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Olfactory Dysfunction as a Predictive Biomarker for Postoperative Delirium Risk Assessment

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ABSTRACT

Postoperative delirium is a common and serious complication of surgery, particularly in older adults. Despite its impact on outcomes and healthcare costs, effective preoperative tools to identify high-risk patients remain limited. This review evaluates the potential role of olfactory dysfunction as a noninvasive biomarker for predicting postoperative delirium, based on its strong association with brain vulnerability and neurodegenerative risk. Olfactory dysfunction is prevalent in patients with neurodegenerative and psychiatric disorders, as well as in aging populations—groups already at high risk for postoperative cognitive complications. It reflects key pathophysiological mechanisms shared with delirium, including neuroinflammation, cholinergic disruption, and corticolimbic network breakdown. Recent studies in surgical populations, including cardiac procedures, suggest that preoperative olfactory testing correlates with increased incidence and severity of postoperative delirium. Olfactory testing is inexpensive, rapid, and scalable, making it a feasible addition to preoperative evaluations. Its integration may enable personalized risk stratification and proactive cognitive management in perioperative care. Olfactory dysfunction offers a promising, biologically grounded strategy to identify patients at risk for postoperative delirium. Future studies should standardize testing protocols, validate its predictive value, and explore its role within multimodal perioperative risk models.

Keywords: olfactory dysfunction, postoperative delirium, perioperative risk stratification, neurodegeneration, neuroinflammation

1. Introduction

Postoperative delirium (POD) is a common, serious, and often underrecognized complication affecting surgical patients, particularly older adults and those with preexisting vulnerabilities. Characterized by sudden and variable impairments in focus, consciousness, and cognitive function, POD has been reported in up to 50% of elderly patients undergoing major surgery, with even higher rates following procedures such as cardiac and spine surgery[1,2]. POD is an independent risk factor associated with increased morbidity, prolonged hospitalization, long-term cognitive impairment, institutionalization, and mortality[3,4]. It also poses a substantial financial burden, with delirium-related healthcare costs exceeding $32 billion annually in the United States[5]. Despite this impact, preoperative identification of at-risk patients remains limited by the absence of simple, scalable, and validated biomarkers.

One promising avenue for early risk stratification is olfactory dysfunction, which has been well documented as an early and specific clinical finding in several neurodegenerative diseases and psychiatric disorders[6-9]. Olfactory dysfunction frequently precedes the clinical manifestations of these conditions and reflects early neuroinflammation involving central brain areas such as the orbitofrontal cortex, hippocampus, and amygdala—regions also implicated in the pathophysiology of delirium[10,11].

Recent studies have identified OD as a predictor of POD in patients undergoing cardiac surgery, reinforcing the hypothesis that olfactory impairment may serve as a predictive biomarker of underlying brain vulnerability that predisposes patients to cognitive complications following surgical stress[2,12,13]. However, its role in predicting POD across other surgical populations remains underexplored.

This review aims to summarize the current understanding of olfactory dysfunction in neurological, psychiatric, infectious, and surgical contexts, and to critically examine its potential utility as a preoperative biomarker for POD risk assessment. By connecting insights from neurodegeneration, viral illness, and surgical outcomes, we seek to define the rationale for integrating olfactory testing into perioperative clinical practice to enhance risk stratification, guide targeted interventions, and ultimately reduce the burden of POD.

2. Postoperative Delirium

POD is a complex and multifactorial neuropsychiatric syndrome that typically arises within hours to days following surgical procedures. It is characterized by an acute disturbance in attention, cognition, and consciousness, and is most common in individuals with baseline cognitive impairment and elderly patients[14,15]. Clinically, POD presents as either a hyperactive, hypoactive, or mixed subtype, with symptoms ranging from agitation and hallucinations to lethargy and inattention[14,15]. Several perioperative factors have been linked to its development, including type of surgery, anesthetic exposure, preexisting comorbidities, and perioperative pharmacological interventions[16,17].

The pathophysiology of POD involves a convergence of several interacting biological pathways. A central mechanism is the systemic inflammatory response triggered by surgical trauma. Proinflammatory cytokines, such as IL-6, IL-1β, and TNF-α, are released peripherally and cross the blood-brain barrier (BBB), activating microglial cells and initiating a neuroinflammatory cascade[11,18]. While this response serves to protect the brain, it can also result in neurotoxicity and synaptic dysfunction, contributing to acute cognitive decline[19]. Neurotransmitter imbalances also play a role in the manifestation of POD. Cholinergic hypoactivity is a key mechanism underlying attentional deficits and altered arousal states characteristic of delirium[11]. Dopaminergic excess, on the other hand, contributes to agitation and hallucinations. The interplay between these systems, along with imbalances in serotonergic, glutamatergic, and GABAergic signaling, underscores the neurochemical basis of delirium[11]. Additionally, mitochondrial dysfunction resulting from surgical stress can generate oxidative stress, leading to

further neuronal injury through DNA damage, energy failure, and the production of reactive oxygen species[20,21].

Electrophysiological and functional neuroimaging studies have demonstrated that POD is associated with disrupted brain network connectivity. Decreased coherence and lower signal amplitude in EEG—especially in the alpha and beta frequency bands—are commonly observed[22]. fMRI studies have confirmed persistent disruptions in functional connectivity in patients with POD, even months after surgery, particularly in regions associated with attention and executive function[22,23].

Aging further exacerbates these vulnerabilities. Age-related reductions in cerebral perfusion, cortical volume, and metabolic reserve reduce the brain's ability to respond to stressors. Furthermore, aging is associated with diminished cholinergic transmission and impaired synaptic plasticity, both of which contribute to increased susceptibility to delirium[24].

Endocrinological factors, such as elevated glucocorticoid levels during perioperative stress, have also been implicated in POD. High cortisol levels have been associated with hippocampal atrophy, impaired neurogenesis, and increased neuronal vulnerability—mechanisms that may contribute to cognitive deterioration[25]. Dysregulation of melatonin secretion, due to sleep-wake cycle disruption in the ICU or postoperative environment, may also impair circadian regulation and exacerbate delirium risk[11].

Ultimately, POD results from a synergistic interplay of neuroinflammatory, neurotransmitter, oxidative, metabolic, endocrine, and network-level disruptions. No single cause can account for its onset, and diverse perioperative factors—including pharmacological agents, anesthetic depth, pain, and environmental stressors—can modulate these biological pathways [11,26]. This complex pathophysiology presents a challenge for prevention and treatment. A deeper understanding of these mechanisms is essential for clinicians to implement targeted strategies for identifying at-risk individuals and developing interventions aimed at preserving cognitive integrity in the perioperative setting.

3. Olfactory Dysfunction

The sense of smell is the earliest specialized sensory function to emerge in animal evolution and is also the initial special sense to develop during human embryonic and fetal growth[27]. The olfactory system is uniquely structured among the sensory modalities, distinguished by its direct anatomical and functional connections to the brain's limbic and memory-related regions. The olfactory information bypasses the thalamus on its way to the cortex. Importantly, the anatomical vulnerability of the olfactory system—particularly the delicate unmyelinated axons traversing the cribriform plate and the direct projection to brain regions involved in memory, cognition, and emotional regulation—makes it highly sensitive to early pathological changes. This explains why OD often serves as an early clinical marker in neurodegenerative diseases, and potentially as an indicator of central nervous system vulnerability in perioperative contexts such as postoperative delirium[10,28].

Clinically, OD can present with various phenotypes, each reflecting different underlying pathophysiological mechanisms:

- Anosmia: A complete loss of the sense of smell, often resulting from severe damage to the olfactory epithelium, nerve, or central olfactory pathways.
- Hyposmia: A reduced sensitivity to odors, which may be subtle and easily overlooked by patients, yet often represents early neurodegenerative or inflammatory changes.
- Parosmia: A qualitative distortion of smell perception, where odors are perceived as unpleasant or different from their original character (e.g., coffee may smell like gasoline). Parosmia is commonly reported following viral infections, including COVID-19.
- Phantosmia: The perception of odors in the absence of an external stimulus, typically unpleasant, which can arise from spontaneous

activity within olfactory structures or central nervous system lesions.

Olfactory dysfunction is associated with several major neurological and psychiatric conditions, frequently appearing years before the onset of classic clinical symptoms. For example, anosmia is a hallmark of prodromal of dementia associated with Parkinson's disease[29], while hyposmia has been linked to early Alzheimer's disease[30] and major depressive disorder[31]. Recognizing these manifestations provides an opportunity for early identification of brain vulnerability, with important implications for perioperative risk assessment and long-term cognitive health.

4. Causes of Olfactory Disfunction

Olfactory dysfunction can result from a variety of pathological processes affecting different levels of the olfactory system, from the nasal cavity to central brain regions. Understanding the etiologies of OD is crucial because it not only impacts sensory function and quality of life but also provides important insights into broader neurological health. The causes of OD can be broadly classified into conductive, sensorineural, and central mechanisms, each reflecting disruption at distinct anatomical or physiological points along the olfactory pathway. In many cases, OD serves as an early indicator of systemic disease processes, including aging, viral infections, head trauma, and neurodegenerative disorders. Identifying the underlying cause of olfactory impairment is essential for accurate diagnosis, targeted interventions, and the use of OD as a potential biomarker for predicting broader cognitive vulnerabilities such as POD. This section provides a comprehensive overview of the major causes of OD, their mechanisms, clinical implications, and relevance to perioperative medicine.

4.1 AGING

OD is highly prevalent in the aging population, affecting approximately 50% of adults over 65 and increasing to over 70% of individuals aged 80 and older[32,33]. Age-related OD is multifactorial, involving changes across peripheral, central, and systemic levels of the olfactory pathway.

At the peripheral level, there is a decreased turnover of ORNs in the olfactory epithelium. Normally, ORNs are regenerated throughout life, but this regenerative capacity diminishes with age, leading to a gradual loss of receptor neurons and reduced sensitivity to odorants[32]. In addition, the mucosal environment of the nasal cavity undergoes changes, including decreased mucous production and altered mucin composition, which impair the solubilization and transport of odorant molecules to the receptors[33].

At the central nervous system level, aging is associated with atrophy of the olfactory bulb and shrinkage of olfactory-related cortical regions[34,35]. These structural changes correlate with functional impairments in odor detection, discrimination, and identification. Moreover, synaptic loss, reduced neuroplasticity, and altered neurotransmitter levels (particularly acetylcholine and dopamine) in olfactory circuits further exacerbate functional decline[33].

In addition to intrinsic aging processes, accumulation of environmental insults—such as lifelong exposure to pollutants, toxins, viral infections, and medications—contributes to the gradual degeneration of both the olfactory epithelium and central olfactory pathways[28].

Collectively, these structural and functional changes make aging one of the strongest risk factors for olfactory loss. Importantly, age-related OD may serve as a surrogate marker for broader brain vulnerability, reflecting early neurodegenerative changes that predispose individuals to cognitive decline, dementia, and postoperative cognitive complications such as POD[28]. Therefore, assessing olfactory function in older adults has both clinical and prognostic significance beyond sensory evaluation alone.

4.2 VIRAL INFECTIONS

Viral infections are among the most common causes of OD, accounting for a substantial proportion of both transient and permanent cases of smell impairment. Upper respiratory tract infections (URTIs)

caused by viruses such as influenza, parainfluenza, rhinovirus, respiratory syncytial virus, and common cold coronaviruses frequently lead to acute OD[36,37]. The mechanisms include inflammation of the olfactory epithelium, damage or loss of ORNs, and in some cases, direct viral invasion of the olfactory bulb and central olfactory pathways, leading to longer lasting or even permanent deficits[38].

- Viral infections may induce OD through multiple mechanisms[38-40]:
- Inflammation or damage to the olfactory epithelium, causing reversible anosmia or hyposmia.
- Direct injury to ORNs or sustentacular cells essential for epithelial support and integrity.
- Immune-mediated disruption of olfactory signal transduction due to cytokine release and epithelial remodeling.
- CNS invasion via retrograde spread along the olfactory nerve, as shown in animal models of influenza and SARS-CoV-2.

The COVID-19 pandemic brought unprecedented attention to virus-induced OD. Unlike other URTIs, SARS-CoV-2 infection frequently caused sudden-onset anosmia or hyposmia in the absence of nasal obstruction or rhinorrhea[41]. OD was reported in up to 80% of mild-to-moderate COVID-19 cases, often as the first or only symptom, especially in younger, otherwise healthy individuals[42]. This unique clinical presentation sparked a surge of research into the mechanisms of viral neuropathogenesis and olfactory vulnerability.

4.3 HEAD TRAUMA

Head trauma is a well-recognized and clinically significant cause of OD, particularly affecting younger adults, athletes, military personnel, and individuals exposed to repetitive concussive or blast injuries [43-46]. Traumatic brain injury (TBI) disrupts olfactory function through multiple mechanisms, and OD occurs in approximately 5–15% of all TBIs, with significantly higher rates observed following moderate to severe injuries[45]. Even mild TBIs (concussions) can lead to transient or permanent olfactory deficits, underlining the vulnerability of the olfactory system to mechanical forces[45].

Several mechanisms contribute to trauma-induced Olfactory Dysfunction[47,48]:

- Shearing of unmyelinated olfactory nerve fibers at the cribriform plate, disrupting the connection between the olfactory epithelium and the bulb.
- Contusions or hemorrhage affecting the olfactory bulb or ventral frontal lobes, leading to neuronal loss and scar formation.
- Damage to central olfactory processing regions, particularly the orbitofrontal cortex and anterior temporal lobes, which are critical for odor identification, discrimination, and hedonic processing.
- Secondary effects such as inflammation, edema, ischemia, and increased intracranial pressure, further compromising olfactory pathways and function.

The extent and permanence of OD following TBI often correlate with the severity of the injury, but even in cases of mild trauma, anosmia or hyposmia can persist, sometimes unnoticed until formal testing. Importantly, trauma-induced OD is frequently associated with broader cognitive, emotional, and functional impairments, including:

- Memory deficits
- Executive dysfunction
- Depression and anxiety
- Poor rehabilitation outcomes and reduced quality of life

Given the olfactory system's early and selective vulnerability in TBI, the presence of OD may serve as a clinical marker of underlying brain injury, helping to predict long-term neurocognitive risk and functional decline.

4.4 OLFACTORY DISFUNCTION IN PARKINSON'S DISEASE, ALZHEIMER'S DISEASE, AND PSYCHIATRIC DISORDERS

OD is increasingly recognized as a hallmark of several neurodegenerative and psychiatric conditions, often manifesting years before the onset of core clinical symptoms[10]. As a sensory modality deeply embedded within limbic, cortical, and brainstem circuits, the olfactory system is uniquely vulnerable to early pathological changes in diseases such as Parkinson's disease, Alzheimer's disease, schizophrenia, and major depressive disorder (MDD)[49-53]. In these disorders, olfactory dysfunction is not merely a symptom but a marker of neurobiological disruption, involving synucleinopathies, tauopathies, dopaminergic and cholinergic dysfunction, and altered brain connectivity[10].

This vulnerability reflects the olfactory system's direct connections to critical brain areas responsible for memory, emotion, and executive function—notably the entorhinal cortex, amygdala, hippocampus, and orbitofrontal cortex[54]. Importantly, OD often arises during the preclinical or prodromal stages of these disorders, offering a window for early diagnosis and risk stratification, long before cognitive or motor impairments are clinically evident. These features position olfactory testing as a valuable tool not only in neurology and psychiatry, but also in perioperative medicine, where identifying latent brain vulnerability may help predict complications such as postoperative delirium.

4.4.1 Olfactory Dysfunction in Parkinson's Disease

Olfactory dysfunction is among the earliest and most consistent findings in Parkinson's disease, occurring in more than 90% of patients, frequently many years prior the onset of motor symptoms[55]. It is so prevalent that olfactory dysfunction has been proposed as a prodromal biomarker and even a diagnostic aid for Parkinson's disease[56]. Affected domains typically include odor identification, discrimination, and threshold detection that can be assessed via tools such as the U-Smell-it, Sniffin' Sticks battery, and University of Pennsylvania Smell Identification Test (UPSIT).

Neuropathologically, olfactory dysfunction in Parkinson's disease correlates with early α-synuclein aggregation in the olfactory bulb, anterior olfactory nucleus, piriform cortex, and entorhinal cortex—areas among the first affected in stage 1 and 2 of Parkinson's disease[57]. Lewy body deposition disrupts olfactory transmission long before substantial involvement of the substantia nigra, explaining why smell loss precedes motor symptoms[58,59]. Functional imaging studies, including PET and fMRI, confirm altered olfactory network connectivity in Parkinson's disease patients[60].

Clinically, olfactory dysfunction in Parkinson's disease predicts more rapid motor progression, higher non-motor symptom burden, worse quality of life, and greater risk of cognitive decline and dementia[29]. Thus, olfactory dysfunction serves as an early indicator of limbic and cortical vulnerability, highlighting its potential utility in perioperative cognitive risk assessment.

4.4.2 Olfactory Dysfunction in Alzheimer's Disease

Olfactory dysfunction is similarly an early and prominent feature of Alzheimer's disease. It frequently presents as impaired odor identification, discrimination, and threshold sensitivity, often preceding cognitive deficits by several years[50].

Neuropathologically, olfactory dysfunction in Alzheimer's disease correlates with early deposition of amyloid-β plaques and neurofibrillary tangles (NFTs) in olfactory-related cortical areas, including the entorhinal cortex, hippocampus, and orbitofrontal cortex[61]. Clinically, olfactory impairments also extend to emotional processing, hedonic evaluation, and associative memory. In the perioperative context, identifying olfactory dysfunction could enhance risk stratification for POD and help tailor interventions for patients at elevated risk for postoperative cognitive decline.

4.4.3 Olfactory Dysfunction in Schizophrenia and Other Psychiatric Disorders

Olfactory dysfunction is a well-documented phenomenon in schizophrenia. Multiple studies have shown that individuals with schizophrenia present

clinical impairments in olfactory identification and discrimination, though odor sensitivity often remains unaffected.

The relationship between olfactory dysfunction and schizophrenia is multifaceted. Olfactory impairments in schizophrenia are associated with negative symptoms, cognitive deficits, and structural brain abnormalities, particularly in the olfactory bulb and related brain regions[62-64]. For instance, inflammation-related pathology in the olfactory epithelium and subsequent changes in the olfactory bulb have been implicated in the pathophysiology of schizophrenia[62].

Furthermore, olfactory dysfunction has been suggested as a potential endophenotype for schizophrenia, given its presence in first-degree relatives and individuals at high risk for the disorder[65,66]. This suggests that olfactory impairments could serve as a marker for genetic vulnerability to schizophrenia.

In major depressive disorders, olfactory dysfunction is also prevalent, and individuals often exhibit reduced activation in secondary olfactory areas, which are also involved in sensory integration and attention allocation. This suggests a top-down mechanism where higher cortical dysfunction impacts olfactory processing[67]. Additionally, longitudinal data indicate that olfactory dysfunction can predict the development of depression in older adults, highlighting its potential role as an early marker for depressive symptoms[9].

Bipolar disorder presents a more complex picture, with mixed findings regarding olfactory function. Some studies report impairments in odor identification, particularly in those with psychotic features, while others find no significant differences compared to healthy controls[68,69]. olfactory dysfunction has also been reported, with variable findings, in bipolar disorder, posttraumatic stress disorder[70] , and obsessive-compulsive disorder[71,72].

4.4.5 Shared Pathophysiological Mechanisms Linking Olfactory Dysfunction and Neurodegenerative and Neuropsychiatric Disorders

Despite the apparent clinical heterogeneity across neurodegenerative and psychiatric disorders, a growing body of evidence supports converging pathophysiological mechanisms that contribute to olfactory dysfunction. These shared pathways not only explain the high prevalence of olfactory dysfunction across multiple disease states but also highlight its potential as a noninvasive biomarker of central nervous system vulnerability.

Anatomical Vulnerability

The olfactory system's unique neuroanatomy renders it particularly susceptible to early pathological changes. Olfactory receptor neurons project directly to the olfactory bulb, which then relays information to key brain areas involved in memory, emotion, and cognition, including the piriform cortex, entorhinal cortex, hippocampus, amygdala, and orbitofrontal cortex[54,73]. These same regions are among the earliest affected in disorders such as AD, Parkinson's Disease, and schizophrenia[28]. Importantly, olfactory pathways bypass the thalamus and connect mono- or disynaptically to limbic structures, providing direct access for pathological processes such as protein aggregation or inflammatory spread.

Protein Aggregation

Several neurodegenerative diseases feature the accumulation of misfolded proteins in olfactory regions early in their course. In Parkinson's disease, α-synuclein inclusions are consistently observed in the olfactory bulb, anterior olfactory nucleus, and amygdala as early as Braak stage 1[57]. In Alzheimer's disease, β-amyloid plaques and hyperphosphorylated tau tangles accumulate in the entorhinal cortex and hippocampus, disrupting olfactory signaling and correlating with early olfactory deficits[74]. These proteinopathies not only impair sensory processing but also indicate broader network vulnerability.

Neurotransmitter Dysregulation

Olfactory dysfunction is closely associated with disturbances in neurotransmitter systems that also underlie neurocognitive and psychiatric symptoms. The cholinergic system, essential for attention and memory, modulates both olfactory bulb excitability and olfactory learning, and its dysfunction is well documented in both Alzheimer's disease and POD[75].

The dopaminergic system, disrupted in Parkinson's disease and schizophrenia, plays a role in odor discrimination and reward-based olfactory learning[76]. Serotonergic and glutamatergic signaling pathways, implicated in depression, anxiety, and schizophrenia, also contribute to olfactory processing through effects on cortical integration and synaptic plasticity[77].

Neuroinflammation

Both central and peripheral inflammatory processes can impair olfactory function. Microglial activation, proinflammatory cytokine release, and blood-brain barrier disruption have been observed in olfactory structures across neurodegenerative diseases and in systemic illnesses such as COVID-19[78,79]. Chronic neuroinflammation may directly damage the olfactory epithelium and bulb or act indirectly via altered glial-neuronal interactions. These immune-mediated alterations may be reversible in early stages but can contribute to long-term olfactory and cognitive dysfunction if sustained.

5. Implications of Olfactory Dysfunction for Postoperative Delirium

The pathophysiological overlap between OD and POD is striking. Both conditions involve limbic-prefrontal disconnection, neurotransmitter imbalances—especially cholinergic deficiency—and vulnerability to inflammatory stressors. POD has been associated with disrupted functional connectivity in the default mode and salience networks, including areas also involved in olfactory perception[11]. Therefore, OD may serve as a proxy for underlying neurobiological fragility, helping to identify surgical patients at increased risk for delirium and guiding targeted preventive strategies.

In patients submitted to cardiac surgery, POD is one of the most common and debilitating neurological complications with incidence ranges from 30% to 50%, particularly among older adults and individuals with preexisting cognitive impairment[80,81]. Patients undergoing cardiac surgery are particularly vulnerable due to a combination of surgical stress, anesthetic exposure, and cardiopulmonary bypass (CPB)–induced cerebral changes[82].

Olfactory dysfunction is particularly relevant in surgical populations, especially in patients undergoing cardiac procedures, where it may serve as a sentinel marker of brain vulnerability. Studies report that approximately 30–33% of cardiac surgery patients exhibit preoperative OD[2,13], which has been independently associated with increased risk, incidence, and severity of POD. For example, OD predicted a nearly twofold increase in POD risk, even after controlling for age and baseline cognition[13]. These findings suggest that OD may reflect latent neurodegenerative changes or impaired neurovascular resilience that become unmasked by the physiological and inflammatory stress of surgery. The use of cardiopulmonary bypass (CPB)—a known driver of cerebral microemboli, impaired autoregulation, and systemic inflammation—may further exacerbate these vulnerabilities. Importantly, POD in this population is strongly linked to worse outcomes, including prolonged mechanical ventilation, longer ICU and hospital stays, delayed recovery, higher institutionalization rates, long-term cognitive decline, and increased 1-year mortality[82,83]. In this context, OD should not be viewed as a benign sensory impairment but as a clinically meaningful and noninvasive biomarker of perioperative neurocognitive risk.

6. Postoperative Delirium and the Need for Predictive Tools

POD is a common complication among surgical patients, particularly older adults and those undergoing high-risk procedures. Established risk factors include advanced age, sensory deficits, high ASA physical status, pre-existing cognitive impairment, and the type and duration of surgery. However, current preoperative assessment tools often lack sufficient predictive accuracy. Instruments like the Mini-Mental State Examination (MMSE) and Mini-Cog are useful for identifying overt cognitive deficits but may fail to detect subtle or preclinical brain vulnerabilities[84].

Diagnostic tools such as the Confusion Assessment Method (CAM) and its derivatives, including the

3D-CAM, are validated for detecting delirium but are not designed for prediction. Their diagnostic performance can be limited, especially in cases of hypoactive delirium[85]. Moreover, the incidence and severity of POD vary considerably depending on patient-specific factors and the nature of the surgical procedure, underscoring the need for predictive models that incorporate objective biomarkers of neural integrity and vulnerability.

Given the multifactorial pathophysiology of POD—encompassing systemic and neuroinflammation, neurotransmitter imbalance, oxidative stress, and network disintegration—there is growing interest in developing novel biomarkers capable of identifying central nervous system (CNS) vulnerability prior to surgery. An ideal biomarker should be easily measurable, scalable, and provide meaningful predictive power beyond standard cognitive screening tools.

Olfactory dysfunction meets these criteria. It is consistently associated with aging, neurodegenerative diseases, and psychiatric disorders, all of which are established risk factors for POD[10]. Additionally, OD reflects dysfunction in corticolimbic networks, cholinergic signaling, and neuroinflammatory pathways—biological systems implicated in the pathogenesis of delirium[11,86]. The availability of simple, validated, and cost-effective tools to assess OD enhances its potential as a candidate biomarker for POD risk stratification.

7. The Case for Olfactory Dysfunction as a Biomarker for Postoperative Delirium

Olfactory dysfunction is increasingly recognized as a sensitive and practical indicator of latent brain vulnerability. Its diagnostic value has been demonstrated in various neuropsychiatric and neurodegenerative conditions, and COVID-19-related neurological syndromes[67,87-89]. These associations support OD's role as a noninvasive marker of CNS integrity, with potential relevance for perioperative cognitive risk prediction.

From a mechanistic standpoint, OD mirrors several pathophysiological pathways implicated in delirium. Both conditions share an inflammatory profile characterized by microglial activation and elevated cytokine expression. Cholinergic dysfunction—a hallmark of both Alzheimer's disease and delirium—also impairs olfactory processing, underscoring the relevance of acetylcholine-mediated signaling in both systems[11]. Moreover, the olfactory system is closely linked to corticolimbic regions involved in attention, memory, and arousal regulation—functions disrupted in POD[18,23,81].

Clinically, OD offers several advantages as a screening tool. Tests such as the Brief Smell Identification Test (BSIT), UPSIT, u-Smell-it, and other low-cost kits can be administered quickly and objectively, require minimal training, and are inexpensive compared to other neurological assessments[90]. These features make OD assessment suitable for integration into routine preoperative workflows, particularly in geriatric populations and patients undergoing high-risk procedures.

Importantly, OD can complement existing risk factors to enhance the predictive value of preoperative assessments. For example, a patient with normal MMSE performance but impaired olfaction may be at greater risk for POD due to underlying neural vulnerability not captured by conventional tools. Incorporating OD into a multimodal risk model could prompt proactive interventions such as tailored anesthesia strategies, intensified postoperative monitoring, and early mobilization efforts.

8. Conclusions and Perspectives

Olfactory dysfunction has long been recognized as an early and sensitive marker of neurological vulnerability in a range of neurodegenerative and psychiatric disorders. Its anatomical and functional links to limbic and prefrontal brain regions—combined with its strong associations with inflammation, neurotransmitter dysregulation, and network disruption—place it at the crossroads of several mechanisms implicated in POD.

This review highlights the growing body of evidence connecting preoperative OD with increased risk of POD, particularly in older adults and patients undergoing high-risk surgeries. OD's noninvasive, inexpensive, and scalable nature, coupled with its strong biological plausibility, makes it a compelling candidate for incorporation into routine perioperative risk assessments. Testing tools such as the BSIT, the UPSIT, and the u-Smell-it offer practical avenues for clinical implementation with minimal training and infrastructure.

While current perioperative cognitive screening tools remain limited in predictive specificity, the integration of OD testing represents a promising step toward precision risk stratification. Its ability to detect subclinical brain vulnerability may facilitate earlier interventions, targeted monitoring, and preventive strategies tailored to individual patient profiles.

Future research should prioritize the validation of OD-based screening across diverse surgical populations, establish normative thresholds by age and comorbidity, and evaluate its predictive utility in conjunction with other clinical, imaging, or biomarker data. Longitudinal studies are also needed to determine whether OD predicts not only acute delirium but also long-term cognitive outcomes following surgery.

In sum, olfactory dysfunction offers a unique opportunity to bridge basic neuroscience and perioperative medicine. Its integration into surgical workflows could transform our approach to cognitive risk management, reduce the burden of postoperative delirium, and ultimately improve outcomes for vulnerable surgical patients.

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None

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