortality. We reported an association between a delirium episode during hospitalization and the prevalence of cognitive dysfunction among cases who survived after the initial hospital admission.

3. Methods

The three-month mortality and related risk factors, as well as clinical characteristics of patients were described in our previous study (24). The present study followed these patients for one year. Briefly, 100 delirious participants (79.9 ± 15.1 years, 24% female) were selected from the general hospital from January to October 2018. Twelve patients died in hospital and cumulative three-month mortality was 40%. Finally, 60 patients were followed for one year. Inclusion criteria were patients participating in the previous study (three-month cohort) and signing a consent letter. Exclusion criteria were sedation or unconsciousness of patients. The mini-mental state examination (MMSE) was performed in all individuals. We followed up the patients' cognitive dysfunction and death, that were the primary outcomes. Follow-up phone calls were conducted from 23 October 2018 to 21 November 2019 to record the death dates. We interviewed living patients to evaluate cognition function for 12 months after enrollment. Four patients missed the follow-up and were deleted from the study. This research was conducted based on the Helsinki Declaration guidelines and approved by the local Ethics Committee of Mazandaran University of Medical Sciences, Iran (ethics code: IR.MAZUMS.IMAMHOSPITAL.REC.1399.049). Informed consent was obtained from all patients or their relatives.

Cognitive impairment was measured using the MMSE as a 20-item scale to assess cognitive impairment more generally. MMSE cannot discriminate between delirium and dementia. It is scored from 0 - 30 and evaluates seven cognitive domains of (1) orientation to time (0 - 5); (2) orientation to place (0 - 5); (3) three-word registration (0 - 3); (4) three-word delayed recall (0 - 3); (5) working memory (0 - 5); (6) language: the comprehension of a three-step command, naming, repeating, and writing (0 - 8); and (7) visuoconstruction: copy of intersecting pentagons (0-1) (25).

Scores 25 - 30 indicate normal cognition; 21 - 24: mild dementia; 10 - 20: moderate dementia; and ≤ 9 : severe dementia.

The analyses were conducted with SPSS software version 22. We analyzed the data using *t*-test, chi-square, and Fisher's exact test. Also, the number of survival days according to delirium diagnosis was assessed by Kaplan-Meier curves with the log-rank test. Cox semi-parametric regression was applied for evaluating the impact of underlying variables on the occurrence of outcomes. Using the log-rank test, effective factors were identified and significant variables along with variables with $P < 0.3$ were entered into the model. Then, using the backward elimination, we determined the remaining variables in the semi-parametric Cox model. $P < 0.05$ was considered significant.

4. Results

During the 12-month follow-up, 30 of the 100 individuals remained alive. Survival rate is illustrated in Figure 1. The possibility of one-year mortality using the Kaplan-Meier method was 31%. The mean survival time of patients was 180.8 ± 15.14 days with a confidence interval of 151.16 - 210.53 and also the median survival of patients was 90.3 ± 25 days with a confidence interval of 40.45 - 139.5 (Figure 1A). The survival rate of females was longer compared with males; however, this difference was not significant ($P = 0.48$, Figure 1B). Kaplan-Meier survival curves regarding effective factors associated with mortality rates are presented in Figure 2. There was a significant association in the one-year mortality rate and underlying factors, such as cancer ($P = 0.008$), cirrhosis ($P = 0.04$), trauma ($P = 0.001$), $BUN \geq 50$ mg/dL ($P = 0.02$), $Cr \geq 1.2$ mg/dL ($P = 0.04$), hypocalcemia ($P = 0.005$), and thrombocytopenia ($P = 0.002$). Table 1 indicates the semi-parametric Cox regression model results for the survival rate. According to this model, the hazard ratio in patients with hypocalcemia was 5.62 times higher than other patients. Moreover, patients with thrombocytopenia and trauma had a hazard ratio of 2.84 and 0.14, respectively.

According to the MMSE scores, 14 (46.7%) participants had normal cognition, 2 (6.7%) had mild dementia, 10 (33.3%) had moderate dementia, and 1 (3.3%) had severe dementia. Table 2 shows the mean (\pm SD) scores of MMSE domains. The total MMSE score in our patients was $23.55 (\pm 5.34)$, with a score of 30 obtained by 4 (13.3%) individuals. Of those scoring less than 30, the recall, working memory, and visuoconstruction domains were the commonest to contain an error (100%) followed by the language (92.3%), two-orientation (30.8%), and registration (7.7%) domains. Table 3 indicates the results of univariate analysis for MMSE score. Individuals who developed cognitive impairment

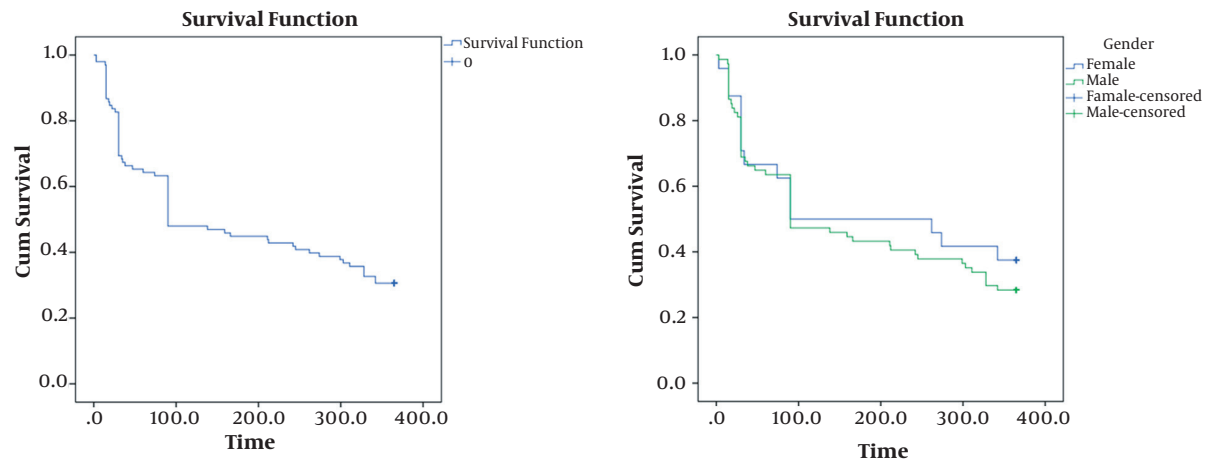


Figure 1. A, Kaplan-Meier survival curve; B, Kaplan-Meier survival curve with gender as covariate ($P = 0.48$).

Table 1. The Result of Semi-Parametric Cox Regression Model for Survival Data^a

Variables		HR	SE	Chi-Square	Significant Level	95% CI	
						Lower Limit	Upper Limit
Ca							
No	-	-	-	-	-	-	
Yes	5.62	4.14	2.34	0.02*	1.32	2.38	
PLT							
No	-	-	-	-	-	-	
Yes	2.84	1.17	2.54	0.01*	1.27	6.37	
Trauma							
No	-	-	-	-	-	-	
Yes	0.14	0.1	-2.67	0.008*	0.03	0.59	

Abbreviations: Ca, calcium; CI, confidence interval; HR, hazard ratio; PLT, platelets; SE, standard error.

^a Significant ($P < 0.05$).

were older ($P < 0.001$). The overall MMSE scores and sub-scores showed no difference between male and female patients ($P = 0.58$). There was a significant association between cognitive impairment rate and underlying factors, such as pulmonary infections ($P = 0.02$), trauma ($P = 0.02$), and renal failure ($P = 0.04$).

Table 2. Mini Mental State Exam (MMSE) Domain Scores

Domain	Score
Orientation	9.55 ± 1.28
Registration	2.93 ± 0.38
Recall	2.92 ± 1.46
Working memory	1.85 ± 0.81
Visuoconstruction	0.22 ± 0.42
Language	6.11 ± 2.06
Total	23.55 ± 5.34

^a Values are expressed as mean ± SD.

5. Discussion

In the present prospective research, the association between delirium and the one-year survival and cognitive dysfunction was assessed. The major findings are as follows: (1) the possibility of one-year survival was 31%; (2) the one-year mortality rate showed a significant association with underlying factors, such as cancer, cirrhosis, trauma, hypocalcemia, thrombocytopenia, and renal disease; (3) the probability of cognitive dysfunction was 53.3%; (4) the frequency of cognitive impairment showed a significant association with underlying factors, like pulmonary infections, trauma, and renal failure. Our findings are crucial for older hospitalized cases.

The incidence of cognitive dysfunction due to delirium was 53.3%, which is consistent with other studies (26, 27). However, the delirium effect on survival after discharge is controversial. Our results are consistent with the findings of studies that reported the mortality risk for delirious cases following one-year hospitalization (7, 28). In contrast,

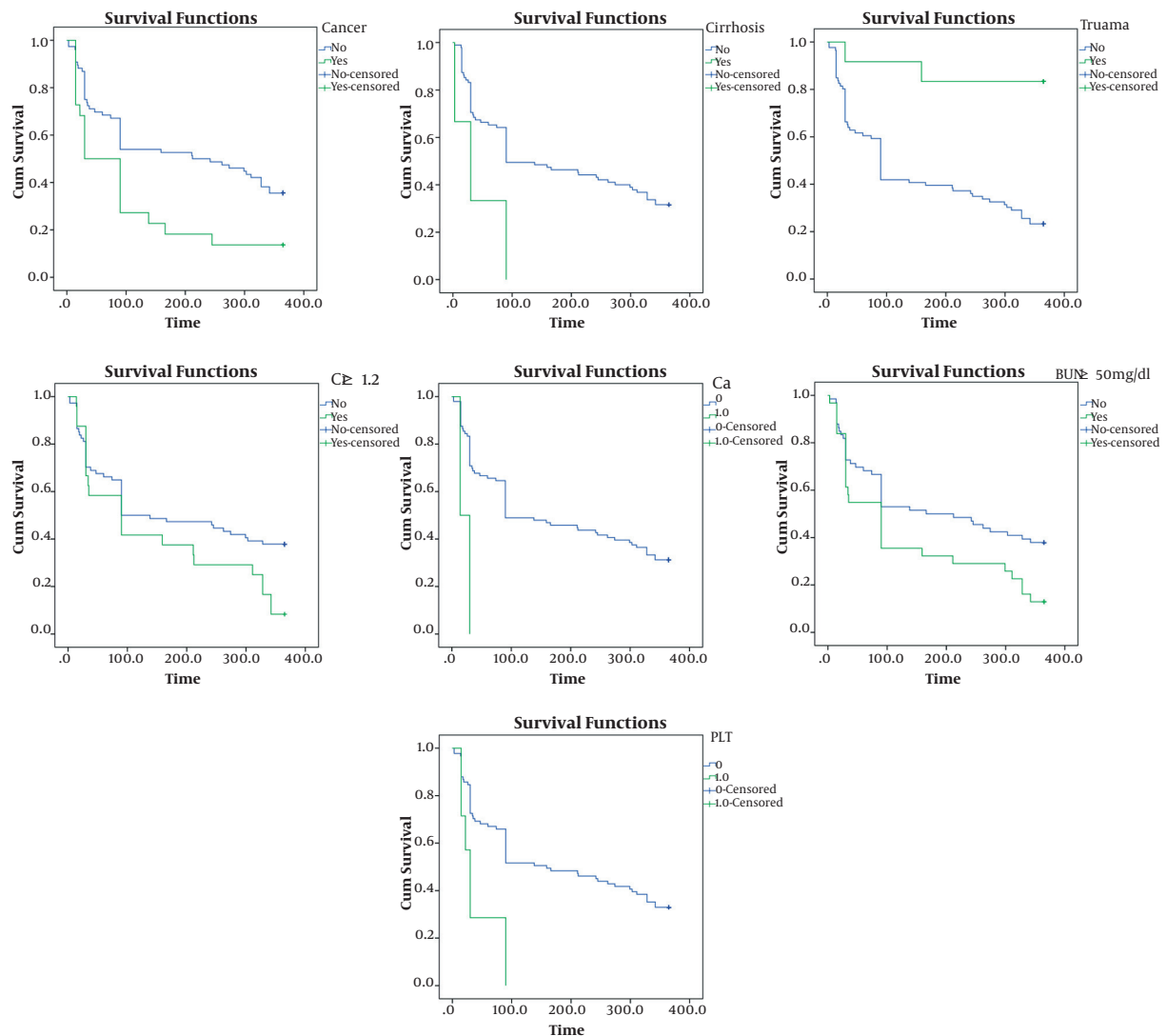


Figure 2. Kaplan-Meier survival curves for different related factors. A, cancer; B, cirrhosis; C, trauma; D, BUN; E, Cr; F, Ca; G, PLT (Abbreviations: BUN, blood urea nitrogen; Ca, calcium; Cr, creatinine; PLT, platelets).

Wolters et al. reported no significant association between delirium and one-year survival (29). According to Leslie et al., the risk of mortality in delirium cases (at least 70 years old) in the hospital elevated by 62% after 12 months of discharge (30). However, in our results, there was no significant association between age and one-year survival after delirium. One explanation for this inconsistency can be the heterogeneity of patients referring to the general hospital. Therefore, younger patients (17 participants aged below 55) with serious clinical conditions and delirium were included in our study. In line with our results, Mitchell et al. (2017) showed that delirium in hospital had an as-

sociation with all-cause one-year mortality following hip fracture in older cases with no dementia (31). Also, similar to previous studies, the other underlying factors can affect mortality rate including cancer (32), hepatic (33), renal (34), and hematologic diseases (35, 36).

Our findings are in line with the existing literature, which showed that substantial cognitive under performance is a possible consequence of delirium (13, 37, 38). In line with previous studies, our findings showed the association between cognitive impairment rate and underlying factors such as trauma (39), pulmonary (40, 41), and renal diseases (42). This relationship has several possible

Table 3. The Results of the Univariate Analysis for MMSE Total Score ^a

Variables	MMSE < 24	MMSE ≥ 25	P-Value
Age	81.6 ± 9.7	52.7 ± 17.7	< 0.001*
Sex			0.58
Female	5 (55.6)	4 (44.4)	
Male	10 (55.6)	8 (44.4)	
Underlying Disorders			
Pulmonary infections			
Yes	6 (85.7)	1 (14.3)	0.02*
No	7 (35)	13 (65)	
Trauma			
Yes	1 (12.5)	7 (87.5)	0.02*
No	12 (63.2)	7 (36.8)	
Renal failure			
Yes	0	4 (100)	0.04*
No	13 (56.5)	10 (43.5)	

Abbreviation: MMSE, mini mental state exam.

^a Significant (P < 0.05).

explanations and mechanisms; that delirium can be associated with brain damage which may be irreversible. There is good evidence supporting the relationship between delirium and neuroinflammation and neuronal apoptosis, cerebral atrophy, and decreased white-matter integrity (43-45). Another possibility is that the other changes in delirium can cause or exacerbate brain damage through malnourishment (46), dehydration (47), trauma (48), and psychological stress (49, 50). Our results support those reported by McCusker et al. indicating a relationship between delirium and lower scores in the MMSE 12 months after hospitalization (51). Our findings also strongly support an association between delirium and dementia (52, 53). The long-term cognitive deficit has recently been shown after delirium in older adults, that is possibly distinct from classical dementia signatures (54).

Our study had some limitations. First, we were unable to identify a relation between underlying factors and specific domains of MMSE due to the small sample size. Future researchers are suggested to conduct studies with larger sample sizes. Second, we did not follow the patients in a shorter period of time to evaluate patients who died about cognitive impairment symptoms after hospital discharge, in more checkpoints. Our findings add to other studies because of assessing the relationship between delirium and cognitive impairment in non-surgical cases outside the critical care units, with normal cognitive status in the baseline that were admitted in the general hospital. Our results are crucial for clinical practice to identify the underlying factors linked to death and cognitive dysfunction in hospitalized delirious elderly people in an Iranian population. We provided appropriate data for a preventive strategy and clinical management regarding cases who experienced delirium in the general hospital, allowing a reduc-

tion in post-discharge cognitive impairments and mortality.

5.1. Conclusion

In conclusion, delirium should be regarded as an important and serious problem because of the possibility of mortality risk. Assessment and screening for delirium are necessary for all older hospitalized inpatients. A brief cognitive assessment is effective to identify delirium, enhance proper management, and reduce its associated complications. Family members should be trained and involved in care, particularly for monitoring of risk factors upon discharge.

Footnotes

Authors' Contribution: S.H.H., designed the study, supervised collecting the data, and revised the manuscript; M.K.C., involved in collecting the data and worked on the manuscript; R.R., analyzed the data and wrote the draft of manuscript; N.A.O., M.K.C., and S.D.H.T., discussed the results and commented on the manuscript. All authors contributed to the final version of the manuscript.

Conflict of Interests: All authors have no conflict of interests to declare.

Ethical Approval: The local Ethics Committee of Mazandaran University of Medical Sciences approved this study (ethical code: IR.MAZUMS.IMAMHOSPITAL.REC.1399.049).

Funding/Support: This research was funded by a specific project grant of Mazandaran University of Medical Sciences.

Informed Consent: All the participants provided their informed written consent for participation in the present study.

References

- Andrew MK, Freter SH, Rockwood K. Prevalence and outcomes of delirium in community and non-acute care settings in people without dementia: A report from the Canadian Study of Health and Aging. *BMC Med.* 2006;**4**:15. doi: [10.1186/1741-7015-4-15](#). [PubMed: [16796755](#)]. [PubMed Central: [PMC1574341](#)].
- Maldonado JR. Delirium in the acute care setting: characteristics, diagnosis and treatment. *Crit Care Clin.* 2008;**24**(4):657-722. vii. doi: [10.1016/j.ccc.2008.05.008](#). [PubMed: [18929939](#)].
- 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**(4):392-9. doi: [10.1002/gps.4344](#). [PubMed: [26302258](#)].
- Koirala B, Hansen BR, Hosie A, Budhathoki C, Seal S, Beaman A, et al. Delirium point prevalence studies in inpatient settings: A systematic review and meta-analysis. *J Clin Nurs.* 2020;**29**(13-14):2083-92. doi: [10.1111/jocn.15219](#). [PubMed: [32065410](#)].
- Wilson JE, Ely EW. Delirium in the ICU. *Qatar Med J.* 2020;**2019**(2). doi: [10.5339/qmj.2019.qccc.31](#).
- Inouye SK, Schlesinger MJ, Lydon TJ. Delirium: a symptom of how hospital care is failing older persons and a window to improve quality of hospital care. *Am J Med.* 1999;**106**(5):565-73. doi: [10.1016/S0002-9343\(99\)00070-4](#). [PubMed: [10335730](#)].
- Kiely DK, Marcantonio ER, Inouye SK, Shaffer ML, Bergmann MA, Yang FM, et al. Persistent delirium predicts greater mortality. *J Am Geriatr Soc.* 2009;**57**(1):55-61. doi: [10.1111/j.1532-5415.2008.02092.x](#). [PubMed: [19170790](#)]. [PubMed Central: [PMC2744464](#)].
- Oh ES, Fong TG, Hsieh TT, Inouye SK. Delirium in older persons: Advances in diagnosis and treatment. *JAMA.* 2017;**318**(12):1161-74. doi: [10.1001/jama.2017.12067](#). [PubMed: [28973626](#)]. [PubMed Central: [PMC5717753](#)].
- Khalighi E, Tarjoman A, Abdi A, Borji M. The prevalence of delirium in patients in Iran: A systematic review and meta-analysis. *Future Neurol.* 2019;**14**(4):FNL34. doi: [10.2217/fnl-2018-0044](#).
- McKenzie J, Joy A. Family intervention improves outcomes for patients with delirium: Systematic review and meta-analysis. *Australas J Ageing.* 2020;**39**(1):21-30. doi: [10.1111/ajag.12688](#). [PubMed: [31250961](#)].
- Hughes CG, Brummel NE, Vasilevskis EE, Girard TD, Pandharipande PP. Future directions of delirium research and management. *Best Pract Res Clin Anaesthesiol.* 2012;**26**(3):395-405. doi: [10.1016/j.bpa.2012.08.004](#). [PubMed: [23040289](#)]. [PubMed Central: [PMC3638881](#)].
- Caplan GA, Teodorczuk A, Streatfield J, Agar MR. The financial and social costs of delirium. *Eur Geriatr Med.* 2020;**11**(1):105-12. doi: [10.1007/s41999-019-00257-2](#). [PubMed: [32297239](#)].
- MacLulich AM, Beaglehole A, Hall RJ, Meagher DJ. Delirium and long-term cognitive impairment. *Int Rev Psychiatry.* 2009;**21**(1):30-42. doi: [10.1080/09540260802675031](#). [PubMed: [19219711](#)].
- Morandi A, Di Santo SG, Zambon A, Mazzone A, Cherubini A, Mossello E, et al. Delirium, dementia, and in-hospital mortality: The results from the Italian Delirium Day 2016, A National Multicenter Study. *J Gerontol A Biol Sci Med Sci.* 2019;**74**(6):910-6. doi: [10.1093/geronol/gly154](#). [PubMed: [29982365](#)].
- Rothenhausler HB, Ehrentraut S, Stoll C, Schelling G, Kapfhammer HP. The relationship between cognitive performance and employment and health status in long-term survivors of the acute respiratory distress syndrome: results of an exploratory study. *Gen Hosp Psychiatry.* 2001;**23**(2):90-6. doi: [10.1016/S0163-8343\(01\)00123-2](#). [PubMed: [11313077](#)].
- Jackson JC, Hart RP, Gordon SM, Shintani A, Truman B, May L, et al. Six-month neuropsychological outcome of medical intensive care unit patients. *Crit Care Med.* 2003;**31**(4):1226-34. doi: [10.1097/01.CCM.0000059996.30263.94](#). [PubMed: [12682497](#)].
- Hopkins RO, Weaver LK, Collingridge D, Parkinson RB, Chan KJ, Orme J. Two-year cognitive, emotional, and quality-of-life outcomes in acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 2005;**171**(4):340-7. doi: [10.1164/rccm.200406-763OC](#). [PubMed: [15542793](#)].
- Hopkins RO, Jackson JC, Wallace C. Neurocognitive impairments in ICU patients with prolonged mechanical ventilation. *J Int Neuropsychol Soc.* 2005;**11**(Suppl 1):60.
- Sukantarat KT, Burgess PW, Williamson RC, Brett SJ. Prolonged cognitive dysfunction in survivors of critical illness. *Anaesthesia.* 2005;**60**(9):847-53. doi: [10.1111/j.1365-2044.2005.04148.x](#). [PubMed: [16115244](#)].
- Jones C, Griffiths RD, Slater T, Benjamin KS, Wilson S. Significant cognitive dysfunction in non-delirious patients identified during and persisting following critical illness. *Intensive Care Med.* 2006;**32**(6):923-6. doi: [10.1007/s00134-006-0112-y](#). [PubMed: [16525845](#)].
- Mitchell ML, Shum DHK, Mihala G, Murfield JE, Aitken LM. Long-term cognitive impairment and delirium in intensive care: A prospective cohort study. *Aust Crit Care.* 2018;**31**(4):204-11. doi: [10.1016/j.aucc.2017.07.002](#). [PubMed: [28736089](#)].
- Saxena S, Lawley D. Delirium in the elderly: A clinical review. *Postgrad Med J.* 2009;**85**(1006):405-13. doi: [10.1136/pgmj.2008.072025](#). [PubMed: [19633006](#)].
- Cameron ID, Dyer SM, Panagoda CE, Murray GR, Hill KD, Cumming RG, et al. Interventions for preventing falls in older people in care facilities and hospitals. *Cochrane Database Syst Rev.* 2018;**9**. CD005465. doi: [10.1002/14651858.CD005465.pub4](#). [PubMed: [30191554](#)]. [PubMed Central: [PMC6148705](#)].
- Mehrabani P, Hosseini SD, Rafeiee R, Hosseini SH. Three-month mortality and related risk factors in delirium patients: A prospective Cohort study. *Shiraz E-Med J.* 2020;**21**(5). e93460. doi: [10.5812/semj.93460](#).
- Fayers PM, Hjermstad MJ, Ranhoff AH, Kaasa S, Skogstad L, Klestad P, et al. Which mini-mental state exam items can be used to screen for delirium and cognitive impairment? *J Pain Symptom Manage.* 2005;**30**(1):41-50. doi: [10.1016/j.jpainsymman.2005.05.001](#). [PubMed: [16043006](#)].
- Davis DH, Muniz-Terrera G, Keage HA, Stephan BC, Fleming J, Ince PG, et al. Association of delirium with cognitive decline in late life: A neuropathologic study of 3 population-based Cohort studies. *JAMA Psychiatry.* 2017;**74**(3):244-51. doi: [10.1001/jamapsychiatry.2016.3423](#). [PubMed: [28114436](#)]. [PubMed Central: [PMC6037291](#)].
- Lloyd DG, Ma D, Vizcaychipi MP. Cognitive decline after anaesthesia and critical care. *Continuing Education in Anaesthesia Critical Care & Pain.* 2012;**12**(3):105-9. doi: [10.1093/bjaceaccp/mks004](#).
- Reynish EL, Hapca SM, De Souza N, Cvorov V, Donnan PT, Guthrie B. Epidemiology and outcomes of people with dementia, delirium, and unspecified cognitive impairment in the general hospital: prospective cohort study of 10,014 admissions. *BMC Med.* 2017;**15**(1):140. doi: [10.1186/s12916-017-0899-0](#). [PubMed: [28747225](#)]. [PubMed Central: [PMC5530485](#)].
- Wolters AE, van Dijk D, Pasma W, Cremer OL, Looije MF, de Lange DW, et al. Long-term outcome of delirium during intensive care unit stay in survivors of critical illness: a prospective cohort study. *Crit Care.* 2014;**18**(3):R125. doi: [10.1186/cc13929](#). [PubMed: [24942154](#)]. [PubMed Central: [PMC4095683](#)].
- Leslie DL, Zhang Y, Holford TR, Bogardus ST, Leo-Summers LS, Inouye SK. Premature death associated with delirium at 1-year follow-up. *Arch Intern Med.* 2005;**165**(14):1657-62. doi: [10.1001/archinte.165.14.1657](#). [PubMed: [16043686](#)].
- Mitchell R, Harvey L, Brodaty H, Draper B, Close J. One-year mortality after hip fracture in older individuals: The effects of delirium and dementia. *Arch Gerontol Geriatr.* 2017;**72**:135-41. doi: [10.1016/j.archger.2017.06.006](#). [PubMed: [28628893](#)].

32. Bush SH, Lawlor PG, Ryan K, Centeno C, Lucchesi M, Kanji S, et al. Delirium in adult cancer patients: ESMO clinical practice guidelines. *Ann Oncol*. 2018;**29**(Suppl 4):iv143-65. doi: [10.1093/annonc/mdy147](https://doi.org/10.1093/annonc/mdy147). [PubMed: [29992308](https://pubmed.ncbi.nlm.nih.gov/29992308/)].
33. Ovchinsky N, Frazier W, Auletta JJ, Dvorak CC, Ardura M, Song E, et al. Consensus report by the pediatric acute lung injury and sepsis investigators and pediatric blood and marrow transplantation consortium joint working committees on supportive care guidelines for management of veno-occlusive disease in children and adolescents, part 3: Focus on cardiorespiratory dysfunction, infections, liver dysfunction, and delirium. *Biol Blood Marrow Transplant*. 2018;**24**(2):207-18. doi: [10.1016/j.bbmt.2017.08.035](https://doi.org/10.1016/j.bbmt.2017.08.035). [PubMed: [28870776](https://pubmed.ncbi.nlm.nih.gov/28870776/)].
34. Mossello E, Rivasi G, Tortu V, Giordano A, Iacomelli I, Cavallini MC, et al. Renal function and delirium in older fracture patients: Different information from different formulas? *Eur J Intern Med*. 2020;**71**:70-5. doi: [10.1016/j.ejim.2019.10.022](https://doi.org/10.1016/j.ejim.2019.10.022). [PubMed: [31711727](https://pubmed.ncbi.nlm.nih.gov/31711727/)].
35. Solanki K, Pir SHA, Khoury C, Cervantes JF. A rare case of delirium: Acquired thrombotic thrombocytopenic purpura in an HIV patient. *Blood*. 2018;**132**(Suppl 1):5007. doi: [10.1182/blood-2018-99-120231](https://doi.org/10.1182/blood-2018-99-120231).
36. Sarkar S, Choudhury S, Ezhumalai G, Konthoujam J. Risk factors for the development of delirium in alcohol dependence syndrome: Clinical and neurobiological implications. *Indian J Psychiatry*. 2017;**59**(3):300-5. doi: [10.4103/psychiatry.IndianJPsychiatry_67_17](https://doi.org/10.4103/psychiatry.IndianJPsychiatry_67_17). [PubMed: [29085088](https://pubmed.ncbi.nlm.nih.gov/29085088/)]. [PubMed Central: [PMC5659079](https://pubmed.ncbi.nlm.nih.gov/PMC5659079/)].
37. Girard TD, Jackson JC, Pandharipande PP, Pun BT, Thompson JL, Shintani AK, et al. Delirium as a predictor of long-term cognitive impairment in survivors of critical illness. *Crit Care Med*. 2010;**38**(7):1513-20. doi: [10.1097/CCM.0b013e3181e47be1](https://doi.org/10.1097/CCM.0b013e3181e47be1). [PubMed: [20473145](https://pubmed.ncbi.nlm.nih.gov/20473145/)]. [PubMed Central: [PMC3638813](https://pubmed.ncbi.nlm.nih.gov/PMC3638813/)].
38. Jackson JC, Gordon SM, Hart RP, Hopkins RO, Ely EW. The association between delirium and cognitive decline: A review of the empirical literature. *Neuropsychol Rev*. 2004;**14**(2):87-98. doi: [10.1023/b:nerv.0000028080.39602.17](https://doi.org/10.1023/b:nerv.0000028080.39602.17). [PubMed: [15264710](https://pubmed.ncbi.nlm.nih.gov/15264710/)].
39. Bruce AJ, Ritchie CW, Blizzard R, Lai R, Raven P. The incidence of delirium associated with orthopedic surgery: A meta-analytic review. *Int Psychogeriatr*. 2007;**19**(2):197-214. doi: [10.1017/S104161020600425X](https://doi.org/10.1017/S104161020600425X). [PubMed: [16973101](https://pubmed.ncbi.nlm.nih.gov/16973101/)].
40. Girard TD, Thompson JL, Pandharipande PP, Brummel NE, Jackson JC, Patel MB, et al. Clinical phenotypes of delirium during critical illness and severity of subsequent long-term cognitive impairment: A prospective cohort study. *Lancet Respir Med*. 2018;**6**(3):213-22. doi: [10.1016/S2213-2600\(18\)30062-6](https://doi.org/10.1016/S2213-2600(18)30062-6). [PubMed: [29508705](https://pubmed.ncbi.nlm.nih.gov/29508705/)]. [PubMed Central: [PMC6709878](https://pubmed.ncbi.nlm.nih.gov/PMC6709878/)].
41. Janz DR, Abel TW, Jackson JC, Gunther ML, Heckers S, Ely EW. Brain autopsy findings in intensive care unit patients previously suffering from delirium: A pilot study. *J Crit Care*. 2010;**25**(3):538 e7-12. doi: [10.1016/j.jcrc.2010.05.004](https://doi.org/10.1016/j.jcrc.2010.05.004). [PubMed: [20580199](https://pubmed.ncbi.nlm.nih.gov/20580199/)]. [PubMed Central: [PMC3755870](https://pubmed.ncbi.nlm.nih.gov/PMC3755870/)].
42. Wan RYY, Ostermann M. Acute kidney injury and delirium: Kidney-brain crosstalk. In: Vincent JL, editor. *Annual update in intensive care and emergency medicine 2019*. Switzerland: Springer, Cham; 2019. p. 397-404.
43. Morandi A, Rogers BP, Gunther ML, Merkle K, Pandharipande P, Girard TD, et al. The relationship between delirium duration, white matter integrity, and cognitive impairment in intensive care unit survivors as determined by diffusion tensor imaging: The VISIONS prospective cohort magnetic resonance imaging study*. *Crit Care Med*. 2012;**40**(7):2182-9. doi: [10.1097/CCM.0b013e318250acdc](https://doi.org/10.1097/CCM.0b013e318250acdc). [PubMed: [22584766](https://pubmed.ncbi.nlm.nih.gov/22584766/)]. [PubMed Central: [PMC3378755](https://pubmed.ncbi.nlm.nih.gov/PMC3378755/)].
44. Kalvas LB, Monroe TB. Structural brain changes in delirium: An integrative review. *Biol Res Nurs*. 2019;**21**(4):355-65. doi: [10.1177/1099800419849489](https://doi.org/10.1177/1099800419849489). [PubMed: [31067980](https://pubmed.ncbi.nlm.nih.gov/31067980/)]. [PubMed Central: [PMC6794667](https://pubmed.ncbi.nlm.nih.gov/PMC6794667/)].
45. Simone MJ, Tan ZS. The role of inflammation in the pathogenesis of delirium and dementia in older adults: A review. *CNS Neurosci Ther*. 2011;**17**(5):506-13. doi: [10.1111/j.1755-5949.2010.00173.x](https://doi.org/10.1111/j.1755-5949.2010.00173.x). [PubMed: [20553303](https://pubmed.ncbi.nlm.nih.gov/20553303/)]. [PubMed Central: [PMC6493838](https://pubmed.ncbi.nlm.nih.gov/PMC6493838/)].
46. Osiezagha K, Ali S, Freeman C, Barker NC, Jabeen S, Maitra S, et al. Thiamine deficiency and delirium. *Innov Clin Neurosci*. 2013;**10**(4):26-32. [PubMed: [23696956](https://pubmed.ncbi.nlm.nih.gov/23696956/)]. [PubMed Central: [PMC3659035](https://pubmed.ncbi.nlm.nih.gov/PMC3659035/)].
47. Lawlor PG. Delirium and dehydration: Some fluid for thought? *Support Care Cancer*. 2002;**10**(6):445-54. doi: [10.1007/s00520-001-0334-z](https://doi.org/10.1007/s00520-001-0334-z). [PubMed: [12353122](https://pubmed.ncbi.nlm.nih.gov/12353122/)].
48. Ganau M, Lavinio A, Prisco L. Delirium and agitation in traumatic brain injury patients: an update on pathological hypotheses and treatment options. *Minerva Anesthesiol*. 2018;**84**(5):632-40. doi: [10.23736/S0375-9393.18.12294-2](https://doi.org/10.23736/S0375-9393.18.12294-2). [PubMed: [29479930](https://pubmed.ncbi.nlm.nih.gov/29479930/)].
49. Bruck E, Schandl A, Bottai M, Sackey P. The impact of sepsis, delirium, and psychological distress on self-rated cognitive function in ICU survivors-a prospective cohort study. *J Intensive Care*. 2018;**6**:2. doi: [10.1186/s40560-017-0272-6](https://doi.org/10.1186/s40560-017-0272-6). [PubMed: [29340154](https://pubmed.ncbi.nlm.nih.gov/29340154/)]. [PubMed Central: [PMC5759266](https://pubmed.ncbi.nlm.nih.gov/PMC5759266/)].
50. Griffiths RD, Jones C. Delirium, cognitive dysfunction and posttraumatic stress disorder. *Curr Opin Anaesthesiol*. 2007;**20**(2):124-9. doi: [10.1097/ACO.0b013e3280803d4b](https://doi.org/10.1097/ACO.0b013e3280803d4b). [PubMed: [17413395](https://pubmed.ncbi.nlm.nih.gov/17413395/)].
51. McCusker J, Cole M, Dendukuri N, Belzile E, Primeau F. Delirium in older medical inpatients and subsequent cognitive and functional status: A prospective study. *CMAJ*. 2001;**165**(5):575-83. [PubMed: [11563209](https://pubmed.ncbi.nlm.nih.gov/11563209/)]. [PubMed Central: [PMC81415](https://pubmed.ncbi.nlm.nih.gov/PMC81415/)].
52. Insel KC, Badger TA. Deciphering the 4 D's: cognitive decline, delirium, depression and dementia-A review. *J Adv Nurs*. 2002;**38**(4):360-8. doi: [10.1046/j.1365-2648.2002.02196.x](https://doi.org/10.1046/j.1365-2648.2002.02196.x). [PubMed: [11985687](https://pubmed.ncbi.nlm.nih.gov/11985687/)].
53. Garcez FB, Apolinario D, Campora F, Curiati JAE, Jacob-Filho W, Avelino-Silva TJ. Delirium and post-discharge dementia: Results from a cohort of older adults without baseline cognitive impairment. *Age Ageing*. 2019;**48**(6):845-51. doi: [10.1093/ageing/afz107](https://doi.org/10.1093/ageing/afz107). [PubMed: [31566669](https://pubmed.ncbi.nlm.nih.gov/31566669/)].
54. Davis DH, Muniz Terrera G, Keage H, Rahkonen T, Oinas M, Matthews FE, et al. Delirium is a strong risk factor for dementia in the oldest-old: A population-based cohort study. *Brain*. 2012;**135**(Pt 9):2809-16. doi: [10.1093/brain/awt190](https://doi.org/10.1093/brain/awt190). [PubMed: [22879644](https://pubmed.ncbi.nlm.nih.gov/22879644/)]. [PubMed Central: [PMC3437024](https://pubmed.ncbi.nlm.nih.gov/PMC3437024/)].