

Olfactory Dysfunction Predicts Frailty and Poor Postoperative Outcome in Older Patients Scheduled for Elective Non-Cardiac Surgery

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Abstract

OBJECTIVES: Frailty has been suggested to take part in the recently demonstrated link between olfactory dysfunction and overall mortality risk. Preoperative assessment of frailty is essential to detect the most vulnerable patients scheduled for surgery. The aim of this study was to evaluate whether olfactory dysfunction is a reliable predictor of preoperative frailty and postoperative outcome.

DESIGN: This was a single-center prospective observational study conducted between July and October 2020 in Brussels, Belgium.

SETTING AND PARTICIPANTS: 155 preoperative patients aged from 65 years old and scheduled for elective non-cardiac surgery.

MEASUREMENTS: Olfactory function was examined using the Sniffin' Sticks 12-item identification test. Frailty was assessed using the Edmonton Frail Scale (EFS) and handgrip strength. The clock drawing test (CDT) from the EFS was also analyzed separately to evaluate cognitive function. Patients were followed for postoperative complications and mortality over one year.

RESULTS: Olfactory dysfunction was significantly associated with the EFS score, anosmic patients having a higher median EFS score than normosmic patients (6[4-7] vs 4[2-5], $p = .025$). Anosmic patients had an increased odds of being frail after adjusting for possible confounding factors (OR: 6.19, 95% CI: 1.65-23.20, $p = .007$) and were more at risk of poor postoperative outcome (including complications and death) (OR: 4.33, 95% CI: 1.28-14.67, $p = .018$).

CONCLUSIONS: Olfactory dysfunction is associated with preoperative frailty determined by the EFS and with poor post-surgical outcome at one-year.

Key words: Olfaction, frailty, Edmonton frail scale, clock drawing test, postoperative complications.

Introduction

Olfactory dysfunction is defined as impaired ability to smell, which may be moderate (hyposmia) or severe (anosmia). This sensory loss, though rarely evaluated clinically, increases in frequency with age making it quite common in the older population (1). Recently, olfactory dysfunction was shown to be predictive of overall mortality in older adults (2–4). The greater risk of death depended on the severity of the olfactory dysfunction, with anosmic subjects having a higher tendency to die than their hyposmic peers, which in turn were more likely to die than normosmic individuals (2). The reasons behind this association are still unclear and may comprise neurodegenerative diseases, a

direct effect of olfactory dysfunction on nutrition, danger warning and social interaction, general poor health and, last but not least, accelerated brain aging which in fact represents a lowered physiologic repair function (5). When evaluating risk in older adults, frailty status is currently considered as more relevant than chronological age and medical comorbidities, because frailty status relates to available physiological reserves (6). In particular, preoperative assessment of frailty is crucial to detect the most vulnerable patients scheduled for a surgical intervention (7). Surgery acts as a heavy physical stressor, making frail patients at greater risk of perioperative complications and mortality (8). So far, only a few studies investigated olfactory dysfunction in light of frailty status, making evidence still sparse (9–13). Besides, no such study has ever been conducted in a population of preoperative older adults.

The aim of this study was to evaluate whether olfactory dysfunction assessed using the Sniffin' Sticks 12-item identification test is associated with preoperative frailty and postsurgical outcome.

Method

Study population and design

We conducted a prospective observational study at the Cliniques universitaires Saint-Luc (Brussels, Belgium) between July and October 2020. The study protocol was approved by the institutional Ethics Committee (2020/22JAN/050) and was registered on <https://clinicaltrials.gov/> (NCT04700891). Written informed consent was obtained from all participants after receiving an explanation of the study.

The study included preoperative patients aged from 65 years old and scheduled for inpatient minor, intermediate or major elective non-cardiac surgery under general anesthesia (classified as such according to the European Society of Anaesthesiology cardiovascular assessment guidelines) (14). All types of surgeries were considered with the exception of cardiac, head and neck surgery. Patients were selected by looking into the surgical program and excluded at screening if they had a history of neurological or psychiatric disorder, severe head trauma, chronic rhinosinusitis, post-infectious olfactory loss, current acute upper respiratory tract infection

or any history of past or current COVID-19 infection. Refusal rate among potential participants was about 5-10%. Out of the 167 patients initially included, 5 were excluded at screening (meeting of an exclusion criteria) and 7 did not effectively undergo surgery under general anesthesia, resulting in a final sample size of 155 patients. Olfactory and frailty assessments were performed on the day before surgery. The information collected included demographic variables, education level, smoking status, age-adjusted Charlson comorbidity index, American Society of Anesthesiologists (ASA) physical status, history of active neoplasia and chemotherapy, and number of daily medications since it is acknowledged that these variables may interfere with olfaction and/or morbimortality. We also reported grade and duration of surgery.

Olfactory function assessment

Olfactory function was assessed using the Sniffin' Sticks 12-item identification test (Burghart Messtechnik GmbH, Wedel, Germany), which is a validated psychophysical testing method (15). The 12 odors were presented to the patients using pen-like odor dispensing devices placed approximately 2cm in front of the nostrils. The patients were asked every time to make a forced choice from lists of four descriptors each. For each correct answer, one point was awarded and points were added to obtain an olfactory score ranging from 0 to 12. They were then classified in three groups according to their score: anosmia (≤ 6), hyposmia (7-10) and normosmia (≥ 11). The assessment of olfactory function based solely on the Sniffin' Sticks 12-item identification test was chosen to allow a rapid assessment that could be implemented as a routine clinical test (15).

Outcome measures

Evaluation of frailty status

The Edmonton Frail Scale (EFS) was used to determine frailty status of each patient by evaluating nine domains: functional performance, cognitive function, general health, functional independence, social support, used medications, nutrition, mood and continence. The EFS is an instrument which can be administered quickly by non-geriatricians (16). It has been validated with respect to geriatric specific screening tools (17) and is considered one of the most appropriate preoperative frailty assessment tool (18). Test results range from 0 to 17 points, a higher score representing a higher level of frailty. The cut-off value for frailty was defined as $\geq 6/17$ (17).

The cognitive assessment of the EFS consists of a clock drawing test (CDT) in which the circle of the clock face is already provided. The patients are asked to put in all the numbers and to set the hands to 10 after 11. Besides the EFS evaluation, each clock was scored using Rouleau's scale (19) in which 8 is the maximum score and represents the best performance. We defined the patients as either "cognitively intact" (score of $\geq 6/8$) or "cognitively impaired" (score of $\leq 5/8$).

Maximal handgrip strength was measured to evaluate maximum voluntary hand force using a digital Jamar-type handgrip dynamometer on both hands. The highest of the two measures was used. Handgrip strength is known to be significantly associated with sarcopenia and frailty (20).

Evaluation of postoperative complications and mortality

Patients were followed for postoperative complications and mortality during one year after the date of the surgery, using the Clavien-Dindo classification (21). Grade 1 complications (defined as minor risk events not requiring specific therapy) were not considered as meaningful events. Grade 2 to 4 were listed as "complications". Grade 5 corresponded to "death of the patient". Complication and death events were grouped as "poor outcome". The data was obtained using local hospital medical records and the Belgian health network (if the patients had authorized this medical record sharing) which allows an overall view of patients' medical information.

Study endpoints

The endpoints of this study were : (1) to evaluate the association between olfactory identification function using the Sniffin' Sticks 12 item identification test and, on the one hand, the EFS score, on the other hand, performance at CDT, (2) to assess whether olfactory identification function is a predictor of postoperative complications and mortality at one-year and to examine its potential added value to frailty evaluation on postoperative outcome prediction.

Statistical analysis

Data were analyzed using SPSS version 27.0. The Kolmogorov-Smirnov test was used to check the normality of the data. Ordinal and continuous data were not normally distributed and were expressed as medians (interquartile range). Nominal variables were compared between frail and non-frail patients with a Pearson χ^2 test whereas ordinal and continuous data were compared using a Mann-Whitney U-test. Baseline patient characteristics which were significant in the univariable analysis at a threshold p value $< .1$ were entered into a multivariable logistic regression model to predict the presence of frailty. Age and gender were also added to the model given their known relationship with the outcome and the other variables. A Kruskal-Wallis test was used to compare the EFS score between categories of olfactory function. A Pearson χ^2 test was used to compare clock drawing test performance between categories of olfactory function and multivariable logistic regression was used to predict poor cognitive performance. Prediction of poor outcome at one year after surgery was analyzed with binary logistic regression. We compared the performance of the olfactory score and the EFS score to predict poor postoperative outcome by building up receiving operating characteristic (ROC) curves. Logistic regression models and ROC curves were adjusted for age and sex. Any p value $< .05$ was considered significant.

Table 1. Baseline and operative characteristics of perioperative patients according to their frailty status (evaluated by the Edmonton Frail Scale)

Characteristic	Overall patients (n=155)	Non-frail patients (EFS < 6) (n=98)	Frail patients (EFS ≥6) (n=57)	p Value
Age (y)	73 (68-78)	72 (68-77)	74 (69-80)	.266
Female (%)	94 (60.6)	56 (57.1)	38 (66.7)	.242
Body mass index	26.3 (23.4-30.1)	26.8 (23.3-30.5)	25.3 (23.3-29.6)	.424
Lower education level (%) (≤ 9 years)	71 (45.8)	41 (41.8)	30 (52.6)	.151
Smoking				.500
Non smoker (%)	88 (56.8)	54 (55.1)	34 (59.7)	
Former Smoker (%)	49 (31.6)	34 (34.7)	15 (26.3)	
Present smoker (%)	18 (11.6)	10 (10.2)	8 (14.0)	
Olfactory function				.022
Normosmia	32 (20.6)	26 (26.5)	6 (10.5)	
Hyposmia	101 (65.2)	62 (63.3)	39 (68.4)	
Anosmia	22 (14.2)	10 (10.2)	12 (21.1)	
Number of daily medications	4 (3-7)	4 (2-6)	6 (4-8)	.002
Active neoplasia (%)	57 (36.8)	38 (38.8)	19 (33.3)	.498
Chemotherapy in the past year (%)	25 (16.1)	13 (13.3)	12 (21.1)	.204
Age-adjusted Charlson comorbidity index score	4 (3-6)	4 (3-5)	5 (3-7)	.089
ASA physical status				.017
I-II (%)	82 (52.9)	59 (60.2)	23 (40.4)	
III-IV (%)	73 (47.1)	39 (39.8)	34 (59.6)	
Grade of surgery				.843
Minor (%)	44 (28.4)	29 (29.6)	15 (26.3)	
Intermediate (%)	96 (61.9)	59 (60.2)	37 (64.9)	
Major (%)	15 (9.7)	10 (10.2)	5 (8.8)	
Duration of surgery (min)	152 (107-222)	155 (106-227)	150 (107-219)	.936

Note. EFS = Edmonton Frail Scale; ASA = American Society of Anesthesiologists

Results

Study population

We included a total of 155 preoperative patients with a median age of 73 years (68-78) and whereof 94 (60.6%) were female patients (Table 1). 57 patients (36.8%) were categorized as frail before surgery. Body mass index, education level, smoking status, the presence of active neoplasia or recent chemotherapy did not differ between frail and non-frail patients. There was a tendency to a higher age-adjusted Charlson comorbidity index score in frail patients ($p = .089$). In the frail group, 34 patients (59.6%) were classified ASA physical status III or IV whereas they were only 39 (39.8%) in the non-frail group ($p = .017$). Median number of daily medications was significantly higher in frail patients ($p = .002$). Overall, 44 patients (28.4%) had minor surgery, 96 (61.9%) had intermediate surgery and 15 (9.7%) had major surgery, and these proportions were similar across frailty groups. Median duration of surgery was not different between frail and non-frail patients.

Association between preoperative olfactory function and frailty

Out of the whole study population, 32 patients (20.6%) were classified as normosmic, 101 (65.2%) as hyposmic and

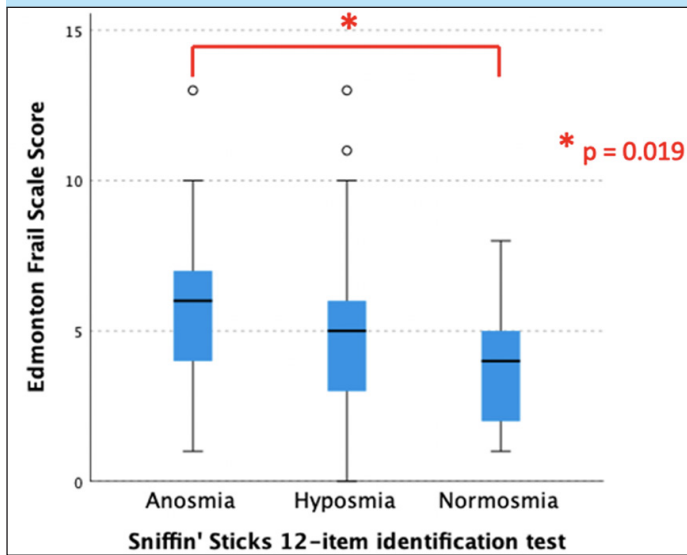
22 (14.2%) as anosmic. We found that preoperative olfactory function differed significantly according to frailty status as defined by the EFS ($p = .022$). 21.1% of the frail patients (12/57) were anosmic compared to only 10.2% of the non-frail patients (10/98). Parallel to this, there was a higher proportion of normosmic patients in the non-frail group (26.5%) in comparison to the frail group (10.5%).

Moreover, the EFS score was significantly related with the identification of olfactory dysfunction: anosmic patients had a significantly higher median EFS score than normosmic patients (6[4-7] vs 4[2-5], $p = .025$) (Figure 1).

Multivariable logistic regression analysis was performed to associate olfactory function and the presence of preoperative frailty, while adjusting for other significant (p value < .1 in the univariable analysis) baseline patient characteristics. The results are summarized in Table 2. When adjusting for age, gender, comorbidities, ASA physical status and number of daily medications, we found that anosmic patients still had an increased odds of being frail (odds ratio [OR]: 6.19, 95% CI: 1.65-23.20, $p = .007$). Hyposmia, however, failed to remain significantly associated with frailty.

The median maximum handgrip strength of normosmic patients (32.7kg) was greater than that of hyposmic and anosmic patients (23.9kg and 26.0 kg), but this difference was not significant.

Figure 1. Edmonton Frail Scale score according to preoperative olfactory function

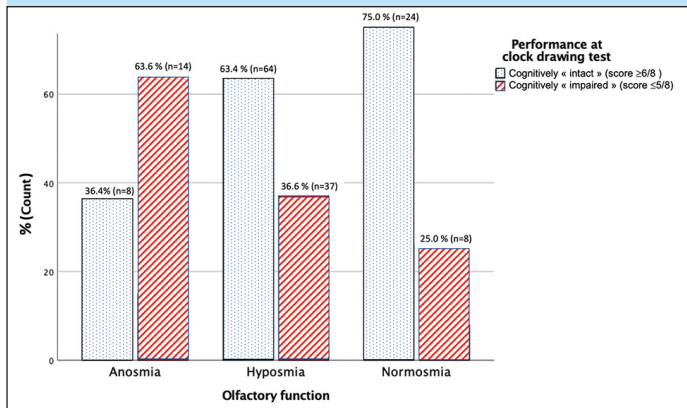


*p <.05

Association between preoperative olfactory function and performance at clock drawing test

Olfactory dysfunction was also associated with performance at CDT ($\chi^2(2) = 8.507, p = .014$). The results are showed in Figure 2. 63.6% of anosmic patients against only 25% of normosmic patients were categorized as “cognitively impaired” based on the CDT score. Even when controlling for education level in a multivariable logistic regression model, anosmia was still predictive of lower performance at CDT (OR: 4.37, 95% CI: 1.22-15.68, $p = .024$).

Figure 2. Performance at clock drawing test according to preoperative olfactory function



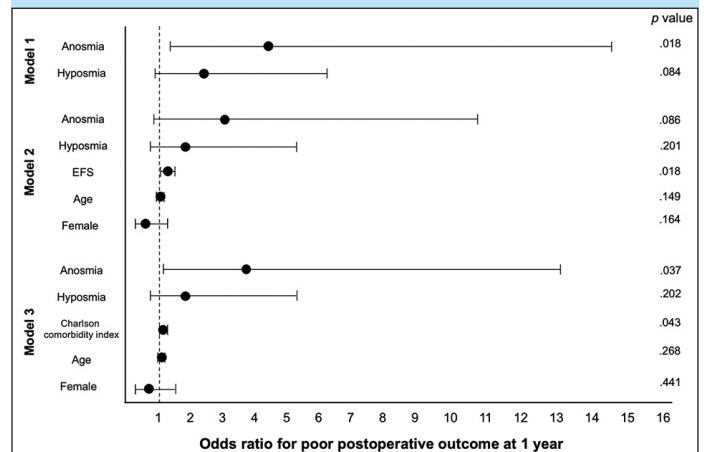
Association between preoperative olfactory function and outcome after surgery

Within one year after surgery, 43 patients (28.1%) presented at least one postoperative complication and 9 patients (5.9%) died. Among the 22 anosmic patients, 9 (40.9%) suffered from a postoperative complication and 2 (9.1%) died. Among the 101 hyposmic patients, 6 (6.1%) had a complication and 29 (29.3%) were dead. Only 1 (3.1%) of the 32 normosmic patients died

and only 5 (15.6%) presented a postoperative complication.

In a logistic regression analysis, anosmic patients were found to be more at risk of poor postoperative outcome (which comprised complications or death) than normosmic patients (OR: 4.33, 95% CI: 1.28-14.67, $p = .018$) (Figure 3, Model 1). When we controlled for frailty (using Edmonton Frail Scale score) in Model 2, the effect of anosmia on poor outcome was decreased and did not reach statistical significance (OR: 3.04, 95% CI: 0.86-10.78, $p = .086$). However, the addition of an interaction term between olfactory function and frailty had no effect on this model. In Model 3, we adjusted for comorbidities (using age-adjusted Charlson comorbidity index), which lowered only slightly the effect of anosmia on poor outcome (OR: 3.76, 95% CI: 1.08-13.07, $p = .037$).

Figure 3. Odds ratios and 95% confidence intervals of logistic regression models predicting poor postoperative outcome at 1 year from preoperative olfactory dysfunction (Model 1)



We carried out ROC curve analyses for the EFS and the olfactory score to evaluate their respective performance in predicting poor postoperative outcome. The ROC curves showed similar patterns, displaying an area under the curve (AUC) of 0.669 for both the EFS and the olfactory score. In our study, the positive predictive value (PPV) of the EFS for having poor postoperative outcome was 48.2% and the negative predictive value (NPV) of not developing postoperative complication or death was 74.2%. Yet, the PPV increased to 66.7% if the frail patients were also classified as anosmic and the NPV increased to 84.6% if the patients were both non-frail and normosmic.

Discussion

This study is the first prospective observational study to investigate the relationships between preoperative olfactory function, preoperative frailty and postsurgical outcome in older patients. First, we show that preoperative olfactory dysfunction (assessed using the Sniffin’ Sticks 12-item identification test) is associated with preoperative frailty determined by the EFS and with poorer cognitive performance in a population of older patients evaluated before they undergo elective surgery. Our study also demonstrates a relationship between olfactory dysfunction and poor postoperative outcome. Importantly, the predictive value of the EFS on poor postoperative outcome was improved by taking into account anosmia or normosmia

Table 2. Univariable and multivariable logistic regression analysis for prediction of preoperative frailty, including preoperative olfactory identification function, age, gender and baseline characteristics whose level of significance reached p value < .1 in the univariable analysis

Variable	Univariable			Multivariable		
	OR	95% CI	p Value	OR	95% CI	p Value
Olfactory identification function						
Anosmia	5.20	1.53-17.64	.008	6.19	1.65-23.20	.007
Hyposmia	2.73	1.03-7.22	.044	2.55	0.89-7.26	.081
Baseline characteristic						
Age	1.03	0.98-1.08	.220	1.02	0.97-1.08	.466
Female	1.50	0.76-2.96	.243	2.16	0.98-4.79	.058
Age-adjusted Charlson comorbidity index score	1.14	0.99-1.30	.067	1.01	0.84-1.20	.932
ASA physical status III-IV	2.24	1.15-4.35	.018	2.11	0.90-4.91	.085
Number of daily medications	1.16	1.05-1.29	.005	1.16	1.03-1.31	.014

Note. OR = Odds Ratio; CI = Confidence Interval; ASA = American Society of Anesthesiologists

classification.

Depending on age, tests and cut-offs used, frequency of olfactory dysfunction differs a lot and may concern up to 3 out of 4 older adults (22). Among our cohort, we found 65.2% hyposmic patients and 14.2% anosmic patients using the Sniffin' Sticks 12-item identification test.

There was a clear link between olfactory function and the preoperative EFS score, anosmia being associated with preoperative frailty and normosmia being more prevalent in robust patients. Previous studies exploring smell and frailty are sparse and may present methodological weaknesses (13). A first study conducted in 768 Japanese community-dwelling adults aged ≥ 65 years failed to find a significant association between self-assessed olfactory dysfunction and a modified Fried's frailty criteria (9). Another study including 1035 Italian subjects of the same age range showed a relationship between self-assessed olfactory dysfunction and Fried's frailty criteria (11). Both these studies suffer from the subjectivity of self-assessing olfaction (23). Harita et al used a Japanese-adapted 12-item identification test in 141 community-dwelling older adults. They found a significant correlation between olfactory impairment and the Study of Osteoporotic Fractures index of frailty (10). Lastly, Bernstein et al also demonstrated a strong association between olfactory dysfunction (examined with an 8-item identification test) and a 39-item frailty index in their study totalizing 3547 participants aged ≥ 40 years (12). These two latter studies were cross-sectional studies and data were reported by the participants, which could have led to some biases.

Nevertheless, our results are in line with those data and thus contributes to the validation of olfactory dysfunction as being associated with frailty. In the multivariable model, we controlled for comorbidities and for ASA physical status which did not attenuate the relationship between anosmia and frailty. Harita et al also found that the results were not modified by adjusting for health-related confounding factors (10).

Olfactory dysfunction is a well-known biomarker for neurodegenerative diseases, suggesting more largely a substantial link with cognition (24, 25). In our study, anosmic preoperative older adults were more likely to exhibit lower

scores at CDT, which supports the possibility that olfactory dysfunction may relate to preoperative cognitive impairment. Recently, the concept of cognitive frailty has emerged associating physical frailty and cognitive impairment (26). The two latter are thought to share the same mechanisms and to both lead to poor outcome (27). Therefore, this might account for the fact that olfactory dysfunction is associated with both frailty and cognitive impairment in our data.

In our cohort, over the year that followed surgery, 28.1% of the patients developed a complication and nearly 6% died. Obviously, the figures of perioperative morbidity and mortality varies greatly in the literature according to type of surgeries, the type of patients and the urgency of surgery. Given our "real-life" older population, the wide range of surgeries performed with an elective setting, these outcome data seem comparable to other studies (28–30). Importantly, we show that anosmia is a predictor of poor postoperative outcome. In our cohort, the small number of death events precludes any valuable conclusion on its own. Yet, regarding complications, incidence was 2.5 times higher in anosmic than in normosmic patients.

The present results in a perioperative context brings more evidence to the previously described link between olfactory dysfunction and mortality (5). Also, our results may shed some light on the underlying mechanisms. Controlling for frailty in the prediction of poor postoperative outcome strongly decreased the effect of anosmia on postsurgical outcome. We also adjusted for comorbidities in a different model, which had in this case less effect on anosmia. In a study including 125 older patients undergoing elective surgery, it was found that age and the EFS score were the only variables to remain statistically significantly associated to postoperative complications, unlike various medical comorbidities (31). All this suggests a prominent role of frailty in mediating the association between olfactory dysfunction and bad outcome. On the other hand, the effect of general poor health, that is, suffering from multiple comorbidities, seems of less importance.

Not surprisingly, we noted a quite poor performance of both the EFS and the Sniffin' Sticks 12-item identification test when building ROC curves to further predict the presence of poor postoperative outcome. Obviously, postoperative outcome

does not depend exclusively on frailty. Furthermore, frailty assessment will always remain tricky, explaining why so many different frailty instruments currently exist in the literature without a single one being truly a silver bullet. What is more interesting was the added value of anosmia or normosmia on the predictive values of the EFS. Olfactory testing, as a quick bedside tool, demonstrates here its potential clinical value and could thus add up to the available battery of frailty tests.

It is important to recognize some limitations of our study. First, our cohort may suffer from a small sample size, which limited power in some analyses, notably concerning 1-year mortality rate. Second, our preoperative population as well as the type of surgery was very diversified and may lack standardization in order to improve specificity in the outcome results. Third, follow-up was based on chart review and may thus have missed some postoperative events. Finally, patients did not systematically take a COVID-19 PCR-test before surgery, which could have led to some confounding bias regarding olfactory function.

Conclusion

In conclusion, we bring new evidence regarding the link between olfaction, frailty and postoperative outcome. Olfactory dysfunction is definitely associated with preoperative frailty, which, in turn, seems to play a key role in mediating the relationship between olfactory dysfunction and poor outcome. From a clinical perspective, quick assessment of olfactory status seems to improve the performance of frailty evaluation in the prediction of postsurgical outcome. Larger prospective studies with more standardized population are needed to strengthen these findings.

Ethical Standards: The study was carried out in accordance with the ethical standards of the Belgian and European legislations and with the approval of our institutional Ethics committee which has received accreditation from the Association for the Accreditation of Human Research Protection Program.

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Conflict of interest: The authors have no conflicts of interest to disclose.

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