



University of Dundee

Postoperative delirium in older patients with cancer

O'Hanlon, Shane; Baxter, Mark; Hosie, Annmarie

Published in:
Current Opinion in Supportive and Palliative Care

DOI:
[10.1097/SPC.0000000000000588](https://doi.org/10.1097/SPC.0000000000000588)

Publication date:
2022

Licence:
CC BY-NC

Document Version
Peer reviewed version

[Link to publication in Discovery Research Portal](#)

Citation for published version (APA):
O'Hanlon, S., Baxter, M., & Hosie, A. (2022). Postoperative delirium in older patients with cancer: the role of psychological distress and social support. *Current Opinion in Supportive and Palliative Care*, 16(1), 38-47. <https://doi.org/10.1097/SPC.0000000000000588>

General rights

Copyright and moral rights for the publications made accessible in Discovery Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from Discovery Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain.
- You may freely distribute the URL identifying the publication in the public portal.

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Post-operative delirium in older patients with cancer: The role of psychological distress and social support

Authors

O'Hanlon, Shane;^{1,2} Baxter, Mark;^{3,4} Hosie, Annmarie^{5,6,7}

Affiliations

¹ Department of Geriatric Medicine, St Vincent's University Hospital, Dublin, Ireland

² University College Dublin, Ireland

³ Division of Molecular and Clinical Medicine, School of Medicine, University of Dundee, United Kingdom

⁴ Tayside Cancer Centre, Ninewells Hospital, NHS Tayside, Dundee, United Kingdom

⁵ School of Nursing and Midwifery, Sydney, The University of Notre Dame Australia, Darlinghurst, NSW, Australia

⁶ St Vincent's Health Network Sydney, Darlinghurst, NSW, Australia

⁷ IMPACCT – Improving Palliative, Aged and Chronic Care through Research and Translation, University of Technology Sydney, Ultimo, NSW, Australia

Corresponding Author

Dr Shane O'Hanlon, Department of Geriatric Medicine, St Vincent's University Hospital, Dublin, Ireland

Phone: +353 12214549, Email: shaneohanlon@svhg.ie

Manuscript details

Words: 2692

Tables: 2

Figures: 0

References: 58

Funding disclosure

No funding was received for the drafting of this manuscript. MB as a Clinical Academic Fellow funded by the Scottish Chief Scientist Office. MB has received speaker fees from Ipsen.

Abstract

Purpose of review

Delirium is a common and important adverse event in the perioperative period. Older people with cancer are at significant risk, and outcomes are poor. There is increasing awareness of the effect of psychological distress and social support on pathogenesis and outcomes of delirium in this setting. This review aimed to describe recent research in this evolving area.

Recent findings

Across six recent studies of post-operative delirium in older people with cancer, delirium incidence ranged from 8-19.8%. Poor social support and high levels of distress are implicated in the development of post-operative delirium. Distress can be related to negative emotional reaction to diagnosis, preconception of cancer diagnosis, and interactions with the healthcare system. Prevention of delirium is key, and multicomponent interventions show evidence of effectiveness. 'Emotional distress' has been included in a new core outcome set for studies of interventions to prevent and/or treat delirium.

Summary

Post-operative delirium in older adults with cancer is common and is associated with increased morbidity and mortality. Psychological distress and social support play an important role but there are many unmet research needs in this area.

Keywords

Delirium, cancer, aged, psychological distress, social support

Introduction

Delirium is an acute neurocognitive disorder characterised by acute and fluctuating disturbances to attention, awareness and cognitive function that are directly related to adverse physiology.¹ It occurs more commonly in older patients and is a major problem in the post-operative setting with incidence of up to 45%.² Patients with cancer are particularly vulnerable to delirium.³ In those having surgery for cancer, predisposing factors of malnutrition, sarcopenia and frailty are common. Delirium can be highly distressing, for patients, as well as for family, friends and staff;⁴ while psychological distress and a lack of social support are also implicated in its development.⁵ An episode of delirium increases the risk of adverse outcomes, including subsequent cognitive, functional and psychological impairment, all of which can add to additional needs for social and health care support. Delirium also increases length of hospital stay, mortality and health care costs.^{2, 6}

This review will discuss the relationship between psychological distress, social support and post-operative delirium (POD) in older adults with cancer, with a focus on research articles published in the past two years. As no previous reviews of this area were identified, older publications that remain relevant are also included where there is a paucity of recent evidence. Our search strategy used key words including “psychological distress”, “social support”, “delirium”, “surgery” and “geriatric” in MEDLINE. Fifty-six papers were reviewed, of which 24 were excluded as they were not relevant. Of the 32 papers remaining, 23 examined distress, five examined social supports (three were relevant to both) and seven were recent studies of POD in older people with cancer which are summarised in Table 1. No large trials examining a direct relationship between distress or social support and delirium were found.

Role of psychological distress and social support

We here define psychological distress (‘distress’) as a “negative emotional state characterized by physical and/or emotional discomfort, pain, or anguish”⁷ and social support as “the formal (e.g., community groups, churches) and informal (e.g., family, friends) networks that assist and encourage people with disabilities to cope better”.⁸ Common causes of distress are listed in Table 2.

There is increasing awareness that psychological distress and social support are relevant to POD, and recovery more generally, in older adults with cancer. For example, one study of 1,211 older adults with cancer referred to a geriatrics service showed that up to half of the sample had poor social function and over half had elevated levels of distress.⁹ Of the patients with high distress and poor social support, only one-quarter received mental health care, suggesting that these issues are under-recognised and rarely addressed in clinical practice.

In patients who need cancer surgery, increased levels of distress have been reported for a variety of reasons. A 2018 qualitative study found distress was related to negative emotional reaction to diagnosis, preconception of cancer diagnosis, and interactions with the healthcare system.¹⁰ Those who underwent surgery due to malignant and benign neoplasms reported significantly higher mean stress scores and higher rates of elevated hospital and surgery related stress than those without cancer.¹¹ Anxiety, as measured by the Hospital Anxiety and Depression Scale-Anxiety (HADS-A), was shown to be a significant predictor of delirium in older patients in the orthopaedic surgical setting, with an odds ratio of 3.119 (95% CI: 1.144-8.500, $p=0.026$).¹² A recent small study in cancer patients ($n=91$) demonstrated similar findings, with an odds ratio of 4.37 (95% CI: 1.051-18.178, $p=0.043$) for those with HADS-A >7 pre-operatively.¹³ Of note, the American College of Surgeons Commission on Cancer recommended distress screening and provision of mental health services in cancer centres in 2016,¹⁴ however it is not known to what degree this has been implemented.

Broader psychosocial risk factors, which included low social support, occurred in three-quarters of older adults undergoing curative cancer surgery in one study and were associated with post-operative complications.¹⁵ Unfortunately the study did not assess for delirium, but poor social support may result in lack of self-care, poor nutrition and difficulties with activities of daily living, which are known predisposing factors for delirium.⁵ Lower social support and higher levels of anxiety were shown to be associated with poorer recovery after colorectal cancer surgery in a 2016 study.¹⁶ Low perceived availability of social support was also associated with distress in younger (aged 30-70 years) breast cancer patients.¹⁷ Our review of the literature highlighted that there remains a significant knowledge

gap about the exact relationship between social support and delirium, especially in older adults with cancer. Further research should focus on the mechanisms involved, clarify the extent of the association, and explore whether targeted interventions such as CGA (Comprehensive Geriatric Assessment) can improve outcomes for this group. Data on social support should be routinely collected in cancer studies that involve older people.

While there is considerably more research on distress and delirium, there is also room for improvement. Delirium in hospital causes many patients to experience fear, anxiety and incomprehension, and afterwards guilt and shame;⁴ and family caregivers and clinicians experience distress and uncertainty in response.¹⁸⁻²⁰ Relief of patient (and family) distress motivates clinicians to intervene;²¹ yet these outcomes have been rarely measured in delirium intervention studies. This evidence-practice gap may soon be rectified by inclusion of 'emotional distress' in a new core outcome set for studies of interventions to prevent and/or treat delirium for adults in acute care.²²

Delirium pathophysiology

The pathophysiology of delirium is not well understood but likely involves several contributing neurobiological processes.⁵ It is known that delirium can be caused by any interruption of normal physiology, such as infections, hypoxia, surgery, dehydration, constipation, drug side effects and drug withdrawal.¹ Perhaps less well recognised is that distress is hypothesised to be a contributing factor for delirium, particularly in older people and for those with existing cognitive impairment.⁵ Several theories have been proposed as to how stress can cause delirium, including oxidative stress as a mediator and age-related changes in stress-regulating neurotransmitters.⁵ Glucocorticoids may have a role in triggering delirium, as well as impairing recovery from delirium, as cortisol may potentiate the experience of fear and anxiety through the activation of extrahypothalamic corticotropin-releasing hormone.⁵ Older adults with baseline cognitive impairment exhibit sustained high cortisol levels after major stressors, possibly due to impaired feedback regulation of the limbic-hypothalamic-pituitary-adrenal axis.⁵ Repeated or prolonged exposure to glucocorticoids have also been shown to have a

negative impact on brain function, leading to neuronal injury.²³ While these findings provide clues to delirium pathophysiology, more recent work indicates that biomarkers such as these may not be useful to help identify or measure cancer-related distress in older adults, with patient-reported measures likely more reliable.²⁴

Patients with delirium can experience a hyperactive or hypoactive state, both of which can cause distress. The hyperactive state can manifest as restlessness and agitation, often stemming from persecutory delusions. The state of distress may be due to activation of the amygdala activating the locus coeruleus, which triggers noradrenergic activity and leads to more reflexive, emotional responses driven by the amygdala.²⁵ Activation of the sympathetic nervous system, which results in elevated noradrenergic activity, occurs in psychological stress and elevated blood noradrenaline was shown to be significantly associated with POD in older patients undergoing major surgery in 2014.²⁶ Admission levels of noradrenaline have recently also been shown to be associated with the risk of occurrence of ICU-acquired delirium in an older population.²⁷

A recent systematic review relevant to biomarkers in advanced cancer and delirium found no cancer biomarker studies measured delirium and that more robust conduct and reporting of future delirium biomarker studies are required to better understand its pathophysiology in the context of co-existing conditions such as cancer (see Table 1).²⁸

Delirium epidemiology (incidence, risk factors, and outcomes)

Reported incidence of POD in cancer has ranged from 11.5% in a prospective study of head and neck cancer patients²⁹ to 50% in a retrospective study of oesophageal cancer patients, both from 2012.³⁰ In this review, we identified six recent studies reporting occurrence of POD in older people with cancer. Across these, delirium incidence ranged from 8-19.8%, with higher incidence in patients with pre-operative frailty and impaired function (13-13.5%), patients aged 80 years and over (16.8%), and for those with prior cognitive impairment (38.9%) (Table 1).³¹⁻³⁶

Delirium risk factors across settings include older age, prior cognitive impairment, vision impairment, higher illness severity, fracture on admission, infection and physical restraint.³⁷ In older patients with cancer, higher risk of POD might also be related to a combination of cancer biology and treatments, cachexia, psychological stress from their diagnosis, chronic inflammation, and pharmacologic interactions.³⁸ In addition, some patients will have potential adverse effects from neoadjuvant chemotherapy or radiotherapy, such as poor nutrition or hydration, or may be exposed to multiple surgical procedures.

A study of over 38,000 patients demonstrated that disseminated cancer was one of the strongest risk predictors for adverse geriatric outcomes following surgery.³² Other key risk factors were chronic obstructive pulmonary disease (COPD), increasing age, functional dependence, diabetes requiring insulin, sepsis and gender. Male sex predicted increased odds of POD but was protective for new mobility aid use and functional decline. A strong association was also demonstrated between preoperative cognitive impairment and POD (odds ratio 2.57; 95% CI 2.29 to 2.88). This relationship has already been well recognised and thus pre-operative cognitive assessment should be factored into shared decision making for older people having surgery, especially as around one in five older adults having cancer surgery are reported to have cognitive impairment.³⁹ Even mild degrees of cognitive impairment such as impaired executive function were shown to be predictive of POD over a decade ago.⁴⁰

Both patients and carers can experience poor outcomes due to distress related to delirium. The degree of distress can be higher in relatives, especially if there is a degree of cognitive impairment in patients that affects recall of the delirium. Patients' distress can persist for months or years, and is associated with long-term psychological morbidity.²⁰ It also has an effect on broader health outcomes. Gearhart *et al.* performed an observational study examining outcomes in older patients (median age 75 years) having elective or emergency surgery for colorectal cancer.³⁵ Loss of independence upon discharge was seen in 20.5% of patients, and was strongly associated with preoperative cognitive impairment and POD. There is also evidence that POD is associated with longer-term detrimental outcomes.⁴¹

Disappointingly, there is no evidence that preventive strategies for delirium can reduce the likelihood of longer-term poorer outcomes.⁴²

Delirium risk reduction/prevention

Because treatment options are limited, prevention of delirium is a priority. It is especially important for patients with cancer, as adjuvant treatment plans - and thus survival - may be impacted by adverse outcomes from POD. It has long been estimated that POD is preventable in 30-40% of cases.⁴³ A recent systematic review of 22 randomised controlled trials of non-pharmacological interventions to prevent delirium (predominantly targeting sleep, vision and hearing, hydration, communication, orientation, cognition and mobility) in hospitalised patients outside intensive care units found lower delirium incidence compared to usual care (10.5% vs 18.4%, risk ratio (RR) 0.57 (95% CI 0.46 to 0.71)⁴⁴ However, little or no effect of these interventions on delirium duration or severity was found.⁴⁴ There is thus no definitive answer yet as to whether non-pharmacological multicomponent interventions help to mitigate distress or prevent functional decline.

A review of the literature that included broader study types examining non-pharmacological approaches in the prevention of delirium concluded that evidence for multicomponent interventions is sufficiently robust for clinical practice recommendations to be formulated.⁴² However, no conclusive outcome effects have been demonstrated for single-component interventions. As a result it is difficult to know which components of the interventions are most effective. With the exception of family involvement in delirium prevention,⁴⁵ no studies have specifically examined the effect of assessing and addressing social supports on POD. Similarly, no studies were found that examined prevention of preoperative distress to reduce delirium risk.

Prehabilitation is likely to be a future research focus, to determine whether addressing pre-existing impairments through comprehensive geriatric assessment can reduce delirium incidence, severity and duration. In a prospective study of CGA in 2018, patients with cancer who experienced POD were more

likely to have been cognitively impaired, with decreased physical performance and increased functional decline before the episode.⁴⁶

While there is growing evidence that delirium is preventable, there appears to be underuse of strategies to reduce the risk of delirium in clinical practice. Malik *et al.* followed a group of older patients with cancer and a positive Mini-COG screen to examine downstream consequences.⁴⁷ They found that where patients were identified as being at risk of delirium, preventative strategies were recommended to the oncologist in only 44.4% of instances and patients/families in 11.1% of cases of planned surgery. These findings demonstrate the need for structured comprehensive assessment, and improved communication between cancer teams, clinicians and patients/families when frailty and geriatric syndromes are identified. Hospital-wide screening programmes for POD risk in older patients with cancer have been recommended since 2015, as well as preventative measures for those identified to be at risk.⁴⁸

Management

Primary interventions for delirium are to identify and treat the cause/s and circumvent adverse consequences, which include distress. Associations were observed between the severity of delirium and level of delirium-related distress in one observational study of patients and relatives from 2019.⁴⁹ Patients' distress may be reduced by education around the possibility of delirium occurrence in shared decision-making discussions prior to surgery. If patients and caregivers know what to expect, it may help them to prepare and feel less frightened and uncertain during episodes.¹⁹ During an episode, it may also be beneficial to explain to the patient and their family what is happening, how to communicate positively, and that the delirium is likely to improve.¹⁹ Recognising and acknowledging distress are valued expressions of empathy and can reassure the patient that their lived experience is understood by healthcare staff.⁵⁰

Many clinicians actively treat distress or agitation with antipsychotic medication;²¹ however, there is no clear evidence for this.⁵¹ Environmental adjustments to promote natural sleep, orientation and

mobility can be helpful, as well as ensuring clear communication with all involved in the patient's care. Addressing these domains requires highly skilled teamwork and should also involve family members. One study showed that even simulated family presence using pre-recorded and positively-worded video messages reduced agitation in older hospitalised patients with delirium, compared to both usual care and a nature video.⁵² There is evidence from a recent pilot study that art therapy can improve emotional distress, depression, anxiety and pain among patients with cancer, although the study had small numbers of older people and excluded those with dementia.⁵³

Delirium and COVID-19

Delirium has emerged as a well-recognised complication of COVID-19 despite initial reluctance to include it in guidance.⁵⁴ The social isolation of both outpatients and inpatients due to the COVID-19 pandemic has had profound impacts on older people. Additionally, COVID-19 has decreased patients' access to timely diagnosis and oncology treatment, resulting in an increase in baseline predisposing factors for delirium. Clinical manifestations of COVID-19, such as hypoxia, metabolic abnormalities and neurological involvement, have also added to the likelihood of development of delirium. It has been suggested that COVID-19 may potentially lead to accelerated cognitive decline associated with anaesthesia and surgical stress through independent and synergistic mechanisms, and that it should be considered as an independent risk factor for POD.⁵⁵ The pandemic has also led to perioperative inpatient practices that are likely to have increased patients' distress: widespread use of isolation rooms, restriction of family visitation, and personal protective equipment, all contributing to depersonalisation and reduced communication.⁵⁶ Patients were also more likely to have been sedated with benzodiazepines, potentially further increasing their risk of delirium.^{57, 58}

Conclusion

Psychological distress and social support play an important role in development of and recovery from post-operative delirium. Management options for delirium are limited, so emphasis should be on

prevention, with risk assessments and individualised patient-centred care planning. Recent published research has focused on measuring post-operative delirium risk factors and risk prediction in older people with cancer. There are opportunities to further build evidence in delirium pathophysiology, risk reduction/prevention, management, and clinical practice change to implement evidence based practice for this population. Prevention and management interventions should also include patients' social supports, and target and measure distress as an outcome.

Key points

1. Distress and social support are associated with postoperative delirium
2. Older people with cancer are at particular risk of delirium, and require specific assessment for distress and social support
3. Older patients undergoing surgery for cancer should have comprehensive geriatric assessment and tailored multicomponent interventions to reduce the risk of post-operative complications such as delirium
4. In patients who develop postoperative delirium, management should involve treatment of identified causes, supportive communication, and ongoing multi-component interventions
5. More research into delirium pathophysiology, treatment, relief of distress, and the therapeutic role of family and friends for older people with cancer in the perioperative period is required

Acknowledgements

None

Financial support and sponsorship

None

Conflicts of interest

The authors report no conflicts of interest.

One bullet annotations:

10. A qualitative study using one-on-one interviews in an academic setting to explore sources of distress among colorectal cancer patients undergoing surgery. Participants identified sources of distress preoperatively (negative emotional reaction to diagnosis, distress from preconception of cancer diagnosis, and distress interacting with healthcare system). Sources of distress during in-hospital recovery included negative emotional reaction to having a surgery and negative emotions experienced in the hospital. Postoperative sources of distress included mismatch of expectations and experience of recovery, dealing with distressing physical symptoms and complications after surgery, and distress worrying about recurrence.

13. This was a prospective observational cohort study of cancer patients undergoing tumour resections to investigate whether preoperative anxiety predicted onset of postoperative delirium in cancer patients. Preoperative anxiety was evaluated with the Hospital Anxiety and Depression Scale-Anxiety (HADS-A). HADS-A > 7 (OR = 4.370, 95% CI = 1.051-18.178, p = 0.043) predicted delirium onset.

20. A narrative review focusing on distress in delirium and its impact on older patients. While not specific to cancer patients, it provides an overview of distress assessment tools and outlines emerging management strategies.

24. Survey of 238 patients with colon or rectal cancer, to investigate characteristics associated with high distress levels. Found that stress biomarkers may not be more clinically useful than patient-reported measures in assessing distress among colorectal cancer patients.

References

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*. Arlington, VA: American Psychiatric Publisher, 2013.
2. Jin Z, Hu J and Ma D. Postoperative delirium: perioperative assessment, risk reduction, and management. *Br J Anaesth* 2020; 125: 492-504. DOI: 10.1016/j.bja.2020.06.063.
3. El Majzoub I, Abunafeesa H, Cheaito R, et al. Management of altered mental status and delirium in cancer patients. *Ann Palliat Med* 2019; 8: 728-739. 2019/11/19. DOI: 10.21037/apm.2019.09.14.
4. Boehm LM, Jones AC, Selim AA, et al. Delirium-related distress in the ICU: A qualitative meta-synthesis of patient and family perspectives and experiences. *International Journal of Nursing Studies* 2021: 104030. DOI: <https://doi.org/10.1016/j.ijnurstu.2021.104030>.
5. Maldonado JR. Delirium pathophysiology: An updated hypothesis of the etiology of acute brain failure. *International Journal of Geriatric Psychiatry* 2018; 33: 1428-1457. 2017/12/27. DOI: 10.1002/gps.4823.
6. Pezzullo L, Streatfeild J, Hickson J, et al. Economic impact of delirium in Australia: a cost of illness study. *BMJ Open* 2019; 9: e027514. DOI: 10.1136/bmjopen-2018-027514.
7. Psychological Distress MeSH Descriptor Data 2021, <https://meshb.nlm.nih.gov/record/ui?ui=D000079225> (accessed October 22 2021).
8. Social Support MeSH Descriptor Data 2021, <https://meshb.nlm.nih.gov/record/ui?ui=D012944> (accessed October 25 2021).
9. Trevino KM, Nelson CJ, Saracino RM, et al. Is screening for psychosocial risk factors associated with mental health care in older adults with cancer undergoing surgery? *Cancer* 2020; 126: 602-610. 2019/10/19. DOI: 10.1002/cncr.32564.
10. Abelson JS, Chait A, Shen MJ, et al. Sources of distress among patients undergoing surgery for colorectal cancer: a qualitative study. *J Surg Res* 2018; 226: 140-149. 2018/04/18. DOI: 10.1016/j.jss.2018.01.017.
11. Krampe H, Goerling U, Spies CD, et al. Sense of coherence, mental well-being and perceived preoperative hospital and surgery related stress in surgical patients with malignant, benign, and no neoplasms. *BMC Psychiatry* 2020; 20. DOI: 10.1186/s12888-020-02953-x.
12. Ren A, Zhang N, Zhu H, et al. Effects of Preoperative Anxiety on Postoperative Delirium in Elderly Patients Undergoing Elective Orthopedic Surgery: A Prospective Observational Cohort Study. *Clin Interv Aging* 2021; 16: 549-557. 2021/04/06. DOI: 10.2147/cia.S300639.
13. Wada S, Inoguchi H, Sadahiro R, et al. Preoperative Anxiety as a Predictor of Delirium in Cancer Patients: A Prospective Observational Cohort Study. *World J Surg* 2019; 43: 134-142. 2018/08/22. DOI: 10.1007/s00268-018-4761-0.
14. *Cancer Program Standards: Ensuring Patient-Centered Care*. 2016. Chicago, IL: American College of Surgeons Commission on Cancer.
15. Leeds IL, Meyers PM, Enumah ZO, et al. Psychosocial Risks are Independently Associated with Cancer Surgery Outcomes in Medically Comorbid Patients. *Ann Surg Oncol* 2019; 26: 936-944. 2019/01/09. DOI: 10.1245/s10434-018-07136-3.
16. Foster C, Haviland J, Winter J, et al. Pre-Surgery Depression and Confidence to Manage Problems Predict Recovery Trajectories of Health and Wellbeing in the First Two Years following Colorectal Cancer: Results from the CREW Cohort Study. *PLoS One* 2016; 11: e0155434. 2016/05/14. DOI: 10.1371/journal.pone.0155434.
17. Perez-Tejada J, Labaka A, Pascual-Sagastizabal E, et al. Predictors of psychological distress in breast cancer survivors: A biopsychosocial approach. *Eur J Cancer Care (Engl)* 2019; 28. DOI: 10.1111/ecc.13166.
18. O'Malley G, Leonard M, Meagher D, et al. The delirium experience: A review. *Journal of psychosomatic research* 2008; 65: 223-228.

19. Finucane AM, Lugton J, Kennedy C, et al. The experiences of caregivers of patients with delirium, and their role in its management in palliative care settings: an integrative literature review. *Psycho-Oncology* 2017; 26: 291-300. DOI: 10.1002/pon.4140.
20. Williams ST, Dhesi JK and Partridge JSL. Distress in delirium: causes, assessment and management. *European Geriatric Medicine* 2020; 11: 63-70. DOI: 10.1007/s41999-019-00276-z.
21. Hosie A, Agar M, Caplan GA, et al. Clinicians' delirium treatment practice, practice change, and influences: A national online survey. *Palliat Med* 2021; 35: 1553-1563. DOI: 10.1177/02692163211022183.
22. Rose L, Burry L, Agar M, et al. A core outcome set for studies evaluating interventions to prevent and/or treat delirium for adults requiring an acute care hospital admission: an international key stakeholder informed consensus study. *BMC Medicine* 2021; 19: 143. DOI: 10.1186/s12916-021-02015-3.
23. Vyas S, Rodrigues AJ, Silva JM, et al. Chronic Stress and Glucocorticoids: From Neuronal Plasticity to Neurodegeneration. *Neural Plasticity* 2016; 2016: 6391686. DOI: 10.1155/2016/6391686.
24. Eddington HS, McLeod M, Trickey AW, et al. Patient-reported distress and age-related stress biomarkers among colorectal cancer patients. *Cancer Med* 2021; 10: 3604-3612. 2021/05/02. DOI: 10.1002/cam4.3914.
25. Wilson JE, Mart MF, Cunningham C, et al. Delirium. *Nature Reviews Disease Primers* 2020; 6: 90. DOI: 10.1038/s41572-020-00223-4.
26. Deiner S, Lin HM, Bodansky D, et al. Do stress markers and anesthetic technique predict delirium in the elderly? *Dement Geriatr Cogn Disord* 2014; 38: 366-374. 2014/08/30. DOI: 10.1159/000363762.
27. Yasuda Y, Nishikimi M, Nishida K, et al. Relationship Between Serum Norepinephrine Levels at ICU Admission and the Risk of ICU-Acquired Delirium: Secondary Analysis of the Melatonin Evaluation of Lowered Inflammation of ICU Trial. *Crit Care Explor* 2020; 2: e0082. 2020/03/27. DOI: 10.1097/cce.0000000000000082.
28. Amgarth-Duff I, Hosie A, Caplan G, et al. A systematic review of the overlap of fluid biomarkers in delirium and advanced cancer-related syndromes. *BMC Psychiatry* 2020; 20: 182. DOI: 10.1186/s12888-020-02584-2.
29. Shah S, Weed HG, He X, et al. Alcohol-Related Predictors of Delirium After Major Head and Neck Cancer Surgery. *Archives of Otolaryngology–Head & Neck Surgery* 2012; 138: 266-271. DOI: 10.1001/archoto.2011.1456.
30. Takeuchi M, Takeuchi H, Fujisawa D, et al. Incidence and risk factors of postoperative delirium in patients with esophageal cancer. *Ann Surg Oncol* 2012; 19: 3963-3970. 2012/06/16. DOI: 10.1245/s10434-012-2432-1.
31. Pollock Y, Chan CL, Hall K, et al. A novel geriatric assessment tool that predicts postoperative complications in older adults with cancer. *J Geriatr Oncol* 2020; 11: 866-872. 2019/11/09. DOI: 10.1016/j.jgo.2019.09.013.
32. Hornor MA, Ma M, Zhou L, et al. Enhancing the American College of Surgeons NSQIP Surgical Risk Calculator to Predict Geriatric Outcomes. *J Am Coll Surg* 2020; 230: 88-100.e101. 2019/11/02. DOI: 10.1016/j.jamcollsurg.2019.09.017.
33. Mueller A, Spies CD, Eckardt R, et al. Anticholinergic burden of long-term medication is an independent risk factor for the development of postoperative delirium: A clinical trial. *J Clin Anesth* 2020; 61: 109632. 2019/11/02. DOI: 10.1016/j.jclinane.2019.109632.
34. Bruijnen CP, Heijmer A, van Harten-Krouwel DG, et al. Validation of the G8 screening tool in older patients with cancer considered for surgical treatment. *J Geriatr Oncol* 2021; 12: 793-798. 2020/11/12. DOI: 10.1016/j.jgo.2020.10.017.
35. Gearhart SL, Do EM, Owodunni O, et al. Loss of Independence in Older Patients after Operation for Colorectal Cancer. *J Am Coll Surg* 2020; 230: 573-582. 2020/03/30. DOI: 10.1016/j.jamcollsurg.2019.12.021.

36. Ristescu AI, Pintilie G, Moscalu M, et al. Preoperative Cognitive Impairment and the Prevalence of Postoperative Delirium in Elderly Cancer Patients-A Prospective Observational Study. *Diagnostics (Basel)* 2021; 11 2021/02/14. DOI: 10.3390/diagnostics11020275.
37. National Institute for Health and Care Excellence (NICE). *Delirium: prevention, diagnosis and management*. 2010. London, UK: NICE.
38. Bush SH, Lawlor PG, Ryan K, et al. Delirium in adult cancer patients: ESMO Clinical Practice Guidelines. *Annals of Oncology* 2018; 29: iv143-iv165. DOI: 10.1093/annonc/mdy147.
39. Montroni I, Rostoft S, Spinelli A, et al. GOSAFE - Geriatric Oncology Surgical Assessment and Functional rEcovery after Surgery: early analysis on 977 patients. *J Geriatr Oncol* 2020; 11: 244-255. DOI: 10.1016/j.jgo.2019.06.017.
40. Smith PJ, Attix DK, Weldon BC, et al. Executive function and depression as independent risk factors for postoperative delirium. *Anesthesiology* 2009; 110: 781-787. 2009/03/28. DOI: 10.1097/aln.0b013e31819b5bc2.
41. Austin CA, O’Gorman T, Stern E, et al. Association Between Postoperative Delirium and Long-term Cognitive Function After Major Nonemergent Surgery. *JAMA Surgery* 2019; 154: 328-334. DOI: 10.1001/jamasurg.2018.5093.
42. Salvi F, Young J, Lucarelli M, et al. Non-pharmacological approaches in the prevention of delirium. *Eur Geriatr Med* 2020; 11: 71-81. DOI: 10.1007/s41999-019-00260-7.
43. Marcantonio ER, Flacker JM, Wright RJ, et al. Reducing Delirium After Hip Fracture: A Randomized Trial. *J Am Geriatr Soc* 2001; 49: 516-522. DOI: 10.1046/j.1532-5415.2001.49108.x.
44. Burton JK, Craig LE, Yong SQ, et al. Non-pharmacological interventions for preventing delirium in hospitalised non-ICU patients. *Cochrane Database Syst Rev* 2021; 7: Cd013307. 2021/07/20. DOI: 10.1002/14651858.CD013307.pub2.
45. Hosie A, Siddiqi N, Featherstone I, et al. Inclusion, characteristics and outcomes of people requiring palliative care in studies of non-pharmacological interventions for delirium: A systematic review. *Palliat Med* 2019; 33: 878-899. DOI: 10.1177/0269216319853487.
46. Monacelli F, Signori A, Prefumo M, et al. Delirium, Frailty, and Fast-Track Surgery in Oncogeriatrics: Is There a Link? *Dement Geriatr Cogn Dis Extra* 2018; 8: 33-41. 2018/03/09. DOI: 10.1159/000486519.
47. Malik U, Alam Z, Loucks A, et al. Downstream consequences of abnormal cognitive screening in older adults seen pretreatment in a geriatric oncology clinic. *J Geriatr Oncol* 2020; 11: 784-789. 2019/11/12. DOI: 10.1016/j.jgo.2019.10.022.
48. Korc-Grodzicki B, Root JC and Alici Y. Prevention of post-operative delirium in older patients with cancer undergoing surgery. *J Geriatr Oncol* 2015; 6: 60-69. DOI: 10.1016/j.jgo.2014.10.002.
49. Partridge JSL, Crichton S, Biswell E, et al. Measuring the distress related to delirium in older surgical patients and their relatives. *International Journal of Geriatric Psychiatry* 2019; 34: 1070-1077. DOI: 10.1002/gps.5110.
50. Dewar B, Bond P, Miller M, et al. *Staff, patients and families experiences of giving and receiving care during an episode of delirium in an acute hospital care setting*. 2013. Scotland: Healthcare Improvement Scotland.
51. Nikooie R, Neufeld KJ, Oh ES, et al. Antipsychotics for Treating Delirium in Hospitalized Adults: A Systematic Review. *Annals of Internal Medicine* 2019; 171: 485-495. DOI: 10.7326/m19-1860.
52. Waszynski CM, Milner KA, Staff I, et al. Using simulated family presence to decrease agitation in older hospitalized delirious patients: A randomized controlled trial. *Int J Nurs Stud* 2018; 77: 154-161. 2017/11/04. DOI: 10.1016/j.ijnurstu.2017.09.018.
53. Elimimian EB, Elson L, Stone E, et al. A pilot study of improved psychological distress with art therapy in patients with cancer undergoing chemotherapy. *BMC Cancer* 2020; 20: 899. 2020/09/24. DOI: 10.1186/s12885-020-07380-5.
54. O’Hanlon S and Inouye SK. Delirium: a missing piece in the COVID-19 pandemic puzzle. *Age Ageing* 2020; 49: 497-498. 2020/05/07. DOI: 10.1093/ageing/afaa094.

55. Wei P, Lyu W, Wan T, et al. COVID-19: a novel risk factor for perioperative neurocognitive disorders. *Br J Anaesth* 2021; 127: e113-e115. 2021/07/17. DOI: 10.1016/j.bja.2021.06.016.
56. Inouye SK. The Importance of Delirium and Delirium Prevention in Older Adults During Lockdowns. *JAMA* 2021; 325: 1779-1780. DOI: 10.1001/jama.2021.2211.
57. Helms J, Kremer S, Merdji H, et al. Neurologic Features in Severe SARS-CoV-2 Infection. *N Engl J Med* 2020; 382: 2268-2270. 2020/04/16. DOI: 10.1056/NEJMc2008597.
58. Pun BT, Badenes R, Heras La Calle G, et al. Prevalence and risk factors for delirium in critically ill patients with COVID-19 (COVID-D): a multicentre cohort study. *The Lancet Respiratory Medicine* 2021; 9: 239-250. DOI: 10.1016/S2213-2600(20)30552-X.