# Update on Perioperative Delirium



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#### **KEYWORDS**

Delirium • Frailty • Cognitive impairment • Anesthesia • Geriatric

## **KEY POINTS**

- Risk factors for frailty are similar to risk factors for postoperative delirium (POD).
- Patients identified as frail could be referred for a preoperative comprehensive geriatric assessment and geriatricians could contribute to postoperative management with multidisciplinary teams executing evidence-based delirium prevention bundles.
- POD has been found to be associated with worse functional recovery in older surgical patients.
- After decades of observational studies, randomized trials, meta-analyses, and systematic reviews, the evidence has never been strong enough to support the choice of regional over general anesthesia for older surgical patients to prevent POD.
- Patients with mild cognitive impairment who have an episode of delirium have worse cognitive decline after surgery compared with patients with mild cognitive impairment who do not have an episode of delirium.

## INTRODUCTION

Postoperative delirium (POD) is currently recognized as the most common complication in older surgical patients. Although delirium is common, it is not part of the normal physiology of aging. Although it is an unwanted postoperative outcome, it is also a symptom of an aging brain and a cause of other downstream outcomes. Delirium research has rapidly increased in the past 25 years. This update on perioperative delirium highlights 3 important areas of rapid development. These areas include the relationship between delirium and frailty, the comparison of different types of

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anesthesia on incident POD, and an improved description of the long-term cognitive consequences of POD.

# FRAILTY AND COGNITIVE IMPAIRMENT

The concept of frailty has been present throughout the history of medicine but only during the past 25 years has frailty come to be precisely defined and measured. Frailty describes the medical condition in which a person is vulnerable to stressors with little resilience or the ability to fully recover due to the decline in function across multiple organ systems.<sup>1</sup> It is accompanied by physical weakness and often by cognitive impairment. Cognitive impairment and frailty frequently coexist, and one is a risk factor for the other. Cognitive frailty is defined as physical frailty accompanied by cognitive impairment but without dementia and was first proposed by the International Academy of Nutrition and Aging and the International Association of Gerontology and Geriatrics in 2013.<sup>2,3</sup> Expanding frailty to a multidimensional syndrome incorporates the vulnerability of older adults associated with cognitive impairment.<sup>2,4</sup> Cognitive frailty describes patients with cognitive vulnerability and reduced resilience and represents cognitive impairment caused by physical conditions and possibly an antecedent to neurodegenerative disease.<sup>2</sup> Physical and cognitive frailty have been associated with decline and dysfunction in the frontal cognitive domains, such as executive function and attention.<sup>2,5</sup>

# FRAILTY AND AGING

Although the prevalence of frailty and cognitive frailty increase with age, frailty differs from healthy aging. Healthy aging is accompanied by physiologic changes but these changes do not lead to the severe depletion of reserve and vulnerability even to small stressors.<sup>1</sup> Frailty is present in anywhere from 11% to 59% of community-dwelling adults.<sup>6</sup> It has increased prevalence among people with end-stage renal disease and malignancies.<sup>6</sup> Frailty is increased in women, people with lower socioeconomic status, and in ethnic and racial minorities.<sup>6</sup> Specifically, cognitive frailty is present in 10.7% to 22.0% of patients and 1.0% to 4.4% in community-dwelling adults.<sup>7</sup>

## POSTOPERATIVE DELIRIUM AND FRAILTY

Because many of the risk factors for frailty are similar to risk factors for POD, frailty has been investigated as a risk factor for delirium. A recent meta-analysis included studies investigating a relationship between preoperative frailty and POD in patients aged at least 65 years, undergoing elective, nonemergent inpatient surgery.<sup>8</sup> Nine studies involving both cardiac (n = 6) and noncardiac surgery (n = 3) were included in the analysis. The meta-analysis included 1008 subjects with a mean age of 74 years of whom 42% were women. Preoperative frailty was present in 18% to 56% of subjects. Overall, the association of POD in frail versus nonfrail patients was significant (odds ratio [OR] 2.14; 95% confidence interval (CI) of 1.43-3.19).<sup>8</sup> A subsequent meta-analysis included retrospective studies of patients who underwent elective and emergency surgery, and all adult patients regardless of age but did not include studies without multivariate analysis.<sup>9</sup> A total of 15 studies and 3250 subjects were analyzed. Preoperative frailty was identified in 27.1% of subjects and was significantly associated with POD compared with nonfrail patients (OR 3.23; 95% CI: 2.56 to 4.07).<sup>9</sup> The authors found that the association between frailty and POD remained significant in multiple subgroup analyses of age, elective or emergency surgery, cardiac or noncardiac surgery, country of the study, instruments used for identification of frailty or POD, or quality score of the study.9

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Similarly, a strong association between frailty and in-hospital delirium in nonsurgical patients has been shown. A recent meta-analysis found that frail medical patients had an OR of 3.61 (95% CI 3.61–7.89) for delirium, and frail patients with emergency or critical illness had an OR of 6.66 (95% CI 1.41–31.47) for delirium.<sup>10</sup>

#### FRAILTY SCALES AND INSTRUMENTS

Frailty can be screened and diagnosed by various tools and instruments. There are 2 main approaches to determining frailty: assessing for a frailty phenotype and assessing for accumulation of medical diseases and deficits. The frailty phenotype first proposed by Fried and Walston comprises 5 components that synergistically cause deterioration: weakness, slowness, fatigue, low activity, and weight loss.<sup>11</sup> The cumulation of medical diseases and deficits approach developed at a similar time and is determined by a count of the number of diseases and medical conditions across all organ systems.<sup>12</sup> Some of the most common phenotype instruments are the fatigue, resistance, ambulation, illness, loss of weight (FRAIL) scale, the Clinical Frailty Scale, the Frailty Phenotype, Gait Speed, and the Gérontopôle Frailty Screening Tool. 11,13-16 The Frailty Phenotype, Gait Speed, and Gérontopôle Frailty Screening Tool all require in-person assessments given the need for the objective measurement of grip strength and gait speed. Although having an objective measurement of strength and resistance has advantages, many preoperative clinics perform patient assessments over the phone limiting the ability to use these types of instruments. Similarly, the Clinical Frailty Scale requires a comprehensive assessment by a provider and is not meant to be performed over the phone.

Alternatively, the FRAIL scale can be administered either over the phone or inperson as a brief questionnaire. Table 1 reviews the different Frailty Scales and Indices. The accumulation of deficit approach does lend itself to screening either during patient history taking or via electronic medical records. The frailty index (FI) first developed by Rockwood, includes assessing for 70 deficits in different organ systems.<sup>14,17</sup> When Rockwood compared his 2 methods, the Clinical Frailty Scale versus the FI in the Canadian Study of Health and Aging (CSHA) database, he found that the clinical frailty scale was easier to operationalize but the FI allowed adverse risk outcomes to be defined more precisely. Since the CSHA FI, other accumulation of deficit instruments have been developed, including the American College of Surgeons National Surgical Improvement Program (ACS-NSQIP) 11-point modified frailty index (mFI), ACS-NSQIP 5-point mFI, European Prospective Investigation into Cancer, and Nutrition-Potsdam Frailty Index.<sup>18-21</sup> The current ACS-NSQIP 5-point mFI has a maximum of 5 points. Patients receive one point for each of the following: (1) functional health status partially or totally dependent, (2) diabetes (noninsulin or insulin dependent), (3) history of chronic obstructive pulmonary disease (COPD) or current pneumonia, (4) congestive heart failure within 30 days, and (5) hypertension requiring medication.<sup>19</sup> This scale has been repeatedly found to be predictive of postoperative complications from the ACS-NSQIP database in a wide variety of surgeries. This 5 element mFI is especially amenable to be asked during a routine preoperative review of systems either through a questionnaire, over the phone, or in-person. Unfortunately, these frailty assessments do not include an assessment of cognition. Screening for cognitive impairment must be performed in addition to frailty screening to determine cognitive frailty.

Intervening on frailty before surgery is an emerging area of research. Patients identified as frail could be referred for a comprehensive geriatric assessment (CGA). A geriatric specialist performing a CGA assesses the complex interaction of a multitude of

Instrument	Elements Tested	Scoring	Requires In-Person
FRAIL Scale <sup>13</sup>	<ul> <li>5 Elements</li> <li>Fatigue: Have you been fatigued all or most of the time in the past 4 weeks?</li> <li>Resistance: Do you have difficulty walking up 10 steps without an aide?</li> <li>Ambulation: Do you have difficulty walking a few hundred yards/meters without aids?</li> <li>Illnesses: Do you have more than 4 medical conditions?</li> <li>Loss of weight: Has the patient lost 5% or more weight in the past year?</li> </ul>	1 point for each element 0: Robust 1–2: Prefrail 3–5: Frail	No
Clinical Frailty Scale <sup>14</sup>	<ul> <li>Clinical Judgment ranging from very fit to severely frail:</li> <li>1. Very fit = Robust, active, exercise regularly</li> <li>2. Well = no active disease, exercise or are active occasionally</li> <li>3. Managing well = controlled medical problems, not regularly active beyond routine walking</li> <li>4. Vulnerable = Not dependent for daily help, symptoms limit activities, slow</li> <li>5. Mildly Frail = More slowly, need help in high order ADL</li> <li>6. Moderately Frail = Need help with ADL, help with stairs, help with bathing</li> </ul>	Score 1 through 7 based on comprehensive assessment and clinical judgement An adjudication should occur by a multidisciplinary team	Yes or extensive clinical knowledge of the patient and their medical history
Frailty Phenotype <sup>11</sup>	5 Elements Weight loss: 10lbs or ≥5% within the past year Exhaustion: feeling tired all the time Low physical activity: inability to walk or needing assistance to walk Slowness: ≥19 s on a timed up and go test Weakness: weak grip strength	1 point for each element 0: Robust 1–2: Prefrail 3–5: Frail	Yes

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Gait Speed <sup>15</sup>	Measured gate speed over 4 m	Gait speed <0.8 m/s is Frail and <0.2 m/s is extreme frailty	Yes
Gérontopôle Frailty Screening	<ol> <li>6 Questions answered by provider:</li> <li>1. Does your patient live alone?</li> <li>2. Has your patient lost weight in the last 3 months?</li> <li>3. Has your patient found it more difficult to get around in the past 3 months?</li> <li>4. Does your patient complain of memory problems?</li> <li>5. Does your patient have a slow gate speed (&gt;4 s for 4 m)?</li> </ol>	If provider answers yes to any question, they are then to ask themselves, "Do you think your patient is frail?" Then the patient is asked if they agree to a comprehensive frailty assessment	Yes
ACS-NSQIP 5 element mFl	<ol> <li>5 elements to assess from interview or medical record</li> <li>1. Functional health status is partially or totally dependent</li> <li>2. Diabetes (noninsulin or insulin dependent)</li> <li>3. History of COPD or current pneumonia</li> <li>4. Congestive heart failure within 30 d</li> <li>5. Hypertension requiring medication</li> </ol>	Ordinal variable from 0 to 1. Calculated as number of positive elements divided number of elements assessed. Cut offs: 0 = Robust 0.2–0.4 = Prefrail 0.6–1 = Frail	No
ACS NSQIP 11 element mFl	<ol> <li>11 elements assessed</li> <li>1-5 of ACSONSQIP 5 element mFI</li> <li>6. History of MI within the past 5 months before surgery</li> <li>7. Previous percutaneous coronary intervention or cardiac surgery</li> <li>8. Impaired sensorium</li> <li>9. Transient ischemic attack</li> <li>10. Stroke</li> <li>11. Peripheral vascular disease with revascularization, amputation or rest pain</li> </ol>	Analyzed as an ordinal variable with stepwise increases from 0 through 0.09, 0.18, 0.27, 0.36, 0.45, 0.54, 0.63, 0.72, 0.81, and 1.0	No
CSHA FI	70 elements over all domains and organ systems	Ordinal variable from 0 to1. Calculated as number of positive elements divided number of elements assessed	No, but requires extensive clinical knowledge of the patient and their medical history

medical problems, frailty, nutritional status, psychological and social statuses, and modifiable risk factors. CGA can identify high-risk medications, including deliriogenic medications, and allow for safe tapering. CGA can also identify if a patient may benefit from preoperative nutritional optimization or prehabilitation.<sup>22</sup> There is equipoise in the literature regarding whether a CGA can reduce a patient's risk of delirium. A recent meta-analysis investigated the effect of a CGA on POD and found that of 6 studies (n = 1611), 3 had a significant reduction in delirium, and 3 did not.<sup>23</sup> The pooled meta-analysis showed no significant difference in patients who had a CGA and those who did not (OR 0.76 [95% CI 0.30–1.96]). However, when only randomized controlled trials were included, there was a significant reduction in delirium in patients with a CGA intervention compared with the control group (OR 0.45 [95% CI 0.29-0.70]). The authors found the absolute risk reduction for the prevalence of delirium was 8.28% (95% CI 3.9-12.6), and the number needed to treat was 13 to prevent a case of delirium.<sup>23</sup> Adding frailty as an inclusion criterion to those who received a CGA could potentially further decrease the number to treat by focusing on a higher risk population. The CGA should also continue into the postoperative period with multidisciplinary teams executing evidence-based delirium prevention bundles such as Hospital Elder Life Program and the ICU Liberation bundles in frail older patients at heightened risk for delirium compared with their robust counterparts.<sup>24,25</sup>

# TYPE OF ANESTHESIA AND POSTOPERATIVE DELIRIUM

Because there is no effective treatment of POD, identifying risk factors and preventive strategies is critically important. Many research studies have compared different anesthetic agents or various anesthetic modalities to identify a particular anesthetic method or drug that confers protection against POD. Identifying an anesthetic that is either protective or a risk factor could translate to changes in clinical practice that would stand to make a big difference in the outcomes of our older surgical patients. Here, we will briefly review recent literature comparing regional versus general anesthesia and the state of the evidence comparing the incidence of POD following total intravenous anesthesia (TIVA) versus inhalational anesthetics for maintenance of anesthesia.

## Regional Versus General Anesthesia and Postoperative Delirium

Investigations comparing regional versus general anesthesia on the incidence of POD in older surgical patients date back to the 1980s. A common hypothesis was that regional anesthesia would decrease the incidence of delirium by avoiding general anesthetics that target the central nervous system to produce loss of consciousness, amnesia, and analgesia. Many anesthetic agents and other medications concomitantly administered during general anesthesia have been shown to have neurotoxic, neuroinflammatory, or anticholinergic effects. Alternatively, regional anesthesia can provide adequate surgical anesthesia without the need for loss of consciousness while also avoiding other potentially deliriogenic medications such as antiemetics or cholinergic agents. However, after decades of observational studies, randomized trials, meta-analyses, and systematic reviews, the evidence was never strong enough to support the choice of regional over general anesthesia for older surgical patients to prevent POD.

Many investigations and scientific reviews focused on patients having surgical hip fracture repair because this operation is commonly performed under either general or regional anesthesia and this is an older patient population in which POD is a common complication. Multiple systematic reviews and meta-analyses suggested no significant difference in the incidence of delirium between the 2 groups.<sup>26</sup> One common

criticism of the studies comparing regional versus general anesthesia is the common use of sedation in the regional group. In these cases, it is not uncommon for patients to receive deep sedation with propofol and other anesthetic agents as an adjunct to the regional anesthetic. The criticism is that the varying levels of sedation could confound study results.

In 2010, a systematic review and meta-analysis included 21 trials investigating the incidence of either POD or postoperative cognitive dysfunction (POCD). There was no effect of anesthesia type on the odds ratio of developing either POD or POCD.<sup>27</sup> In 2016, a Cochrane Review comparing regional versus general anesthesia for hip fracture surgery in adults included an "acute confusional state" as an outcome. Based on 6 studies including 624 participants, there was no difference in the risk of acute confusional state: relative risk (RR) 0.85, 95% CI 0.51 to 1.40;  $I^2 = 49\%$ .<sup>28</sup>

Until recently, the available evidence had been limited to observational studies or very small clinical trials. In 2021, the results of 2 large, multicenter, randomized controlled trials comparing regional and general anesthesia for hip fracture surgery were published. The Regional versus General Anesthesia for Promoting Independence after Hip Fracture trial was a multicenter, pragmatic, randomized superiority trial that enrolled a total of 1600 patients with a mean age of 78 years.<sup>29</sup> The primary outcome was a composite of death and the inability to walk independently at 60 days postoperatively. POD was a secondary outcome. The investigators found that spinal anesthesia was not superior to general anesthesia with regard to survival, recovery of ambulation, and POD. The incidence of delirium was similar in the 2 groups occurring in 20.5% of the spinal anesthesia group and 19.7% in the general anesthesia group (RR 1.04; 95% CI 0.84–1.30). Of note, there was no limitation of the use of sedative agents in the regional anesthesia group.

The RAGA (Regional Anesthesia vs General Anesthesia) trial was a pragmatic, randomized, multicenter trial at university teaching hospitals in southeastern China that randomized 950 patients of mean age 76.5 years.<sup>30</sup> The primary outcome of RAGA was the incidence of delirium during the first 7 days postoperatively. Secondary outcomes included delirium severity, duration, and subtype. One unique aspect of the RAGA trial is that the patients randomized to regional anesthesia did not receive any sedation. Patients randomized to the regional group received a spinal, epidural, or combination of the two. Even in the absence of sedation, regional anesthesia did not significantly decrease the incidence of delirium compared with general anesthesia. POD occurred in 6.2% of the regional anesthesia group compared with 5.1% in the general anesthesia group (RR, 1.2 [95% CI, 0.7 to 2.0]; P = .57]). There were no differences between delirium severity scores or delirium subtype between groups.<sup>30</sup>

In 2022, a systematic review and meta-analysis aimed solely to determine whether general versus regional anesthesia was associated with POD incidence. The analysis included 21 relevant studies encompassing a total of more than 1.7 million patients. The pooled result of the meta-analysis found a significantly higher incidence of delirium after general anesthesia when compared to regional anesthesia (OR = 1.15, 95% CI: [1.02, 1.31],  $I^2 = 83\%$ , *P* for effect = .02). However, after removing 6 studies that were the main sources of high heterogeneity, a post hoc meta-analysis found no difference in POD between the 2 groups (OR = 0.95, 95% CI: [0.83, 1.08],  $I^2 = 13\%$ , *P* for effect = .44).<sup>31</sup>

A recent population-based cohort study compared dementia incidence in patients receiving different anesthetic types for hip fracture surgery. In a group of 268,014, the incidence was highest with general inhalational anesthesia. The incidence rate for inhalational versus regional anesthesia was 1.51 (1.15–1.66) and for TIVA versus regional anesthesia was 1.28 (1.09–1.51).<sup>32</sup>

## Intravenous Versus Inhalational Anesthesia and Postoperative Delirium

General anesthesia is maintained with inhalational agents in up to 90% of surgeries<sup>33</sup>; however, maintenance by infusion of intravenous agents, primarily propofol, is a technique with potential advantages in the geriatric population. No consensus exists regarding the use of inhalational anesthesia versus TIVA to prevent POD in older adults. A recent Cochrane meta-analysis found a lack of conclusive evidence to differentiate TIVA versus inhalational anesthesia in the risk of POD. This is not surprising given the limited number of rigorous clinical trials, the small sample size in each study, frequently inadequate randomization, high attrition or selective reporting bias, imprecise or insensitive tools to measure delirium and cognition, and/or brevity of follow-up.<sup>34</sup>

Recently funded pragmatic, multicenter randomized controlled trials spanning the globe are set to answer the question of "Which is superior? IV or GAS?" VAPOR-C trial (Volatile Anaesthesia and Perioperative Outcomes Related to Cancer) is a study of intravenous versus volatile anesthetics on the duration of disease-free survival in patients with cancer.<sup>35</sup> VITAL (Volatile vs Total intravenous Anaesthesia for major noncardiac surgery: A pragmatic randomized triaL) will compare survival, safety, and cost-effectiveness of volatile anesthetic base anesthesia with TIVA in adults aged 50 years or older.<sup>36</sup> THRIVE (Trajectories of Recovery after Intravenous Propofol vs inhaled VolatilE anesthesia) focuses on the quality of recovery on postoperative day 1 and has a safety outcome of intraoperative awareness.<sup>37</sup> We eagerly await the results of these trials that are poised to be landmark studies in anesthesiology.

#### **DELIRIUM AND LONG-TERM COGNITION**

Delirium is described as an acute attentional deficit, which waxes and wanes. The natural course of POD is that it improves as the patient's health status improves. Although POD seems transient, it is associated with increased health-care costs, a longer length of stay, morbidity, and mortality. The literature has primarily focused on in-hospital delirium and less on long-term (months and years) cognitive trajectory. Studies of long-term cognition are more difficult to perform; they require out of hospital followup, extended study visits, and significant costs for personnel and training. More recently, large studies have described in detail the cognitive performance and trajectory of physical recovery that are vitally important to patients and the health-care system.

The International Study of Postoperative Cognitive Dysfunction was one of the largest early studies of delirium and POCD. In 2008, this study group published data demonstrating an early (7-day) relationship between POD and cognitive dysfunction but did not find a relationship 3 months after surgery. The authors commented that the study was underpowered due to the dropout of what may have been the most vulnerable population. In 2016, The Successful Aging after Elective Surgery (SAGES) group published a study examining cognitive trajectory in patients who did and did not develop POD. They used more in-depth cognitive measures and longer term follow-up and showed a clear decline in postoperative cognitive ability after adjusting for cognitive baseline in a larger (556 person) group followed up for 18 months.<sup>38</sup> The objective decline on cognitive testing was in agreement with the performance as described by patients' families using the Informant Questionnaire on Cognitive Decline in the older adults measure.<sup>39</sup> In fact, the rate of cognitive decline after an episode of POD was similar to patients who have a diagnosis of mild cognitive impairment<sup>40,41</sup>; significantly faster than normal aging although slower than frank dementia. The same group demonstrated that patients with mild cognitive impairment who have an episode of delirium had worsened cognitive decline after surgery compared with patients with mild cognitive impairment who do not have an episode of delirium.<sup>42</sup>

In 2018, a study of ICU patients examined the association between the cause of a delirium episode (ie, sedative-associated, hypoxic, septic) and long-term cognitive outcomes. They found that delirium from any cause was associated with worse long-term cognition 12 months after hospital discharge, even after adjustment for common confounders such as age, comorbidity, preoperative cognition, and educa-tion.<sup>43</sup> The authors noted that these findings are particularly significant because even delirium associated with sedative administration is associated with worse long-term cognition.

The relationship between delirium and long-term cognitive disorders does not belie a relationship between general anesthesia and surgery (per se) and long-term cognitive decline. Whitlock and colleagues<sup>44</sup> published a study that compared cognitive trajectory for patients who had coronary artery bypass graft surgery (CABG) versus percutaneous coronary intervention (PCI) as measured by a summary measure of cognitive tests in the Health and Retirement study, called the memory score. They found that the cognitive trajectory during 10 years was the same for both groups of patients. This suggests that even major surgery and general anesthesia do not "cause" cognitive decline. It is important to note that they did identify a group of patients who developed major neurocognitive disorders after either CABG or PCI. The reason for long-term cognitive function in this study was not identified, and the role of delirium was not investigated because the study used a large dataset that did not collect delirium screening for all patients.

#### A Mechanistic Review of Delirium and Dementia

A recent review article by Drs Fong and Inouye described the interrelationship between delirium and dementia.<sup>45</sup> Patients with dementia more often develop delirium, and as we mentioned, delirium is associated with accelerated cognitive decline. The article summarized the evidence for the mechanism behind both conditions with respect to shared biomarkers, systemic inflammation, neuroinflammation, Alzheimer disease biomarkers, Apolipoprotein E, and functional connectivity. Systemic and neuroinflammation have both been associated with POD. Which inflammatory markers are associated and at what time point (before surgery) versus after surgery has also been described. Some cytokines have been identified as risk factors, and others as markers of disease severity. The Successful Aging After Elective Surgery Study (SAGES) performed a case-control study of patients aged older than 70 years undergoing major noncardiac surgery who did and did not develop delirium.<sup>46</sup> They found that preoperative c-reactive protein (CRP) is a "risk marker" for POD. A preoperative CRP level of 3 mg/L or greater was associated with a 1.5 times greater risk of developing delirium than patients with lower levels of CRP. Other markers of the nuclear factor kappa B pathway are markers for delirium, although they tend to be elevated at the time of delirium. This led the Vasunilashorn group to suggest they are "disease markers." For example, this is the case for cytokines such as interleukin (IL) 6, IL 2, vascular endothelial growth factor, and tumor necrosis factor-alpha (TNF $\alpha$ ) at postoperative day 2.47 A meta-analysis of delirium and inflammation published in 2021 identified 17 studies with a low risk of bias and found that preoperative IL6 and CRP were associated with POD.<sup>48</sup> The meta-analysis did not find evidence for an association of POD with IL8, IL10, TNFα, or insulin-like growth factor (IGF)-1. There was a lack of preoperative association between cortisol and POD; however, the authors commented that the issue of diurnal variation with cortisol might have confounded the findings.

Regarding the association between dementia and delirium, studies suggest that patients with dementia are more susceptible to the deliriogenic effects of inflammation. There is also evidence to suggest that pathways such as neuroinflammation influence the progression of Alzheimer's dementia.<sup>49</sup> Presence of apolipoprotein E4 (Apo E4) allele is a risk factor for dementia but has a less clear association with delirium. Patients with the Apo E4 allele may have a heterogeneous response to inflammation with respect to the development of delirium than patients without the allele.<sup>50–52</sup> Preoperative elevated serum neurofilament light (NfL), a marker for axonal damage, has been associated with POD.<sup>53</sup> The same study demonstrated that elevated NfL at 1 month after surgery is also associated with cognitive decline. This may be evidence for axonal damage as part of the mechanism that links POD and cognitive decline. Dementia and delirium are also both associated with blood–brain barrier (BBB) disruption. One study looked at BBB disruption in a cohort of older hip fracture patients. They found BBB disruption in patients with and without dementia; however, all patients with BBB disruption experienced delirium or subsyndromal delirium.<sup>54</sup>

#### DELIRIUM AND FUNCTIONAL RECOVERY

POD has been found to be associated with worse functional recovery in older surgical patients. In 2000, a study of 126 hip fracture patients who underwent emergent surgery described that delirium was associated with poor functional recovery 1 month later even after adjustment for preoperative cognition and functional status. These outcomes included activities of daily living (ADL) decline, a decline in ambulation, and death or new nursing home placement.<sup>55</sup> Subsequently, in 2017, a large cohort of 556 patients undergoing elective surgery showed that those who experienced delirium had lesser functional recovery up to 18 months after surgery.<sup>56</sup> For this study, function was measured as a composite of the ADLS, Instrumental Activity of Daily Living, and the physical component of the Short Form-12 (SF-12). More studies are needed to measure functional and patient-centered outcomes in older surgical patients months and years after surgery.

#### SUMMARY

POD is not a benign or inert process and may be a modifiable risk factor for dementia. The immediate complications from delirium, such as falls, increased health-care costs, and patient-centered outcomes are familiar. The current data supports that delirium is associated with long-term cognitive decline and dementia. Given the magnitude of the older surgical population and the high incidence, POD is a major public health concern. Several states, such as Massachusetts and New Hampshire, mandated that hospitals implement plans for delirium recognition and prevention. Given the magnitude and severity of delirium and its consequences, these measures are a great starting place but are not adequate. Additional mandates to encourage best practices for delirium prevention will likely evolve in the future as the prevention of delirium gains recognition as a public health priority.

## **CLINICS CARE POINTS**

- Frailty differs from healthy aging. Healthy aging is accompanied by physiologic changes but these changes do not lead to the severe depletion of reserve and vulnerability even to small stressors.
- Frailty can be screened and diagnosed by various validated instruments.

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- Example instruments include FRAIL (Fatigue, Resistance, Ambulation, Illness, Loss of weight) scale, the Clinical Frailty Scale, the Frailty Phenotype, Gait Speed, and the Gérontopôle Frailty Screening Tool.
- A recent meta-analysis found that when only randomized clinical trials were included, there was a significant reduction in delirium in patients with a Comprehensive Geriatric Assessment (CGA) intervention compared with the control group (OR 0.45 [95% CI 0.29– 0.70]).
- Recent multicenter, randomized controlled trials comparing regional and general anesthesia for hip fracture surgery found no differences in the incidence of delirium between groups.

#### DISCLOSURE

Dr Deiner is a director for the ABA; opinions expressed in this paper do not represent the views of the ABA. She has been an expert witness. She has had no industry relationships for >5 years. Drs Mahanna-Gabrielli and Schenning have no conflicts of interest.

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