SPC 160107

# REVIEW

# Postoperative delirium in older patients with cancer: the role of psychological distress and social support

AQ2

Shane O'Hanlon<sup>a,b</sup>, Mark Baxter<sup>c,d</sup>, and Annmarie Hosie<sup>e,f,g</sup>

### **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 postoperative delirium in older people with cancer, delirium incidence ranged from 8 to 19.8%. Poor social support and high levels of distress are implicated in the development of postoperative 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

Postoperative 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

aged, cancer, delirium, psychological distress, social support

# INTRODUCTION

A05 Delirium is an acute neurocognitive disorder characterized 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 postoperative 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 healthcare support. Delirium also increases length of hospital stay, mortality and healthcare costs [2,6].

This review will discuss the relationship between psychological distress, social support and postoperative 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

Curr Opin Support Palliat Care 2021, 14:000-000 DOI:10.1097/SPC.0000000000000588

<sup>&</sup>lt;sup>a</sup>Department of Geriatric Medicine, St Vincent's University Hospital, <sup>b</sup>University College Dublin, Dublin, Ireland, <sup>c</sup>Division of Molecular and Clinical Medicine, School of Medicine, University of Dundee, <sup>d</sup>Tayside Cancer Centre, Ninewells Hospital, NHS Tayside, Dundee, United Kingdom, <sup>e</sup>School of Nursing and Midwifery, Sydney, The University of Notre Dame Australia, <sup>f</sup>St Vincent's Health Network Sydney, Darlinghurst and <sup>g</sup>IMPACCT – Improving Palliative, Aged and Chronic Care through Research and Translation, University of Technology Sydney, Ultimo, AQ3 New South Wales, Australia

Correspondence to Dr Shane O'Hanlon, Department of Geriatric Medi-AQ4 cine, St Vincent's University Hospital, Dublin, Ireland. Tel: +353 12214549; e-mail: shaneohanlon@svhg.ie

# Geriatric oncology

# **KEY POINTS**

- Distress and social support are associated with postoperative delirium.
- Older people with cancer are at particular risk of delirium, and require specific assessment for distress and social support.
- Older patients undergoing surgery for cancer should have comprehensive geriatric assessment and tailored multicomponent interventions to reduce the risk of postoperative complications such as delirium.
- In patients who develop postoperative delirium, management should involve treatment of identified causes, supportive communication and ongoing multicomponent interventions.
- 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.

recent evidence. Our search strategy used key words 'psychological distress', 'social support', 'delirium', 'surgery' and 'geriatric' in MEDLINE. Fifty-six articles were screened, of which 24 were excluded as they were not relevant. Of the 32 articles 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 summarized in Table 1. No trials examining the impact of interventions for distress or social support on 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 1211 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 healthcare, suggesting that these issues are under-recognized and rarely addressed in clinical practice.

Table 1. Summ	ary of recer	it studies of postoperati	ive delirium in older	patients with cancer			
Ref.	Country	Aim	Design	Population/setting	Intervention/interest	Results/findings	Authors' conclusions
Pathophysiology Amgarth-Duff <i>et al.</i> [28]	Australia	To identify overlap between biomarkers associated with deliriurr and biomarkers associated with advanced cancer-relate- clinical issues (i.e. prognosis; cognitive impairment, anorexia cancer-related fatigue, and sickness behaviour)	к г	Eligible: Studies of adult participants with delirium, cancer prognosis or advanced cancer-related issue of interest Included: Sample sizes 7– 2456, 55% male; of 90 studies reporting mean age, overall weighted mean age, overall weighted mean age, overall median age was 54.5 years	Body fluid biomarkers associated with both delirium and advanced cancer-related issues	151 studies reviewed 141 biomarkers were measured in both delirium and advanced cancer studies 24 biomarkers were positively associated with delirium, cancer prognosis or an advanced cancer issue in $\geq 1$ study Six delirium studies reported participants with cancer (14-100%): no cancer participants with cancer (14-100%): no cancer study reported participants with delirium were CRP ( $n = 3$ ) and IL6 ( $n = 3$ ) Grently variable quality of study reporting	Large overlap between biomarkers associated with delirium and those associated with advanced cancer, but heterogeneity and variable quality of included study reports allowed no firm conclusions about true overlap. More robust conduct and reporting of delirium biomarker studies would support better understanding of its pathophysiology in the context of coexisting conditions, including advanced cancer.

Table 1 (Continued)						
Ref. Country	/ Aim	Design	Population/setting	Intervention/interest	Results/findings	Authors' conclusions
Epidemiology (risk factors, occ Pollock <i>et al.</i> [31] USA	urrence and outcomes) To assess a new geriatric assessment (the Vulnerable Elderly Surgical Pathways and Outcomes Assessment - VESPA) ability to predic postoperative surgical complications, four geriatric complications (delirium, pressure ulcer falls and malnutrition), LOS, and postdischarge needs among older adults undergoing oncologic surgeries	Cohort study	Eligible: Consecutive patients ≥70yrs seen in a preoperative clinic in a large university health system for planned elective surgery July 2008 - January 2011 Sample: N = 476, mean age 78.2 years (range 70–97), 48% men; surgical procedures for malignancies: dermatologic (28%), GIT (19%), urological (19%), breast (16%), and head and neck (13%); baseline assessment: 39% reported they did not think they could manage their own care after discharge, 39% had impaired mobility, 13% had impaired function, 11% screened positive for depression, 6% screened positive for cognitive impairment	VESPA administered by a surgical physician assistant within 3 months prior to surgery and included 14 questions about: difficulty with BADL/IADIs; mobility impairment screen positive if any abnormality on TUG tes $> 20$ secs. or at last one fal in past year; Mini-cog test to screen cognitive impairment (cutoff sore of $\leq 3$ out of 5); depression screen using PHQ-2 (modified to be verbal; recall last month, no 2 weeks; and yes/no answers instead of the 4-part responses) VESPA scores range 0-20, higher scores = greater risk of PO complications and cutoff score of $\geq 9$ has 68% sensitivity and 76% specificity in predicting increased risk of PO complications in general geriatric population with AUC of 0.76.	Compared to patients with VESPA scores <9, patients with VESPA scores >9 had: longer LOS (mean 6.6 vs. 2dys; $P < 0.001$ ), more geriatric complications f (39.5 vs. 5.7%; $P < 0.001$ ; t delirium 13.5 vs. 1.5%, I P < 0.001), more surgical complications (29.5 vs. 11.8%; $P < 0.001$ ), more geriatric postdischarge needs (76.0 vs. 31.7%; P < 0.001), including new f functional dependence at discharge (51.0 vs. 9.2%; P < 0.001), including new f functional dependence at discharge (51.0 vs. 9.2%; P < 0.001), and inability to return to prior living situation due to care needs (22 vs. 6.9%; $P < 0.001$ ). Logistic regression model adjusted for age: each additional VESPA scale point was associated with increased probability of geriatric complications (OR = 1.3 [95% CI = 1.2-1.4] P < 0.001), surgical complications (OR = 1.2 [95% CI = 1.1-1.2]; P < 0.001), and geriatric postdischarge needs (OR = 1.3 [95% CI = 1.2-1.3]; P < 0.001; AUC 0.7-0.83 and Hosmer-Lemeshow goodness of fit test range 0.4-0.82	The VESPA identifies older patients with cancer who are at risk for postoperative surgical and geriatric complications and functional needs at discharge.

AQ1

SPC 160107

Postoperative delirium in older patients O'Hanlon et al.

ω

lef.	Country	Aim	Design	Population/setting	Intervention/interest	Results/findings	Authors' conclusions
Hornor <i>et al.</i> [32]	US	To enhance the existing American College of Surgeons (ACS) NSQIP Surgical Risk Calculator (SRC) with functionality to predict geriatric- specific outcomes	Observational	38048 patients ≥65 years undergoing 197 unique operations across 10 surgical subspecialties; patients who were 'totally dependent' preoperatively were excluded	Multiinstitutional data registry 200 prospectively collected variables And measure rates of four geriatric specific postoperative outcomes; pressure ulcer, delirium, new mobility aid use and functional decline	The rate of postoperative delirium was 10.5% Models with and without geriatric risk factors demonstrated excellent performance (C statistic >0.8) with inclusion of geriatric risk factors improving performance Of the 21 ACS NSQIP variables, being male, older age, sepsis, being current smoker, not being independent and having disseminated cancer were the strongest risk predictors of delirium	The ACS NSQIP SRC can predict four unique outcomes germane to geriatric surgical patients, with improvement of predictive capability after accounting for geriatric risk factors
Mueller <i>et al.</i> [33]	Germany	To determine the association between PO anticholinergic load (as per the anticholinergic drug scale - ADS) and POD in cancer patients aged >65 years	Retrospective sub- study (cohort) of a randomised controlled trial	Eligible: Patients aged $\geq 65$ years having surgery for gastrointestinary, genitourinary or gynaecological cancers; exclusions were MMSE <24, insufficient German, refused data archiving/ retrieval, had $\geq 2$ concurrent carcinomas, underwent emergency surgery, life expectancy <2 months, or current participation in another trial Sample: N=651, mean (SD) age 71.8 (4.9) years male 68.5%; mean MMSE 28.6 (SD, 4.9), 60 patients <27; gastrointestinal cancer (n=204), gynaecological cancer (n=92) and urological cancer (n=355); 89.7% had general anoesthesia. Maximum ADS score = 6; median n. daily drugs = 3 (IQR = 3; range 0–15). 28% had > 5 chronic medication, ADS score $\geq 1$ in 105 patients. Most (88.6%) had premedication: midazolam (82%), remaining received clonidine, promethazine, amitriptyline and/or other benzodiazepines; 92 patients received clonidine and/or haloneridal as	ADS classifies anticholinergic activity of >300 medications; scores activity levels from '0' (no anticholinergic activity) to '3' (highest anticholinergic activity); then sums the scores. ADS ≥ 1 was a positive score; ADS was also evaluated continuously Preoperatively administered benzodiazepines were included as covariates, not in the ADS	<ul> <li>POD was diagnosed in 10.1% of patients</li> <li>In multivariate analysis:</li> <li>2.2-fold higher odds for development of POD with positive ADS (OR 2.22; 95% CI 1.21–4.04)</li> <li>Each ADS point increase was independently associated with 1.5-fold higher risk of POD (OR 1.5; 95% CI 1.09–2.05; P=0.01; Fig. 2)</li> <li>Age (per year OR 1.06; CI 95% CI 1.01–1.11; P=0.03) and ASA state (OR 2.16; 95% CI 1.22–3.83; P=0.01), and ICU stay (no vs. yes OR 2.8; 95% CI 1.57–4.998; P&lt;0.01) were also independently associated with POD</li> <li>No association found between preoperative midazolam and POD</li> </ul>	The ADS may represent an additional screening tool to detect increased risk for POD in elderly cancer patients. The ADS is feasible, noninvasive and more cost-effective than laboratory-based analysis. Considering the inconsistencies in current literature, further well designed studies are warranted.

4

Geriatric oncology

Table 1 (Contin	ued)						
Ref.	Country	Aim	Design	Population/setting	Intervention/interest	Results/findings	Authors' conclusions
Bruijnen <i>et al.</i> [34]	The Netherlands	To investigate the differences in postoperative outcomes between fit and frail patients classified by the Geriatric-8	Prospective recruitment, retrospective data collection	Eligible: Patients aged 70 and older requiring elective surgical treatment for a suspected solid malignancy Sample: N=143; mean age 77 (63-100), male 56%.	All patients had a CGA performed preoperatively.	Delirium occurred in 8% (3 vs. 13%, P=0.05) Patients with an impaired G8 had a significantly prolonged hospital stay, higher rate of delirium, and higher 1-year mortality	Patients with an impaired G8 are more at risk for a complicated recovery from surgery and have a higher incidence of delirium.
Gearhart <i>et al.</i> [35]	I US	To determine the impact of frailty and CI on loss of independence (LOI) among colorectal cancer patients	Retrospective	Eligible: Patients undergoing surgery for colorectal cancer Sample: N = 1676; median age 75 (69–81), male 50%; 7% reported CI preoperatively	Risk factors in an older cancer population for loss of independence, length of stay, and 30-day postoperative complication and readmission.	Postoperative delirium occurred in 9.6% of patients and 16.8% of patients aged 80 years and older Risk factors predictive of loss of independence at 30 days included a preoperative mobility aid, postoperative delirium (OR 3.02 (2.00– 4.57), P<0.001), and the need for a new mobility aid Postoperative delirium significantly increased length of stay (OR 1.20 (1.07−1.35), P=0.002)	One in five older patients undergoing an operation for colorectal cancer experience LOI and risk factors include a decline in cognition (including development of postoperative delirium) and mobility.
Ristescu <i>et al.</i> [36]	Romania	To document prevalence of preoperative cognitive impairment (PCI) in cancer patients and to assess the relationship with postoperative delirium (POD) in older adults.	Prospective observational	Eligible: 65 years and older Solid tumour cancer diagnosis Elective surgery Postoperative admission. Excluded if brain metastasis, preoperative diagnosis of dementia, emergency or day surgery, transfer to ICU. Sample: N=131; mean age 72.1 years; prior CI 51.9%	Risks factors for POD in older patients with cancer undergoing surgery.	Postoperative delirium incidence was 19.8%. In those with PCI, POD was 38.9%. Age of patients who developed POD was significantly higher. In multivariate analysis, mini- Cog score 0.3, positive clock draw, word recall, preoperative renal function, use of morphine or metoclopramide and postoperative pain score were predictors of POD/	PCI had a high prevalence and predicted the emergence of POD.

BADL/IADLs, Basic and Instrumental Activities of Daily Living; CCI, Charlson Comorbidity Index; CI, cognitive impairment; dys, days; GIT, gastrointestinal; LOS, length of stay; PCU, palliative care unit; PHQ-2, Patient Health Questionnaire 2; PO, postoperative; POD, postoperative delirium; PPS, Palliative Performance Scale; RCT, randomized controlled trial; SAE, serious adverse event; SR, systematic review; TUG test, Time-Up-and-Go.

ы

Table 2. Potential sources of distress for older people with cancer in the perioperative period				
Environmental	Change in location, e.g., admission to hospital Disorientation Social dislocation through isolation/separation from family, friends and community High activity and noisy environment, e.g., ICUs Communication difficulties Physical restraint			
Physiological	Immobility Pain or discomfort Fasting Dehydration Sleep deprivation Trauma Substance abuse or withdrawal Sensory deprivation (e.g. hearing or visual impairment from loss of usual aids)			
Psychological	Fear Anxiety Incomprehension Shame/guilt Psychiatric conditions including schizophrenia, depression and bipolar disorder			

### **Geriatric oncology**

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 (OR) of 3.119 [95% confidence interval (95% CI): 1.144–8.500, P = 0.026 [12]. A recent small study in cancer patients (n = 91) demonstrated similar findings, with an OR of 4.37 (95% CI: 1.051-18.178, P = 0.043) for those with HADS-A more than 7 preoperatively [13<sup>•</sup>]. 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 these have 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 postoperative complications [15]. Unfortunately, the study did not assess for delirium, although 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.

Although there is considerably more research on distress and delirium, here too there is room to build the evidence, especially regarding intervention. 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 [18,19,20<sup>•</sup>]. 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

## **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 recognized is that distress is hypothesized 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 agerelated 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]. Although 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 cancerrelated distress in older adults, with patient-reported measures likely more reliable [24<sup>•</sup>].

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 coexisting 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 patients [29] 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 to 19.8%, with higher incidence in patients with preoperative 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 38000 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 sex. 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 (OR 2.57; 95% CI 2.29–2.88). This relationship has already been well recognized and thus preoperative 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<sup>•</sup>]. It also has an effect on broader health outcomes. Gearhart *et al.* [35] performed an observational study examining outcomes in older patients (median age 75 years) having elective or emergency surgery for colorectal cancer. Loss of independence upon discharge was seen in 20.5% of patients, and was strongly associated with preoperative cognitive SPC 160107

# **Geriatric oncology**

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 randomized controlled trials of nonpharmacological interventions to prevent delirium (predominantly targeting sleep, vision and hearing, hydration, communication, orientation, cognition and mobility) in hospitalized patients outside intensive care units found lower delirium incidence compared with usual care [10.5 vs. 18.4%, risk ratio 0.57 (95% CI 0.46-0.71)] [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 nonpharmacological multicomponent interventions help to mitigate distress or prevent functional decline.

A review of the literature that included broader study types examining nonpharmacological 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 preexisting 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].

Although 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. [47] followed a group of older patients with cancer and a positive Mini-COG screen to examine downstream consequences. They found that where patients were identified as being at risk of delirium, preventive 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 preventive 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]. Recognizing 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 prerecorded and positively worded video messages reduced agitation in older hospitalized patients with delirium, compared with 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 recognized 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. In addition, 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 depersonalization 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 POD. Management options for delirium are limited, so emphasis should be on prevention, with risk assessments and individualized patient-centred care planning. Recent published research has focused on measuring POD 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.

## Acknowledgements

None.

## **Financial support and sponsorship**

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

## **Conflicts of interest**

The authors report no conflicts of interest.

### REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interestof outstanding interest
- American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Fifth ed. (DSM-5) Arlington, VA: American Psychiatric Publisher; 2013.
- 2. Jin Z, Hu J, Ma D. Postoperative delirium: perioperative assessment, risk reduction, and management. Br J Anaesth 2020; 125:492–504.
- El Majzoub I, Abunateesa H, Cheaito R, et al. Management of altered mental status and delirium in cancer patients. Ann Palliat Med 2019; 8:728-739.
- 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. Int J Nurs Stud 2021; 122.104030.
- 5. Maldonado JR. Delirium pathophysiology: an updated hypothesis of the
- etiology of acute brain failure. Int J Geriatr Psychiatry 2018; 33:1428–1457. 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.
   Psychological Distress MeSH Descriptor Data 2021. https://meshb.nlm.nih.gov/record/ui?ui=D000079225 [Accessed 22 October 2021]
- 8. Social Support MeSH Descriptor Data 2021. https://weshb.nlm.nih.gov/ record/ui?ui=D012944 [Accessed 25 October 2021]
- Trevino KM, Nelson CJ, Saracino RM, et al. Is screening for psychosocial risk factors associated with mental healthcare in older adults with cancer undergoing surgery? Cancer 2020; 126:602–610.
- 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.
- 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.
- 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.
- 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.

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 more than seven (OR=4.370, 95% Cl=1.051-18.178, P=0.043) predicted delirium onset.

- 14. Cancer program standards: ensuring patient-centered care. Chicago, IL: American College of Surgeons Commission on Cancer; 2016.
- 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.
- 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.
- 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:e13166.
- O'Malley G, Leonard M, Meagher D, et al. The delirium experience: a review. J Psychosom Res 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. Psychooncol 2017; 26:291–300.
- 20. Williams ST, Dhesi JK, Partridge JSL. Distress in delirium: causes, assess

ment and management. Eur Geriatr Med 2020; 11:63-70.
 A narrative review focusing on distress in delirium and its impact on older patients.
 Although not specific to cancer patients, it provides an overview of distress assessment tools and outlines emerging management strategies.

- 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.
- 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 Med 2021; 19:143.

1751-4258 Copyright © 2021 Wolters Kluwer Health, Inc. All rights reserved.

# SPC 160107

#### **Geriatric oncology**

- Vyas S, Rodrigues AJ, Silva JM, et al. Chronic stress and glucocorticoids: from neuronal plasticity to neurodegeneration. Neural Plast 2016; 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.

This is a survey of 238 patients with colon or rectal cancer, to investigate characteristics associated with high distress levels. This study found that stress biomarkers may not be more clinically useful than patient-reported measures in assessing distress among colorectal cancer patients.

- Wilson JE, Mart MF, Cunningham C, et al. Delirium. Nat Rev Dis Primers 2020; 6:90.
- 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.
- 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.
- 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.
- Shah S, Weed HG, He X, et al. Alcohol-related predictors of delirium after major head and neck cancer surgery. Arch Otolaryngol Head Neck Surg 2012; 138:266-271.
- 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.
- 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.
- 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. e1.
- 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.
- 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.
- 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.
- 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.
- National Institute for Health and Care Excellence (NICE). Delirium: prevention, diagnosis and management. London, UK: NICE; 2010.
- Bush SH, Lawlor PG, Ryan K, *et al.* Delirium in adult cancer patients: ESMO Clinical Practice Guidelines. Ann Oncol 2018; 29:iv143-iv165.
   Montroni I, Rostoft S, Spinelli A, *et al.* GOSAFE - Geriatric Oncology Surgical
- 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.
- Smith PJ, Attix DK, Weldon BC, et al. Executive function and depression as independent risk factors for postoperative delirium. Anesthesiology 2009; 110:781-787.

- Austin CA, O'Gorman T, Stern E, et al. Association between postoperative delirium and long-term cognitive function after major nonemergent surgery. JAMA Surg 2019; 154:328–334.
- Salvi F, Young J, Lucarelli M, et al. Nonpharmacological approaches in the prevention of delirium. Eur Geriatr Med 2020; 11:71-81.
- Marcantonio ER, Flacker JM, Wright RJ, et al. Reducing delirium after hip fracture: a randomized trial. J Am Geriatr Soc 2001; 49:516–522.
   Burton JK, Craig LE, Yong SQ, et al. Nonpharmacological interventions for
- Burton JK, Craig LE, Yong SQ, et al. Nonpharmacological interventions for preventing delirium in hospitalised non-ICU patients. Cochrane Database Syst Rev 2021; 7:Cd013307.
- 45. Hosie A, Siddiqi N, Featherstone I, *et al.* Inclusion, characteristics and outcomes of people requiring palliative care in studies of nonpharmacological interventions for delirium: a systematic review. Palliat Med 2019; 33:878-899.
- 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.
- 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.
- Korc-Grodzicki B, Root JC, Alici Y. Prevention of postoperative delirium in older patients with cancer undergoing surgery. J Geriatr Oncol 2015; 6:60-69.
- Partridge JSL, Crichton S, Biswell E, *et al.* Measuring the distress related to delirium in older surgical patients and their relatives. Int J Geriatr Psychiatry 2019; 34:1070–1077.
- 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. Scotland: Healthcare Improvement Scotland; 2013.
- Nikooie R, Neufeld KJ, Oh ES, et al. Antipsychotics for treating delirium in hospitalized adults: a systematic review. Ann Intern Med 2019; 171: 485-495.
- 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.
- 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.
- O'Hanlon S, Inouye SK. Delirium: a missing piece in the COVID-19 pandemic puzzle. Age Ageing 2020; 49:497–498.
- 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.
- Inouye SK. The importance of delirium and delirium prevention in older adults during lockdowns. JAMA 2021; 325:1779–1780.
- 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.
- 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. Lancet Respir Med 2021; 9:239–250.

### **Uncited reference**

[22].

AQ6



Curr Opin Support Palliat CareCurrent Opinion in Supportive and Palliative Care Typeset by Thomson Digital for Wolters Kluwer

Dear Author,

During the preparation of your manuscript for typesetting, some queries have arisen. These are listed below. Please check your typeset proof carefully and mark any corrections in the margin as neatly as possible or compile them as a separate list. This form should then be returned with your marked proof/list of corrections to the Production Editor.

# **QUERIES:** to be answered by AUTHOR/EDITOR?

QUERY NO.	QUERY DETAILS	RESPONSE
<aq1></aq1>	As per style, the short title/running head can have a maximum of 65 characters including spaces and author names, and abbreviations/acronyms only as exceptions. Please check the suggested short title for correctness.	F
<aq2></aq2>	Please confirm whether surnames/family names (red) have been identified correctly in the author byline.	<b>P</b>
<aq3></aq3>	Please check and confirm authors' affiliation for correctness.	<b>P</b>
<aq4></aq4>	Please provide zip code for city in correspondence address.	<b>F</b>
<aq5></aq5>	Please check all section heading for correctness.	<b>F</b>
<aq6></aq6>	Please provide in-text citation for ref [22].	<b>F</b>
<aq7></aq7>	Please provide name of authors/ organization for refs [7,8].	
<aq8></aq8>	As the following references are outside the review period, bullets and annotations have been deleted as per style. Refs. [10].	<b>F</b>
<aq9></aq9>	Please provide page range for refs. [11,36].	<b>P</b>