SCIENTIFIC ARTICLE

Impact of postoperative cognitive decline in quality of life: a prospective study

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KEYWORDS
Postoperative care; Postoperative cognitive decline; Quality of life

Abstract
Background: Regardless the progress in perioperative care postoperative cognitive decline (PCD) has been accepted unequivocally as a significant and frequent complication of surgery in older patients. The aim of this study was to evaluate the incidence of postoperative cognitive decline and its influence on quality of life three months after surgery.
Methods: Observational, prospective study in a Post-Anesthesia Care Unit (PACU) in patients aged above 45 years, after elective major surgery. Cognitive function was assessed with Montreal Cognitive Assessment (MOCA); Quality of life (QoL) was assessed using SF-36 Health Survey (SF-36). Assessments were performed preoperatively (T0) and 3 months after surgery (T3).
Results: Forty-one patients were studied. The incidence of PCD 3 months after surgery was 24%. At T3 MOCA scores were lower in patients with PCD (median 20 vs. 25, p = 0.009). When comparing the median scores for each of SF-36 domains, there were no differences between patients with and without PCD. In patients with PCD, and comparing each of SF-36 domains obtained before and three months after surgery, had similar scores for every of the 8 SF-36 areas while patients without PCD had better scores for six domains. At T3 patients with PCD presented with higher levels of dependency in personal activities of daily living (ADL).
Conclusion: Three months after surgery patients without PCD had significant improvement in MOCA scores. Patients with PCD obtained no increase in SF-36 scores but patients without PCD improved in almost all SF-36 domains. Patients with PCD presented higher rates of dependency in personal ADL after surgery.
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PALAVRAS-CHAVE
Cuidado pós-operatório; Declínio cognitivo pós-operatório; Qualidade de vida

Impacto do declínio cognitivo pós-operatório na qualidade de vida: estudo prospectivo

Resumo
Justificativa e objetivo: Independente do progresso do tratamento no período perioperatório, o declínio cognitivo no pós-operatório (DCPO) é inequívocamente aceito como uma complicação importante e frequente da cirurgia em pacientes mais velhos. O objetivo deste estudo foi avaliar a incidência de DCPO e sua influência na qualidade de vida três meses após a cirurgia.

Métodos: Estudo prospectivo observacional conduzido em Sala de Recuperação Pós-anestesia (SRPA) com pacientes de idade superior a 45 anos, após cirurgia eletiva de grande porte. A função cognitiva foi avaliada com o teste de Avaliação Cognitiva de Montreal (MOCA) e a qualidade de vida (QV) com o Questionário sobre Qualidade de Vida (SF-36). As avaliações foram realizadas no pré-operatório (T0) e três meses após a cirurgia (T3).

Resultados: Foram avaliados 41 pacientes. A incidência de DCPO três meses após a cirurgia foi de 24%. Em T3, os escores MOCA foram menores nos pacientes com DCPO (mediana 20 vs. 25, p = 0,009). Ao comparar as medianaes dos escores para cada um dos domínios do SF-36, não observamos diferenças entre os pacientes com e sem DCPO. Ao comparar cada um dos domínios do SF-36 obtidos antes e após três meses de cirurgia, os pacientes com DCPO apresentaram resultados semelhantes para cada uma das oito áreas do SF-36, enquanto pacientes sem DCPO apresentaram resultados melhores em seis domínios. Em T3, os pacientes com DCPO apresentaram níveis mais elevados de dependência na realização de atividades cotidianas.

Conclusão: Três meses após a cirurgia, os pacientes sem DCPO apresentaram melhora significativa dos escores MOCA. Os pacientes com DCPO não apresentaram aumento dos escores SF-36, mas os pacientes sem DCPO apresentaram melhora em quase todos os domínios do SF-36. Os pacientes com DCPO apresentaram taxas mais elevadas de dependência na realização de atividades cotidianas após a cirurgia.

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Introduction

Regardless the progress in perioperative care, postoperative cognitive decline (PCD) has been accepted unequivocally as a significant and frequent complication of surgery in older patients.\(^1\)\(^-\)\(^12\) However, there is still no consensus definition of PCD in the medical community, and broadly, it refers to a temporary decline in cognition associated with surgery.\(^13\) If it last longer than three months is defined as long-term postoperative cognitive decline.\(^13\)\(^,\)\(^14\) If a considerable proportion of patients do not recover three months after surgery (7–69% in cardiac surgery).\(^15\)

The exact etiology of PCD remains unclear and is probably multifactorial.\(^15\)\(^,\)\(^16\) Complications in the perioperative period may anticipate early PCD, but increasing age has been shown to be a significant and independent risk factor for PCD. The incidence of PCD is expected to increase as the population of older surgical patients grows.\(^11\)\(^,\)\(^17\)

Patients submitted to cardiac surgery have been furiously studied, however, the incidence and prevalence of this complication after other types of surgery has not been so exhaustively reported.\(^16\)\(^,\)\(^18\) The International Study of Postoperative Cognitive Dysfunction (ISPOCD) group studied 1218 patients aged 60 years old or older, undergoing major general surgery and reported an incidence of PCD of 25.8–9.9%, one week and three months following surgery, respectively.\(^6\) However, the estimation of the frequency of PCD still varies from 25% to 80%.\(^4\)

The diagnosis of PCD requires valid and accurate preoperative and postoperative neuropsychological testing and the determination of a cut-off point between PCD and normal variation in cognitive performance. PCD diagnosis is not easy to perform and it has no apparent clinical symptoms – patients may present an impairment in one or various cognitive abilities such as memory, attention, concentration, speed of motor and mental response, information processing and learn after surgery and anesthesia that is different from delirium.\(^6\)\(^,\)\(^13\)\(^,\)\(^19\) It has a subtle manner of manifestation, commonly many days or weeks after surgery.\(^2\)\(^-\)\(^4\) Numerous clinicians fail to recognize the subject’s cognitive decline following surgery; but also the patients themselves, due to inattention or embarrassment, may not be aware of their PCD or be reluctant to report any alteration.\(^7\) Until now, there is no standard accepted approach for its diagnosis, and it is essential use several valid and highly sensitive neuropsychological tests, which allow assessing many cognitive areas.\(^2\)\(^-\)\(^4\)\(^,\)\(^19\)\(^-\)\(^21\)

Although cognitive changes are not manifested clinically in some patients, recent studies show that PCD may lead to a prolonged hospital stay, elevated medical costs, increased morbidity and readmission to hospital. PCD has long-term consequences in terms of increased all-cause mortality and declined in Quality of Life (QoL), associated with impairments in daily functioning, premature departure from the labor market, and dependency on economic assistance after hospital discharge.\(^2\)\(^,\)\(^4\)\(^,\)\(^9\)
The purpose of this study was to assess the incidence of PCD and cognitive recovery 3 months following non-cardiac and non-neurological surgery and to determine the impact of cognitive decline in QoL and dependency in activities of the daily living.

Methods

Ethics

Ethical approval for this study (Ethical Committee approval n° 127/12) was provided by Comitê de Ética para a Saúde do Centro Hospitalar de São João, Porto, Portugal (Chairperson: Professor Filipe Almeida) on May 25, 2012. Written consent was obtained from all patients.

The cohort

A total of 221 patients undergoing elective major surgery were enrolled in the multidisciplinary Post-Anesthesia Care Unit (PACU). The inclusion criteria involved adult Portuguese-speaking patients submitted to major elective surgery (defined as surgery that requires two or more days of hospital stay) requiring anesthesia, aged 45 years old and older. Patients could not be included twice, even if they had an unrelated second procedure. Patients were also excluded if they (1) had cognitive impairment at baseline assessment considered for patients with a Mini-Mental State Examination (MMSE) score of less than 24; (2) had not provided or were incapable of providing informed consent; (3) were unable to understand the language used or were illiterate; (4) were unwilling to comply with the protocol or procedures; (5) had been admitted to urgent or emergent surgery; (6) had been admitted for obstetric, neurological or cardiac surgery; and (7) were admitted to intensive care units for postoperative vigilance. All patients were interviewed either on the eve or the day of the surgery (at least 3 h before). It was then conducted a small consultation to obtain consent, to perform MMSE test and to collect the medical history. Patients completed neuropsychological tests at entry to the study (TO) and three months after surgery (T3). These tests included the Montreal Cognitive Assessment test (MOCA), the Medical Outcomes Study 36 items Short Form Health Survey test (SF-36), the Lawton instrumental activities of the daily living scale (Lawton scale) and the Katz Index of Independence in activities of the daily living (Katz’s Index). Anesthesiologists were blinded to patient involvement in the study. Conduct of anesthesia, including the choice of the type of anesthesia was at the discretion of the anesthesiologist.

Patient assessment

The recorded patients’ characteristics were: age, weight, height, body mass index (BMI) and American Society of Anaesthesiologists Physical Status (ASA-PS). The Revised Cardiac Risk Index (RCRI) was also calculated, using the classification system reported by Lee et al., which includes high-risk surgery (i.e., intraperitoneal, intrathoracic, or suprainguinal vascular procedures) and clinical risk factors of ischemic heart disease, compensated or prior heart failure, cerebrovascular disease, diabetes mellitus and renal insufficiency. These variables are included in the Cardiac Risk Stratification for Non-cardiac Surgical Procedures of the 2007 guidelines on Perioperative Cardiovascular Evaluation and Care for Non-cardiac Surgery of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Intraoperative details, including type and duration of anesthesia and surgical procedures, length of PACU stay and any cardiorespiratory events in this unit were also documented.

Evaluation of PCD and quality of life

Each participant underwent neuropsychological testing at two-time points: preoperatively (TO) and three months after surgery (T3).

All patients completed baseline assessments of general cognitive functioning assessed by the Mini-Mental State Examination. MMSE is a valid and recognized test, performed in 5–10 min; that evaluates cognitive status. It grossly evaluates executive cognitive function by measuring orientation, calculations, memory, reading and writing capacities, language and visuospatial ability. Even so, patients with mild forms of cognitive decline frequently score in the normal range in the MMSE.

Montreal cognitive assessment test is a one-page questionnaire that takes 10 min to perform and is suitable to evaluate short-term memory, executive functions, working memory, concentration, visuospatial abilities, attention, language, and temporal and spatial orientation. The score range varies from 0 to 30, and higher scores indicate better cognitive performance. To adjust for educational effects, subjects with 12 or fewer years of education receive an extra point. Several studies were conducted in Portugal concerning the Portuguese experimental version of the MOCA, and the studies’ conclusions appear to assure the validity and clinical utility of this tool. Adopting the criterion used by Baracchini et al., a decline of at least 2 points in MOCA test at T3 was considered as clinically relevant and defined as PCD.

The Medical Outcomes Study 36 Item Short Form Health Survey aims to quantify general health condition and consists of eight sections or domains, which are the weighted sums of the questions in their section. The eight domains are vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health. This questionnaire has also been culturally adapted to the Portuguese and validated in a study by Ferreira et al.

Evaluation of functional capacity was based on the ability of the patient to undertake personal and instrumental activities of daily living. To do so, two questionnaires that assess the functional independence of the subject to accomplish instrumental ADL (I-ADL) and personal ADL (P-ADL) were used: the Lawton I-ADL scale and the Katz’s Index of Independence in ADL, respectively. The Lawton I-ADL scale is easy to perform and provides self-reported knowledge about the functional skills needed to live in the community, such as the ability to use the telephone and to handle...
finances, shopping, housekeeping, food preparation, public transportation and responsibility for own medications.\(^{2,5}\) The Katz ADL scale evaluates basic personal ADL and ranks capability of performance in 6 areas: bathing, dressing, going to the toilet, transferring from bed to chair, continence and feeding.\(^{2,5}\) The patients’ answers were categorized into two classes: capable or incapable to perform each activity or group of activities. They were considered to be dependent if they were incompetent to perform at least one instrumental or personal ADL.

### Statistical analysis

Descriptive analysis of variables was used to summarize data. Ordinal and continuous data found not to follow a normal distribution, based on the Kolmogorov–Smirnov test for normality of the underlying population, are presented as median and interquartile range (IQR). Normally distributed data are presented as mean and standard deviation (SD). Non-parametric tests were performed for comparisons (Wilcoxon signed rank test and the Mann–Whitney U test). The chi-square test or Fisher’s exact test were used to compare proportions between two groups of subjects. The related samples Wilcoxon signed rank test was used to compare SF-36 scores before surgery and three-months after surgery. Differences were considered statistically significant when \(p\) was \(<0.05\). SPSS software for Windows Version 20.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyzes.

### Results

From the 221 patients consecutively admitted in the PACU during the study period, a total of 41 patients were included.
Table 2 SF-36 in patients with PCD.

<table>
<thead>
<tr>
<th>Domain</th>
<th>T0 (median)</th>
<th>T3 (median)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical function</td>
<td>83</td>
<td>75</td>
<td>0.779</td>
</tr>
<tr>
<td>Role physical</td>
<td>59</td>
<td>56</td>
<td>0.635</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>43</td>
<td>67</td>
<td>0.314</td>
</tr>
<tr>
<td>General health</td>
<td>53</td>
<td>49</td>
<td>0.674</td>
</tr>
<tr>
<td>Vitality</td>
<td>40</td>
<td>44</td>
<td>0.905</td>
</tr>
<tr>
<td>Social functioning</td>
<td>75</td>
<td>69</td>
<td>0.918</td>
</tr>
<tr>
<td>Role emotional</td>
<td>79</td>
<td>75</td>
<td>0.921</td>
</tr>
<tr>
<td>Mental health</td>
<td>52</td>
<td>58</td>
<td>0.818</td>
</tr>
</tbody>
</table>

SF-36, 36-Item Short Form Health Survey; PCD, postoperative cognitive decline; T0, before surgery; T3, 3 months after surgery.

One-hundred sixty-three patients were excluded, according to the exclusion criteria: 21 could not perform preoperative assessment, 112 had less than 45 years old, 12 patients were admitted to a surgical intensive care unit, 8 patients were unable to provide informed consent or had an MMSE < 24, 2 patients did not undergo surgery, 2 patients underwent neurosurgery, 3 patients did not speak Portuguese and 3 patient refused to participate. From the remaining 57 patients, only 41 patients have completed all evaluations for cognitive assessment and quality of life at three months follow-up.

The characteristics of the population are summarized in Table 1. The median age was 64 years old. 78% of the patients underwent general or combined anesthesia (general plus locoregional anesthesia, and the median time for its duration was 120 min. Gastrointestinal surgery accounted for) 49% of the cases, plastic and reconstructive surgery to 15%, gynecologic surgery and orthopedics, each 10%, urology to 8%, vascular to 4%, head and neck surgery to 3% and otorhinolaryngology to 1% of the cases. No statistically significant differences between patients with and without PCD were recorded for the studied variables.

The incidence of PCD, 3 months after surgery, was 24% (n = 10). At T0, no differences emerged for the MOCA scores between patients with and without cognitive impairment (median 25 vs. 21, p = 0.139). At T3, however, patients with PCD had worse median MOCA scores (20 vs. 25, p = 0.009). Comparing to preoperative MOCA scores, PCD patients had worse MOCA median scores at T3 (20 vs. 25, p = 0.001), while patients without PCD had better scores (25 vs. 21, p < 0.001).

Table 2 and 3 present median scores of SF-36 domains for both groups of patients, comparing T0 and T3 score. For patients with PCD, and comparing each of SF-36 domains at T0 and T3, there are similar scores for every of the eight SF-36 domains (Table 2). Patients without PCD had better scores at T3 in six domains (Table 3): role limitations caused by physical problems (median 63 vs. 50, p = 0.021), bodily pain (median 74 vs. 62, p = 0.022), general health perception (median 65 vs. 57, p = 0.016), social functioning (median 100 vs. 75, p < 0.001), role limitations caused by emotional problems (median 92 vs. 67, p = 0.014) and mental health (median 68 vs. 52, p < 0.001) and they had similar scores for vitality (p = 0.208) and physical function (p = 0.289) domains.

Table 4 and 5 present the median scores for all SF-36 domains obtained before and after surgery, respectively, comparing patients with and without PCD. As exhibited, at T0 and T3 all scores for SF-36 domains were similar.

In Table 6 it is shown that at T0 there were similar rates of dependency in P-ADL and I-ADL, when comparing patients with and without PCD; however, at T3 patients with PCD presented with higher levels of dependency in P-ADL (50% vs. 16%, p = 0.030). Comparing their rates of dependency at T0 with T3 and for patients with PCD there is a higher dependence scores in I-ADL (50% vs. 10%, p = 0.037) but not for P-ADL (10% vs. 10%, p = 1.0). In the same comparison, patients without PCD had no differences in I-ADL (29% vs. 29%, p = 1.0) or P-ADL dependency (3% vs. 7%, p = 0.572).

Table 4 Comparing groups with and without PCD before surgery for SF-36 (T0).

<table>
<thead>
<tr>
<th>SF-36 domains</th>
<th>Without PCD</th>
<th>With PCD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical function</td>
<td>70</td>
<td>83</td>
<td>0.772</td>
</tr>
<tr>
<td>Role physical</td>
<td>50</td>
<td>59</td>
<td>0.561</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>62</td>
<td>43</td>
<td>0.407</td>
</tr>
<tr>
<td>General health</td>
<td>57</td>
<td>53</td>
<td>0.465</td>
</tr>
<tr>
<td>Vitality</td>
<td>46</td>
<td>40</td>
<td>0.562</td>
</tr>
<tr>
<td>Social</td>
<td>75</td>
<td>75</td>
<td>0.736</td>
</tr>
<tr>
<td>Role emotion</td>
<td>67</td>
<td>79</td>
<td>0.288</td>
</tr>
<tr>
<td>Mental health</td>
<td>52</td>
<td>52</td>
<td>0.513</td>
</tr>
</tbody>
</table>

SF-36, 36-Item Short Form Health Survey; PCD, postoperative cognitive decline; T0, before surgery.

Table 5 Comparing groups with and without PCD for SF-36 3 months after surgery (T3).

<table>
<thead>
<tr>
<th>SF-36 domains</th>
<th>No PCD (median)</th>
<th>PCD (median)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical function</td>
<td>65</td>
<td>75</td>
<td>0.749</td>
</tr>
<tr>
<td>Role physical</td>
<td>63</td>
<td>56</td>
<td>0.192</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>74</td>
<td>67</td>
<td>0.267</td>
</tr>
<tr>
<td>General health</td>
<td>65</td>
<td>49</td>
<td>0.149</td>
</tr>
<tr>
<td>Vitality</td>
<td>50</td>
<td>44</td>
<td>0.269</td>
</tr>
<tr>
<td>Social</td>
<td>100</td>
<td>69</td>
<td>0.200</td>
</tr>
<tr>
<td>Role emotion</td>
<td>92</td>
<td>75</td>
<td>0.153</td>
</tr>
<tr>
<td>Mental health</td>
<td>68</td>
<td>58</td>
<td>0.264</td>
</tr>
</tbody>
</table>

SF-36, 36-Item Short Form Health Survey; PCD, postoperative cognitive decline; T3, 3 months after surgery.
Table 6  Independence in activities of daily living before and after surgery.

<table>
<thead>
<tr>
<th>ADL</th>
<th>No PCD (n = 31)</th>
<th>PCD (n = 10)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-ADL at T0, n (%)</td>
<td>2 (7)</td>
<td>1 (10)</td>
<td>0.578</td>
</tr>
<tr>
<td>P-ADL at T0, n (%)</td>
<td>7 (23)</td>
<td>1 (10)</td>
<td>0.358</td>
</tr>
<tr>
<td>I-ADL at T3, n (%)</td>
<td>1 (3)</td>
<td>1 (10)</td>
<td>0.433</td>
</tr>
<tr>
<td>P-ADL at T3, n (%)</td>
<td>5 (16)</td>
<td>5 (50)</td>
<td>0.030*</td>
</tr>
</tbody>
</table>

ADL, instrumental activities of daily living; P-ADL, personal activities of daily living; T0, before surgery; T3, 3 months after surgery.

Discussion

We report an incidence of PCD of 24%, three months following surgery. In literature, the incidence of PCD is not clearly defined and may vary between 25% and 80%.5,12 Many current reports establish that surgery, particularly cardiac surgery, may result in PCD and that its incidence increases with age, independently of the anesthetic technique.11

PCD can have a considerable impact on quality of life and may result in withdrawal from society.11,13,15,16 In recent years, PCD after non-cardiac surgery has been systematically studied. In particular the ISPOCD (International Study group of Postoperative Cognitive Dysfunction) was successful in uncovering the extent of the problem and defining risk factors. Early PCD occurs in approximately 25% of patients one week after surgery, and then declines to less than 10% after three months.5

PCD refers to deterioration in cognition temporarily associated with operation; thus, the growing number of elderly patients undergoing surgery should aware anesthesiologists and surgeons to its serious repercussions.11

Nevertheless, there is no explicit information if any change in procedures would change the incidence of PCD, but it is possible that preoperative medication, anticholinergic, catecholamine’s, and some events such as hypotension, hypothermia, hypoxia, cerebral atheroembolism or hypoperfusion, poor glycemic control and carotid endarterectomy may contribute to high incidence levels of PCD.7 In our study, we did not found differences related to patient demographic variables or anesthesia or surgical characteristics.

In the multiple PCD studies there has not been a standard methodology used12 and the choice of neuropsychological test instruments, the criteria to consider, the timing of testing and retesting, and inclusion and exclusion criteria have all varied.14

The use of highly sensible and specific neuropsychological tests allows for the identification of subtle cognitive deficits with excellent test/retest validity, but with highest risk of type II errors (failing to detect PCD). For this study, the MOCA test was chosen because it is easy and quick to perform and enables the evaluation of several functional domains of cognition. Even so, it may fail to identify some patients with milder forms of PCD.15,16

Perioperative interventions have long-range effects on the individual, so strategies to preserve long-term cognitive performance and quality of life are required.17

The risk of cognitive decline increases with age and is further enhanced after hospitalization for surgery, resulting in significant morbidity and reduced quality of life.18 Actually, there is no individual approach to avoid cognitive deterioration1 but the maintenance and/or restoration of functional independence, including cognition, in the elderly hospitalized patient constitutes a major challenge for the health care system.

The postoperative cognitive decline may diminish improvements in QOL and strategies to reduce cognitive decline may allow patients to achieve the maximum improvement in QOL after surgery. This has been the subject of various studies19 and like them the present study demonstrated that cognitive decline limited improvement in QOL.

Even mild cognitive deficits before surgery may be a marker for increased risk of cognitive decline19 and also it has been accepted that PCD generally resolve within 1–3 months in most patients in whom new cognitive symptoms develop during postoperative period.33,39,40

Three months after surgery a significant improvement in quality of life in patients without PCD was demonstrated by an increase in almost all scores of SF-36 domains, but amongst patients with PCD, no improvement was seen in any of the SF-36 scores. This limitation in quality improvement is also demonstrated in PCD patients by a significant more dependency in P-ADL three months after surgery comparing with patients without PCD.

This study has several limitations. It is an observational study, with a small sample of patients. It has many dropouts and losses to the follow-up (explained, in part, by the need to have complete interviews before and after the surgery, for follow-up consultation). Furthermore, we did not studied clinical variables after surgery, including complications and medications that may have affected not only the losses to follow-up but also the results in cognitive performance, quality of life and independence in ADL.

Conclusions

The principal findings of this study were as follow: (1) the incidence of PCD was of 24%; (2) patients with PCD shown no improvements in quality of life scores; and (3) patients without PCD shown better scores in almost all SF-36 domains and an increase in dependency, after surgery.

PCD is a real event, with real complications and consequences in the quality of life, which requires a better understanding, especially in terms of etiologic factors in order to prevent them. It should not be overestimated as it decreases the quality of life and enhances the degree of dependence for activities of daily living, and high-quality perioperative care and support are social and financial are essential.

Authorship

All authors confirm that they have read and approved the paper.

All authors confirm that they have met the criteria for authorship as established by the ICMJE, believe that the
paper represents honest work, and can verify the validity of the results reported.

All persons designated, as authors are qualified for authorship.

Each author participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All authors have substantial contributions to conception and design, acquisition of data, analysis and interpretation of data, drafting the article or revising it critically for important intellectual content.

All authors made their final approval of the version if is to be published.

Conflicts of interest

The authors declare no conflicts of interest.

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