SYSTEMATIC REVIEW

Effectiveness of Radioiodine Therapy for Graves' Hyperthyroidism: A Quality-of-Life Assessment

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ABSTRACT

Introduction: Graves' disease, an autoimmune disorder characterized by hyperthyroidism, is commonly managed through radioactive iodine therapy, antithyroid drugs, and thyroidectomy. Previous reports suggest that individuals undergoing radioactive iodine therapy exhibit superior overall quality of life and satisfaction compared to those opting for alternative therapeutic modalities. This study systematically reviewed evidence on the effectiveness of radioiodine therapy for Graves' hyperthyroidism, specifically emphasizing its impact on patients' quality of life.
Methods: A systematic review was conducted on studies evaluating the quality of life of adult patients with Graves' hyperthyroidism following radioiodine therapy. A literature search was carried out utilizing the PubMed, ScienceDirect, and Sage Journals online databases. The search results were screened according to the eligibility criteria for inclusion in a narrative synthesis.
Results: The search yielded 203 items, of which four articles fulfilled the eligibility criteria and were included in the review. radioiodine therapy demonstrated improvements in the quality of life of patients with Graves' disease compared to other therapeutic modalities or no treatment at all. Enhancement in quality of life was observed across various scales, encompassing physical symptoms (goiter, hyperthyroidism, eye symptoms, and hypothyroidism), psychological symptoms (depression and anxiety), functioning and well-being (fatigue, cognitive impairment, and emotional vulnerability), and participation (social life disruptions, daily life interference, and cosmetic complaints).
Conclusion: Findings concerning quality of life underscore the long-term effectiveness of radioiodine therapy as a preferred intervention for Graves' disease, contributing valuable insights for clinical decision-making.

Keywords: Graves' disease; radioiodine therapy; quality of life; psychological well-being

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Highlights:
1. This systematic review comprehensively synthesizes research findings regarding the impact of radioiodine therapy on the long-term quality of life of patients with Graves' hyperthyroidism compared to surgery or antithyroid medication.
2. The findings suggest that radioiodine therapy offers improvement in the quality of life, which may be indicated by physical and psychological symptoms, functioning, well-being, and participation.

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INTRODUCTION

Graves' disease is an autoimmune condition characterized by the excessive production of hormones by thyroid follicle cells. This overproduction occurs due to the activation of circulating antibodies against the thyroid-stimulating hormone receptor (De Leo et al., 2016; Davies et al., 2020). Common symptoms of Graves' disease include fatigue, weight loss, anxiety, irritability, amenorrhea, and, in severe cases, exophthalmos (Bartalena, 2017; Gontarz-Nowak et

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al., 2020; Hakim et al., 2021; Ahn et al., 2022; Lutfiyah et al., 2024).

There are three management options for Graves' disease: antithyroid drugs, radioiodine therapy, and thyroidectomy. Each therapy has its advantages and disadvantages (Brito et al., 2020; Bartalena et al., 2022; Cohen et al., 2022). Patients newly diagnosed with Graves' disease are typically administered antithyroid drugs for the initial 12 to 18 months. For patients with Graves' disease who experience relapse or persistent hyperthyroidism accompanied by elevated thyroid-stimulating hormone receptor antibodies, additional treatment options may be administered, including 12 months of radioiodine therapy or thyroidectomy (Kahaly et al., 2018; Idham & Prajitno, 2022).

Radioiodine therapy is indicated for the management of hyperthyroidism and thyroid cancer. This therapy induces permanent changes in thyroid tissue by emitting two types of radiation, i.e., gamma and beta rays. Gamma radiation is more useful for diagnostic purposes, while beta radiation has therapeutic effects (Lacoeuille et al., 2018; Pokhrel & Bhusal, 2023). Radioiodine therapy can be employed in patients with low-volume disease or in combination with surgery for extensive cases. Locally or regionally advanced disease can be initially treated with debulking surgery followed by radioiodine therapy. Generally, radioiodine therapy is less effective for large tumors with a diameter exceeding 1–2 cm (Okosieme et al., 2020; Sellem et al., 2020; Kim et al., 2022). The objective of this systematic review was to evaluate the effectiveness of radioiodine therapy for Graves' disease, focusing on quality-of-life aspects, including both clinical and functional complaints.

METHODS

Strategy for the literature search

This systematic review sought to analyze studies evaluating the quality of life of patients undergoing radioiodine therapy for Graves' disease. The studies were retrieved from the PubMed, Scopus, and Sage Journals online databases. The literature search utilized the following Medical Subject Headings (MeSH) terms representing the focus of the review: "Graves' disease," "radioiodine therapy," and "quality of life." Boolean operators were incorporated to form the complete search strategy for each database, as shown in Table 1 (Wang et al., 2021). The literature search was conducted from database inception to December 31st, 2023. Ethics considerations were not applicable for this type of research.

Screening of the search results according to eligibility criteria

Two independent reviewers (MFA and AJJ) performed the screening process for the search results according to the following inclusion criteria: 1) longitudinal studies (cohort/case-control) and randomized controlled trials (RCT) published as original articles; 2) research involving patients subjected to radioiodine therapy for Graves' disease compared with other therapeutic modalities; 3) studies focusing on quality of life measured during or after the administration of therapeutic regimens. The exclusion criteria encompassed studies published in languages other than English or Indonesian, as well as duplicates. A third reviewer (JHP) was involved to resolve any disagreements between the two reviewers (Muka et al., 2020).

Table 1. Literature search strategy framework

PICO elements	Description	Search terms	Boolean operator applications
Patients	Adult patients over the age of 18 years diagnosed with Graves' disease and hyperthyroidism	Graves' disease	"Graves' disease" OR "basedow disease" OR "exophthalmic goiter" OR "hyperthyroidism, autoimmune"
Intervention	Radioiodine therapy for the treatment of Graves' disease	Radioiodine	"Radioactive iodine" OR "radioiodine" OR "RAI" OR "iodine-131" OR "I-131"
Comparison	Antithyroid drugs and thyroidectomy for the management of Graves' disease	N/A	N/A
Outcome	Quality of life of patients undergoing therapy for Graves' disease, measured using the ThyPRO questionnaire	Quality of life	"Quality of life" OR "QoL" OR "health-related quality of life" OR "HRQOL"

Notes: PICO=patient, intervention, comparison, outcome; RAI=radioactive iodine; I-131=iodine-131; ThyPRO=thyroid-specific patient-reported outcome; QoL=quality of life; HRQoL=health-related quality of life; N/A=not available.

Extraction and analysis of the data

The following data were extracted from the included studies: author, publication year, country, number of samples, age distribution, the frequency of Graves' disease treatment types (antithyroid drugs, surgery, or radioiodine therapy), follow-up duration, and the results of quality-of-life assessment using the thyroid-specific patient-reported outcome (ThyPRO) questionnaire. The extracted data were presented in a characteristic table, accompanied by narrative synthesis and qualitative analysis of the studies to draw the main conclusions of the review (Muka et al., 2020).

The thyroid-specific patient-reported outcome (ThyPRO) questionnaire was utilized as a tool for assessing the quality of life of patients suffering from thyroid disorders. This tool provided a validated and well-tested evaluation of the quality of life for patients with benign thyroid diseases. The questionnaire, comprising 85 items, addressed various aspects of quality of life related to thyroid diseases, including symptoms, physical functioning, emotional well-being, and social factors. The ThyPRO questionnaire facilitated physicians in symptom management and enhanced communication with patients. Additionally, data from the ThyPRO assessment could be utilized to compare patient outcomes across different institutions, ultimately improving the quality of patient care (Watt et al., 2015; Giusti et al., 2020).

Assessment of the risk of bias

To evaluate the potential risk of bias in the included studies, a qualitative assessment approach was employed, given that no formal risk assessment tools were utilized. The studies were examined based on key domains that commonly contribute to bias, including selection bias, performance bias, detection bias, attrition bias, and reporting bias. The assessment focused on study design, population selection, comparability of intervention groups, measurement consistency, and the completeness of reported data (Viswanathan et al., 2018).

Selection bias was evaluated by examining the appropriateness of randomization, the clarity of inclusion and exclusion criteria, and the potential presence of confounders that could impact the results. Performance bias was assessed according to the standardization of treatment protocols across study groups and whether any form of blinding was implemented during the administration of radioiodine therapy. To address detection bias, the consistency and reliability of outcome assessment methods, particularly the use of the ThyPRO questionnaire, were analyzed. Attrition bias was identified by evaluating the completeness of follow-up data and whether missing data were accounted for using statistical techniques such as intention-to-treat analysis. Finally, reporting bias was assessed by determining the transparency in reporting all relevant outcomes, ensuring that results were not selectively disclosed based on significance levels (Viswanathan et al., 2018).

RESULTS

Selection of studies for inclusion in the systematic review

The database search yielded 203 articles: 50 from PubMed, 128 from ScienceDirect, and 25 from Sage Journals. Seven duplicates were excluded before the first-stage screening. In the initial screening of titles and abstracts, 182 articles were excluded, leaving 14 articles for full-text retrieval. One article was not available as open access, thereby excluded prior to the second-stage screening. In the second-stage screening of the 13 full-text articles, 6 were excluded for not evaluating quality-of-life outcomes, 2 for not evaluating radioiodine therapy, and 1 for including only pediatric populations. Consequently, four articles were retained for systematic review and qualitative synthesis. The selection process for the included articles is illustrated in the PRISMA flow diagram (Figure 1).

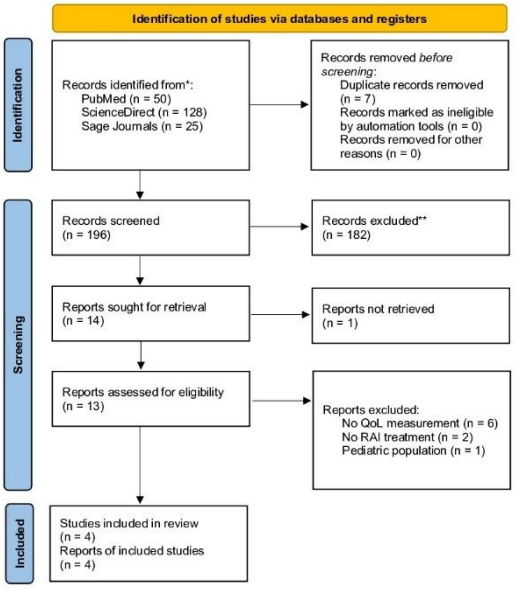

Figure 1. PRISMA flow diagram for the selection process of the included articles

Characteristics of the selected studies

Table 2 depicts the characteristics of the studies included in the systematic review. A total of four studies encompassing 1,260 patients with Graves' disease-related hyperthyroidism were identified, primarily originating from the European continent (50%) and published between 2016 and 2019 (Taïeb

Table 2. Characteristics of the included studies

Author (year)	Country	n	Sex	Age	Intervention		
					ATD	Surgery	RAI
Törring et al. (2019)	Sweden	975	M: 19% F: 81%	Median: 47	352	10	405
Mangelen & Cunanan (2017)	Philippines	58	M: 64.59% F: 35.41%	Mean: 41.82	30	N/A	28
Conaglen et al. (2018)	New Zealand	123	M: 18% F: 82%	Median: 51	79	31	13
Taïeb et al. (2016)	France	104	M: 76.53% F: 23.47%	Mean: 47.95	47	N/A	104

Notes: ATD=antithyroid drugs; RAI=radioiodine therapy; M=male; F=female.

Table 3. Quality of life of Graves' disease patients undergoing radioiodine therapy compared to other modalities

Study	Follow-up duration	Comparison	ThyPRO domains
Törring et al. (2019)	6-10 years	RAI vs. ATD	Worsening in goiter symptoms, hyperthyroid symptoms, tiredness, anxiety, depression, emotional susceptibility, impaired social life, impaired daily life, impaired sex life, cosmetic complaints
Mangelen & Cunanan (2017)	6 months	RAI vs. ATD	Improvement in goiter symptoms, emotional susceptibility, impaired daily life
Conaglen et al. (2018)	6 months	RAI vs. non-RAI (ATD, surgery)	Improvement in tiredness, anxiety, emotional susceptibility, impaired social life, impaired daily life
Taïeb et al. (2016)	6 months	RAI+LT4 prophylaxis vs. RAI	Improvement in emotional susceptibility, impaired social life, impaired sex life, cosmetic complaints

Notes: ThyPRO=thyroid-specific patient-reported outcome; ATD=antithyroid drugs; RAI=radioiodine therapy; LT4=levothyroxine.

et al., 2016; Mangelen & Cunanan, 2017; Conaglen et al., 2018; Törring et al., 2019). The studies by Mangelen & Cunanan (2017) and Taïeb et al. (2016) reported a higher proportion of male participants, while the other two studies by Törring et al. (2019) and Conaglen et al. (2018) predominantly focused on female participants. The majority of Graves' disease-related hyperthyroid patients were in the 40–50 age range, with the lowest mean age reported as 41.82 years in the study by Mangelen & Cunanan (2017) and the highest median age observed at 51 years in the study by Conaglen et al. (2018). Across all studies, 550 patients received radioiodine therapy. Antithyroid drugs and thyroid surgery were administered to 478 and 41 patients, respectively.

Impact of radioiodine therapy on quality of life

Table 3 illustrates the impact of radioiodine therapy on the quality of life of patients with Graves' hyperthyroidism as assessed by the ThyPRO questionnaire. The majority of studies assessed patients at the six-month post-therapy interval (75%). The study by Conaglen et al. (2018) indicated that radioiodine therapy significantly improved aspects of fatigue, anxiety, emotional vulnerability, social life, and daily life compared to non-radioiodine interventions (e.g., antithyroid drugs, surgery). The addition of levothyroxine (LT4) prophylaxis to radioiodine therapy significantly improved emotional vulnerability, social disruptions, social life, and cosmetic complaints compared to radioiodine therapy alone. The study by Mangelen & Cunanan (2017) demonstrated significant improvements in goiter symptoms, emotional vulnerability, and daily life at the six-month follow-up for the group undergoing radioiodine therapy compared to those treated solely with antithyroid drugs. The study by Törring et al. (2019) also compared these two groups but over a much longer period of 6–10 years. In the long-term assessment, it was found that the group receiving radioiodine therapy actually had worse ThyPRO scores in most domains, including goiter symptoms, hyperthyroid symptoms, fatigue, anxiety, depression, emotional vulnerability, social life

disruptions, daily life disruptions, sexual life disruptions, and appearance.

Risk of bias across the included studies

The risk of bias across the included studies varied, with some demonstrating robust methodologies while others had potential limitations. The study by Törring et al. (2019) had a moderate risk of selection bias due to its large sample size and lack of detailed information on randomization. It also exhibited a high risk of attrition bias, as its extensive follow-up period (6–10 years) led to potential loss of data. There were concerns regarding reporting bias since the study documented negative outcomes of radioiodine therapy, but the influence of confounders remained unclear. In contrast, the study by Mangelen & Cunanan (2017) showed a lower risk of selection bias, as it included a clearly defined population and intervention group. However, the study had a moderate risk of performance bias since no mention of blinding was provided, which might have influenced patient-reported outcomes. Detection bias was minimized through the adaptation of the ThyPRO questionnaire into the local language to enhance comprehension and accuracy.

The study by Conaglen et al. (2018) presented a moderate risk of selection bias due to its relatively smaller sample size, which could limit the generalizability of the findings. Nevertheless, reporting transparency was high, as all domains of the ThyPRO questionnaire were thoroughly assessed and discussed. There was a potential risk of attrition bias due to the shorter follow-up duration of six months, which might have affected the reliability of the long-term quality-of-life findings. Lastly, the study by Taïeb et al. (2016) exhibited a low risk of selection bias due to its randomized controlled design and clearly defined intervention, which compared radioiodine therapy with and without LT4 prophylaxis. Detection bias was also minimized by employing standardized outcome measures. The study exhibited a moderate risk of attrition bias, as some participants were lost to follow-up, although this issue was addressed through statistical adjustments.

DISCUSSION

The systematic review revealed variations in sociodemographic profiles among the included studies. Mangelen & Cunanan (2017) and Taïeb et al. (2016) reported a higher prevalence in male patients compared to female patients, with frequencies of 64.59% and 76.53%, respectively. In contrast, Conaglen et al. (2018) and Törring et al. (2019) predominantly included a female study population, comprising 82% and 81%, respectively. No significant differences in the management of male and female patients were identified across the entire set of studies.

In terms of age, Törring et al. (2019) reported an overall median age of 47 years, with a minimum of 35 years and a maximum of 57 years. Patients undergoing radioiodine therapy for disease management were generally older compared to those treated with antithyroid drugs or surgery. This aligns with the findings of Conaglen et al. (2018), revealing an average age of 64 years for radioiodine therapy recipients, in comparison to 50 and 45 years for patients who received antithyroid drugs or underwent surgery, respectively. However, the study by Mangelen & Cunanan (2017) did not demonstrate a significant age difference between patients receiving radioiodine therapy and those treated with antithyroid drugs, as indicated by mean ages of 41.82 and 44.52, respectively (p=0.4535).

Current evidence indicates that gender and age differences play a crucial role in the course of Graves' disease and the success of its management. A study of the Japanese population conducted by Suzuki et al. (2021) revealed increased severity of Graves' disease in males aged 20–30 years, suggesting a decline in disease severity with advancing age. Moreover, female patients have a higher tendency for remission, and for every additional ten years, the recurrence risk of Graves' disease decreases by 14%. A study in Germany indicated that male patients tend to present at a significantly older age with thyroid eye disease and are inclined to manifest a more severe degree of Graves' disease (Oeverhaus et al., 2023). Therefore, male patients in the adult age group are likely to require more intensive management compared to those in other sociodemographic categories.

The management of Graves' disease involves several therapeutic modalities, with considerations of sociodemographic factors, severity, and other comorbidities. In this systematic review, the management of Graves' disease-related hyperthyroidism was classified into radiation-based therapy (i.e., radioiodine therapy), pharmacotherapy with antithyroid drugs, and surgical procedures. Törring et al. (2019) reported that radioiodine therapy for disease management was more frequently utilized than antithyroid drugs, with 405 and 352 patients, respectively. Subsequently, 233 patients underwent surgical management or repeat radioiodine therapy at presentation. Mangelen & Cunanan (2017) conducted a comparative analysis of various factors between 28 patients undergoing radioiodine therapy and 30 patients receiving antithyroid drugs.

Patients undergoing radioiodine therapy for disease management had a longer disease duration and a later initiation of therapy compared to those treated with antithyroid drugs (Mangelen & Cunanan, 2017). In the study by Conaglen et al. (2018) with 123 patients, 64% received only

antithyroid drugs, 11% underwent radioiodine therapy, and 25% had total thyroidectomy. Significant differences were observed among the three therapy groups in terms of age, thyroid gland size, and thyroid-stimulating hormone receptor antibodies (TRAb) levels. Patients receiving radioiodine therapy were significantly older at presentation compared to those treated with antithyroid drugs and surgical management. However, patients undergoing surgical management were prone to have larger thyroid gland sizes and higher TRAb levels.

Discrepancies were noted in the doses used in radioiodine therapy across the included studies. Mangelen & Cunanan (2017) employed a maximum dose of 14.9 millicuries (mCi), aiming to avoid toxic effects on fertility. Taïeb et al. (2016) reported an average dose of 11 mCi among study participants, while Conaglen et al. (2018) used a fixed dose of 15 mCi, which was relatively higher. However, Törring et al. (2019) did not provide detailed information regarding the doses administered to their study participants.

This systematic review found that three out of four studies evaluating quality of life post-radioiodine therapy (six months to ten years post-procedure) indicated improvements in various ThyPRO domains. The most common improvements were observed in the domains of daily life and emotional vulnerability. However, Törring et al. (2019) showed that the group of patients receiving radioiodine therapy exhibited a deterioration in quality of life across almost all ThyPRO domains, except for the cognitive complaints and overall impact on quality of life, when compared to those treated solely with antithyroid drugs.

To ensure a valid and reliable evaluation, the study by Mangelen & Cunanan (2017) adapted the ThyPRO questionnaire into the local Filipino language and modified certain terms for better understanding by the population. Their research found that patients receiving radioiodine therapy experienced improvements in quality of life, particularly in the ThyPRO domains concerning goiter symptoms, emotional vulnerability, and daily life disruptions, compared to the group treated only with antithyroid drugs. This finding suggests that antithyroid drug recipients are more likely to report difficulty in swallowing and face challenges in managing their lives.

In the study by Conaglen et al. (2018), patients receiving radioiodine therapy exhibited a better quality of life compared to those newly diagnosed with Graves' disease. There were improvements in the ThyPRO domains, including hyperthyroid symptoms, fatigue, anxiety, emotional vulnerability, social life disruptions, and daily life disruptions. However, the ThyPRO assessment revealed no difference in quality of life when comparing patients according to their thyroid status. The study also reported that 99% of patients expressed satisfaction with their therapy and would recommend it to relatives if needed, regardless of the type of therapy. In qualitative assessments, the radioiodine therapy recipients provided the following remarks:

"The procedure is quick; it seems like the best choice and requires the least effort."

"It was easy, without any discomfort. The only downside is that I have to stay away from loved ones for some time."

"It's very challenging for me as a grandmother of children under 5 not to hold or be close to them for such a long time; the care was excellent and painless but time-consuming."

The administration of radioiodine therapy, which carries a risk of long-term hypothyroidism, can significantly impact the deterioration of patients' quality of life. To address this issue, the study by Taïeb et al. (2016) indicated that LT4 prophylaxis given within 15 days post-radioiodine therapy significantly improved quality of life (after six months) in the ThyPRO domains of emotional vulnerability, social life disruptions, sexual life disruptions, and appearance complaints when compared to the group that did not receive such prophylaxis. The benefits of prophylaxis in these domains remain significant even after conducting subgroup analysis by excluding patients who had repeat therapy within six months or those who were lost to follow-up (Taïeb et al., 2016).

This systematic review examined the impact of radioiodine therapy on the overall quality of life in patients with Graves' disease-associated hyperthyroidism. Previous systematic reviews have explored various aspects of treatment for Graves' disease, including the association between radiation absorption and disease response (Taprogge et al., 2021), the comparative efficacy of radioiodine therapy compared to surgery (Salman et al., 2024), and the risk of Graves' ophthalmopathy when comparing radioiodine therapy to antithyroid drugs (Ma et al., 2016). This review aimed to contribute to the existing literature by focusing specifically on quality-of-life outcomes for patients undergoing radioiodine therapy. While all included studies provided valuable insights into quality-of-life outcomes following radioiodine therapy, variations in methodology introduced potential biases. The most significant concerns were related to selection bias, primarily due to non-randomized designs in some studies, and attrition bias, which arose from long follow-up periods. Despite these limitations, the overall findings support the effectiveness of radioiodine therapy, although further investigation into its long-term impacts is warranted.

Although this systematic review successfully demonstrates the potential long-term improvement of quality of life for Graves' disease patients undergoing radioiodine therapy, several study

limitations need to be acknowledged. Firstly, the limited number of studies obtained might be attributed to the use of a small database and less specific keywords, leading to heterogeneity in the discussions. Secondly, the obtained variables varied, preventing in-depth analysis and stopping at the systematic review stage. Finally, no analysis of the risk of bias was conducted for each study, thereby making it impossible to ascertain the quality of the included studies.

CONCLUSION

Radioiodine therapy improves the quality of life of patients with Graves' disease, particularly in comparison to those not receiving any treatment, as well as those undergoing thyroidectomy and antithyroid modalities. Improvements in quality of life are apparent across various domains, including physical symptoms (goiter symptoms, hyperthyroid symptoms, eye symptoms, and hypothyroid symptoms), psychological symptoms (depression and anxiety), functioning and well-being (fatigue, cognitive impairment, and emotional vulnerability), and participation (social disruptions, daily life disturbances, and cosmetic concerns). A comprehensive long-term evaluation of patients treated with radioiodine therapy for Graves' disease is essential, encompassing assessments of not only thyroid status but also quality of life and therapy satisfaction.

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CONFLICT OF INTEREST

The authors declare that there are no relevant conflicts of interest to disclose.

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None.

AUTHOR CONTRIBUTION

MFA, JHP, GIP, and HNO participated in the conceptualization and design of this systematic review. MFA also drafted the article and concurrently collected, assembled, analyzed, and interpreted the data. JHP, GIP, and HNO performed a critical revision of the article for important intellectual content, whereas MFA, GIP, and HNO provided study material. In addition, GIP offered statistical expertise, while MFA and JHP provided funding, and JHP contributed administrative, technical, and logistic support.

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