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Original Articles

Exploring the layers of fatigue in Parkinson's Disease: A comprehensive analysis of its prevalence and contributing factors

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ABSTRACT

Background: Fatigue is a prevalent yet under-recognized non-motor symptom (NMS) of Parkinson's disease (PD), significantly impacting patients' quality of life. Despite its clinical importance, the relationship between fatigue and other motor and non-motor symptoms remains poorly understood. Its frequent co-occurrence with other NMS further complicates both diagnosis and management, often leading to underdiagnosis and suboptimal treatment. This gap in understanding is largely due to the limited exploration of fatigue in PD.

Objective: This study aimed to evaluate the prevalence of fatigue at baseline and up to 10 years after symptom onset in a large, well-characterized PD cohort (PPMI) and to explore its associations with other non-motor symptoms (NMS). By providing insights into the prevalence and correlations of fatigue, our goal is to highlight the need for early identification and management, guiding future research efforts.

Methods: We conducted a retrospective study using the PPMI database. Fatigue was assessed using item 1.13 of the Movement Disorders Society Unified Parkinson's Disease Rating Scale. Logistic regression was used to analyze the impact of different variables on fatigue, while point-biserial correlation analysis gauged the relationship between continuous variables and fatigue.

Results: At baseline study visit, 52% (575) of patients reported experiencing fatigue, with 9% reporting moderate to severe fatigue early in the disease course. Higher scores on several scales were significantly associated with an increased risk of fatigue, though most associations were weak. Significant associations included the REM Sleep Behavioral Disorder Questionnaire (OR: 1.09, 95% CI: 1.06–1.11), Geriatric Depression Scale (OR: 1.07, 95% CI: 1.03–1.11), State-Trait Anxiety Inventory (OR: 1.01, 95% CI: 1.00–1.02), SCOPA-Autonomic Dysfunction (OR: 1.05, 95% CI: 1.03–1.06), Epworth Sleepiness Scale (OR: 1.06, 95% CI: 1.04–1.08), and Apathy (OR: 2.90, 95% CI: 2.4–3.5).

Conclusion: Over half of patients reported fatigue at baseline, underscoring its significant prevalence early in PD. The predominantly weak associations with other NMS highlight the necessity for comprehensive patient screening and targeted interventions, as addressing one NMS may not effectively alleviate others.

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1. Introduction

Parkinson's disease (PD) is recognized as the second most prevalent neurodegenerative disorder globally [1,2]. It is characterized not only by its hallmark motor symptoms but also by a wide range of non-motor symptoms (NMS) that emerge at various stages of the disease. Over the past two decades, NMS have gained increased research attention due to their substantial impact on the quality of life of individuals living with PD.

Fatigue, recognized as an NMS of PD since the 19th century, is a prevalent and disabling symptom, affecting up to 81 % of patients from prodromal to advanced stages. [3–6] Observational studies consistently identify fatigue as one of the most burdensome NMS [3,7–9], significantly impairing functional capacity, the ability to engage in physical activity, and overall quality of life. [10] Despite this historical understanding, fatigue is often overlooked in clinical trials and underrecognized in clinical practice. Moreover, the underlying mechanisms and associations of fatigue in PD remain poorly understood.

Fatigue is a complex phenomenon encompassing two primary aspects. The perception of fatigue is often described as an abnormal and excessive sense of effort or lack of energy that does not improve with rest and interferes with normal function [11]. In contrast, performance fatigability refers to an objective decrement in performance induced by continued activity [12]. Importantly, these aspects of fatigue should not be explained by drug effects, other medical conditions, or psychiatric disorders [11]. In PD, these two aspects of fatigue are dissociable. Previous studies have shown that PD patients experience greater effort when performing physical tasks compared to healthy individuals, even if their performance remains comparable [13]. This suggests that complaints of fatigue may be more about perception than actual performance in PD.

Prior studies assessing prevalence or investigating therapeutic interventions for fatigue in PD have demonstrated inconsistent results [11]. This inconsistency may stem from varied definitions of fatigue (including but not limited to different cut-off thresholds used for diagnosis) and the absence of uniform scales to measure fatigue specifically in PD. Additionally, the presence of confounding factors such as overlap of other NMS, concomitant comorbidities, or medication use, are not always accounted for in the studies and can potentially influence fatigue assessment and it's changes to the tested intervention.

While previous studies have established fatigue as a prevalent and burdensome non-motor symptom in PD, our work offers new insights by examining its prevalence during the earliest years of symptom onset—a less explored phase of the disease. Furthermore, we analyze longitudinal changes in fatigue prevalence over a 10-year period, shedding light on how this symptom evolves over time.

By leveraging the well-characterized Parkinson's Progression Markers Initiative (PPMI) cohort [14], which includes multiple NMS assessment scales and follow-up data spanning up to a decade from symptom onset, we also aim to explore the complex connections between fatigue and other NMS. Our goal is to contribute to the development of more effective, targeted approaches to improve the quality of life for patients with PD.

2. Methods

Our primary objectives were to assess the baseline prevalence of fatigue within a large cohort of PD patients, as well as changes in prevalence over time. Additionally, we aimed to characterize the relationship between fatigue and other NMS assessed during follow-up [8]. We conducted a retrospective study using the PPMI database (https://www.ppmi-info.org) [14], which is, briefly, a longitudinal, observational, multi-center natural history study that assesses progression of clinical features, imaging outcomes, biologic and genetic markers across all stages of PD from prodromal to moderate disease.

Fatigue was evaluated as a binary variable, derived from responses to item 1.13 of the Movement Disorders Society Unified Parkinson's Disease Rating Scale Part I (MDS-UPDRS-I). A response of 0 indicated the absence of fatigue, while responses of 1 (slight fatigue), 2 (mild fatigue), 3 (moderate fatigue), and 4 (severe fatigue) were grouped together as indicative of fatigue, without distinguishing between severity levels. We included several variables capturing additional NMS in PD and demographic information to analyze as covariates. These variables included sex, age at visit, months from PD motor symptom onset (MFSXO), Body Mass Index (BMI), REM Sleep Behavior Disorder Questionnaire (RBDSQ), Epworth Sleepiness Scale (ESS), Geriatric Depression Scale − Short Form (GDS), State-Trait Anxiety Inventory (STAI), Scales for Outcomes in PD − Autonomic Dysfunction (SCOPA-AUT), and the UPDRS-I question on Apathy. Logistic regression analysis using Minitab 21 (Minitab, LLC, United States) was conducted to explore and identify influential variables across both continuous and categorical predictors. This initial analysis was aimed at capturing a broad range of potential factors impacting fatigue. Multicollinearity was evaluated by calculating the variance inflation factor (VIF). Variables with VIF greater than 10 were excluded from the logistic regression. Subsequently, point-biserial correlation analysis was performed using SPSS Statistics (IBM, United States) to explore the strength of associations specifically between continuous variables and fatigue. This method allowed us to assess a bigger range of factors initially and then delve deeper into the continuous variables of interest. Both analyses were employed to ensure a thorough evaluation of the data, and the consistency of findings supports the validity of our approach.

Inclusion criteria required patients to have completed the fatigue question on MDS-UPDRS-I alongside data for all independent variables during the same visit. Each visit was treated as a distinct data point for both regression analysis and correlation, allowing for the consideration of various clinical scenarios across different time points.

Motor scores in the form of MDS-UPDRS Part-III (UPDRS-III) in the off-medication state were not available for every visit/patient and thus excluded from the main regression analysis. Instead, we compared the UPDRS-III off-medication total scores between patients with and without fatigue at the 1-year and at the 10-year ± 3 month time point from symptom onset using a two sample independent *t* test.

We assessed fatigue prevalence during the baseline study visit by calculating the percentage of patients who reported experiencing fatigue. Additionally, we analyzed the severity of baseline visit fatigue among patients who reported experiencing it. We further conducted a longitudinal assessment of fatigue prevalence over a 10-year period within the study population. To achieve this, patients' visits were organized based on the time elapsed since motor symptom onset. Prevalence analysis was at annual (with a margin of ± 3 months) marks following symptom onset, up to the 10-year mark. The difference in fatigue prevalence over time between the unpaired groups was assessed using an analysis of variance (ANOVA) conducted in Minitab 21 (Minitab, LLC, United States).

3. Results

To assess the prevalence of fatigue at baseline, we included all patients with available fatigue data, regardless of their inclusion in the regression analysis. This comprised 1108 patients (60.9 % men), with a mean age (SD) at baseline visit of 62.6 (9.8) years. Baseline visits were mostly conducted within 3.5 years from symptom onset, with a mean time (SD) from onset of 39.19 (39.77) months. At baseline, 52 % (575) of patients reported fatigue (Table 1). The severity of fatigue among these patients was distributed as follows: 71 % (408) slight, 20.2 % (116) mild, 7.3 % (42) moderate, and 1.6 % (9) severe, based on UPDRS-I fatigue-related responses (Fig. 1).

The longitudinal analysis tracked fatigue prevalence over a decade following symptom onset. Fatigue increased gradually, starting at 48.86 % (n = 112) at one year and rising to 69.92 % (n = 96) by the tenth year (Fig. 2). Fluctuations at intermediate time points highlighted the

dynamic nature of fatigue in the cohort. Due to the unpaired nature of our data at different time points, we employed ANOVA to assess the effect of time on fatigue prevalence. The ANOVA revealed a significant effect of time on fatigue prevalence ($F = 5.09$, $p < 0.001$), indicating significant variation over the 10-year period.

To assess the relationship between fatigue and non-motor symptoms (NMS) within this cohort, we analyzed 4742 study visits with complete data from 1055 PD patients (60.75 % male) who met our inclusion criteria. Logistic regression analysis revealed significant associations between fatigue and several factors. Higher scores on the following scales were notably linked to an elevated risk of fatigue: REM Sleep Behavior Disorder Questionnaire (OR: 1.09, 95 % CI: 1.06–1.11), Geriatric Depression Scale (OR: 1.07, 95 % CI: 1.03–1.11), State-Trait Anxiety Inventory (OR: 1.01, 95 % CI: 1.00–1.02), SCOPA-Autonomic Dysfunction (OR: 1.05, 95 % CI: 1.03–1.06), Epworth Sleepiness Scale (OR: 1.06, 95 % CI: 1.04–1.08), and Apathy (OR: 2.90, 95 % CI: 2.4–3.5) (Table 2). Age at visit, sex, and BMI did not significantly influence fatigue. The model's area under the receiver operating characteristic curve for predicting fatigue had an accuracy of 0.76, indicating reasonable discriminatory power.

Logistic regression analysis also revealed a significant association between months from symptom onset and the likelihood of experiencing fatigue in PD patients ($p = 0.001$). Despite the statistical significance, the odds ratio was approximately 1.0022 (95 % CI: 1.0009–1.0036), indicating that each additional month from symptom onset is associated with only a marginal increase in the odds of experiencing fatigue. Additionally, point-biserial correlation analysis showed a correlation coefficient of 0.120 between fatigue presence and months from symptom onset, indicating a statistically significant ($p < 0.001$) but very weak positive correlation.

Point-biserial correlation analysis uncovered statistically significant, albeit very weak to moderate, positive associations between fatigue and key variables identified as influential in the regression analysis. The correlations were as follows: SCOPA-AUT ($r = 0.298$, $p < 0.001$), GDS ($r = 0.279$, $p < 0.001$), STAI ($r = 0.277$, $p < 0.001$), RBDSC ($r = 0.224$, $p < 0.001$), and ESS ($r = 0.226$, $p < 0.001$). These findings suggest that higher scores on scales assessing autonomic dysfunction, depression, anxiety, REM sleep behavior disorder, and daytime sleepiness are associated with increased levels of fatigue in Parkinson's disease patients. Logistic regression and point-biserial correlation were employed to ensure a thorough evaluation of the data, and the consistency of findings supports the validity of our approach.

In our off-medication motor score sub-analysis, we compared patients with and without fatigue at one year and at ten years since symptom onset. At baseline, we analyzed 219 patients, and at the ten-year mark, we analyzed 85 patients. No significant differences were found in off-medication UPDRS-III total scores at either the one-year mark ($p = 0.4511$) or the ten-year mark ($p = 0.444$).

4. Discussion

This large-scale study evaluates the prevalence of fatigue in PD and its correlations with other NMS using a publicly available multicenter database with longitudinal follow-up spanning up to 10 years for some patients. Our findings offer valuable insights into baseline prevalence and severity of fatigue, its changes over time, and potential correlations with other NMS.

Table 1
Demographics and Fatigue Prevalence in the Study Cohort.

Characteristic	Value
Sex, n (%)	Male: 675 (60.9 %)Female: 433 (39.1 %)
Age at Baseline, Mean (SD)	62.6 (9.8) years
Time from Symptom Onset, Mean (SD)	3.3 (3.3) years
Fatigue at Baseline, n (%)	575 (51.9 %)
No Fatigue at Baseline, n (%)	533 (48.1 %)

We observed that over half of the patients (52 %) reported experiencing fatigue at their baseline visit, underscoring its high prevalence within the PD population, even in the early stages of the disease. While 91 % of patients reported slight to mild fatigue, it is notable that 9 % reported moderate to severe fatigue at an early stage.

Our findings align with previous *meta*-analysis by Siciliano et al. [8], who reported a 50 % pooled prevalence of fatigue in PD, moderated by the heterogeneity in measurement scales and cut-off thresholds. Unlike many studies that do not account for disease duration, our assessment incorporated time since symptom onset, with both prevalence and severity evaluated at baseline visits. These visits occurred, on average, 3.5 years after motor symptom onset. This approach strengthens the evidence for the early presence of fatigue in PD and highlights its increasing prevalence over time (Fig. 2).

While previous studies have suggested fatigue is part of a broader spectrum of behavioral symptoms in PD [15] or reflective of motor symptom severity [16–18], most of the available evidence to date suggests that fatigue is an intrinsic symptom associated with PD pathophysiology rather than a secondary manifestation or reactive phenomenon [19]. However, its common clustering with other NMS [3,5,8,20,21] often introduces confounding bias, complicating both diagnosis and treatment. Clinicians may misinterpret fatigue as a manifestation of other NMS rather than recognizing it as an independent symptom requiring targeted intervention.

Our logistic regression analysis identified an elevated risk of fatigue associated with higher scores on the RBDSC, GDS, STAI, SCOPA-AUT, and ESS, as well as with the presence of apathy. While our results may suggest potential interconnections between these NMS, only apathy showed a strong relationship with fatigue. Notably, although these components were statistically significant, the odds ratios—except for apathy—were barely above one, indicating that these relationships should be interpreted with caution. This discrepancy with previous studies that have identified stronger relationships between fatigue and other NMS in PD [8] may be attributed to the predominantly mild fatigue observed in our cohort at baseline, as well as differences in assessment methods across studies—a recurring challenge when comparing research on fatigue in PD.

Although significantly correlated, the weak to moderate strength of these NMS underscores the need for targeted interventions addressing each symptom independently, rather than assuming a strong interconnected nature. Treating depression or anxiety alone may not sufficiently resolve fatigue, emphasizing the importance of thorough screening and continuous follow-up for NMS. In research, accounting for correlated NMS through randomization, stratification, or matching is crucial to minimize confounding bias, particularly for closely related symptoms like apathy.

The inclusion of BMI as one of the variables in our regression aimed to address obesity-related fatigue [22,23], not accounted for in the other questionnaires analyzed. Although BMI was not found to be significant in our analysis, we recognize the importance of thoughtfully evaluating fatigue-predisposing conditions, including weight, body composition, and screening for sleep apnea using appropriate methods [24].

Previous studies have linked fatigue with longer disease duration in PD patients [17,25–27]. For example, a *meta*-analysis found that patients experiencing fatigue had on average, a disease duration of 0.93 years longer than those without fatigue [8]. While our longitudinal prevalence analysis revealed a significant overall increase in fatigue prevalence over time, suggesting its progressive nature, our regression analysis found a significant but small odds ratio for disease duration (months from symptom onset), indicating that disease duration alone may not be a strong predictor of fatigue. Additionally, the weak positive correlation found in our analysis suggests that this may likely be a multifactorial issue. These findings highlight the complexity of fatigue in PD and stress the importance of long-term monitoring.

In our sub analysis, we found no difference in motor symptom

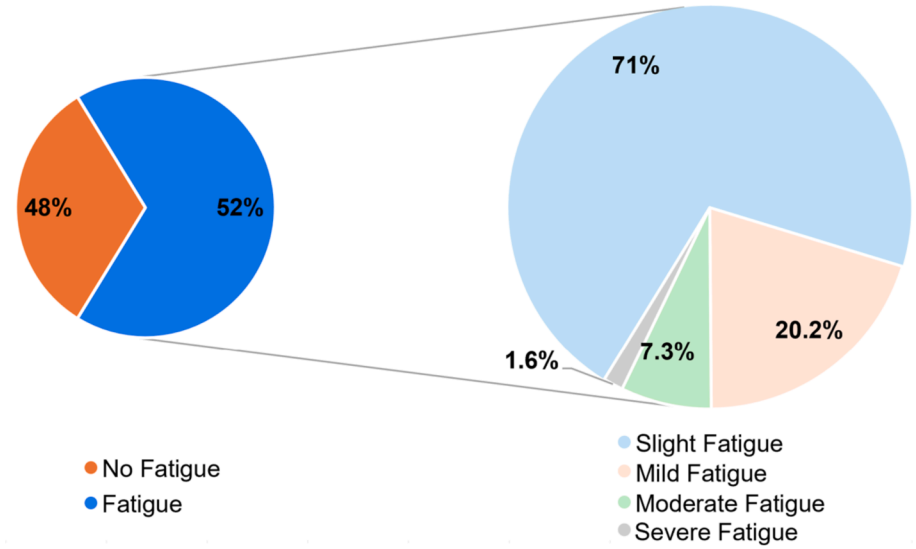

Fig. 1. Prevalence of Fatigue and Distribution of Fatigue Severity. Left Panel: This pie chart illustrates the prevalence of fatigue among patients at the study baseline visit. Percentages are displayed within the chart. The orange section represents patients without fatigue, and the blue section represents patients who reported fatigue. Right Panel: This pie chart depicts the distribution of fatigue severity among patients who reported experiencing fatigue at baseline. Each slice corresponds to a different severity category (Slight, Mild, Moderate, Severe), with percentages indicating the proportion of patients within each category.

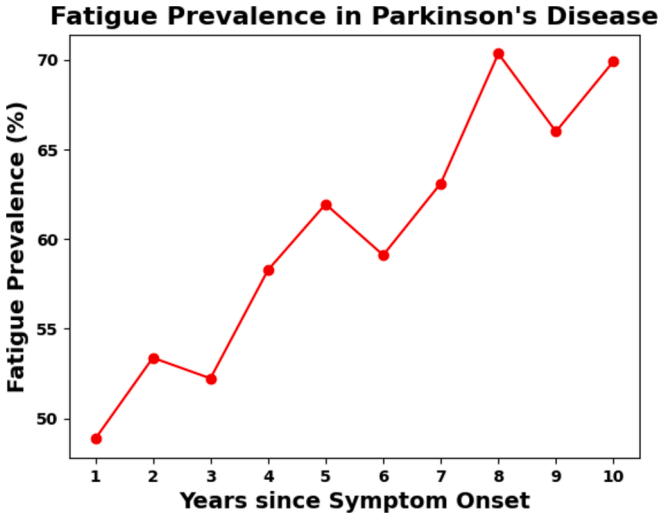

Fig. 2. Fatigue Prevalence Over 10 Years in Parkinson's. The line graph depicts the longitudinal progression of fatigue prevalence over a 10-year period following symptom onset in PD. The graph demonstrates how fatigue prevalence changes over time.

severity (UPDRS-III off-medication scores) between fatigued and non-fatigued groups at both the 1-year and 10-year marks. This suggests that fatigue is dissociable from motor symptom severity and should not be overlooked in patients with good motor symptom control. Our findings align with previous studies indicating that the onset, progression, and intensity of fatigue are not correlated with the severity of motor symptoms throughout the disease course [4,7,19]. This supports the idea that fatigue functions as an independent factor that compromises quality of life. However, this remains a topic needing further exploration, as other studies have found a relationship between fatigue and disease progression and motor severity as measured by the UPDRS score or Hoehn and Yahr stage [28–30], even suggesting that fatigue may predict the progression of motor symptoms over time [31]. Additionally, fatigue has been shown to exhibit fluctuating periods associated with wearing-off moments, characterized by significant slowing of thought and a feeling of tiredness [32,33].

Table 2
Logistic Regression Analysis of Variables Associated with Fatigue in Parkinson's Disease.

Variables	Odds Ratio (OR)	95 % CI	p value
RBDSC	1.087	1.0631—1.1134	< 0.001*
GDS	1.067	1.0302—1.1054	< 0.001*
STAI	1.012	1.0074—1.0175	< 0.001*
SCOPA-AUT	1.047	1.0349—1.0599	< 0.001*
ESS	1.058	1.0397—1.0761	< 0.001*
Apathy	2.900	2.4148—3.4833	< 0.001*
MFSXO	1.002	1.0009—1.0036	0.001*
Age at visit	1.001	0.9942—1.0078	0.775
Sex (Male)	0.900	0.7862—1.0322	0.133
BMI	1.003	0.9961—1.0096	0.406

This table illustrates the Odds Ratios, 95% confidence intervals, and p-values for the variables tested in our logistic regression analysis. Abbreviations: RBDSQ (REM Sleep Behavior Disorder Questionnaire), GDS (Geriatric Depression Scale), STAI (State-Trait Anxiety Inventory), SCOPA-AUT (Scales for Outcomes in Parkinson's Disease-Autonomic Dysfunction), ESS (Epworth Sleepiness Scale), MFSXO (Months From Symptom Onset), BMI (Body Mass Index).
* Denotes significant p-values (<= 0.001).

Currently, there are no established guidelines for treating PD fatigue, partly due to inconsistent and heterogeneous fatigue assessments across studies. Therefore, refining fatigue characterization, standardizing assessment methods, and selecting patients appropriately for clinical studies is imperative. This comprehensive approach will enable a more objective evaluation of suitable approaches for fatigue in PD.

Our study highlights the high prevalence of fatigue in early-stage PD, its fluctuation over time, and its associations with other NMS in a large cohort. This underscores the importance of early recognition and targeted interventions to mitigate its impact on patients' quality of life. Despite their frequent co-occurrence, these symptoms are distinct [5] and likely have different biological underpinnings, responding variably to treatments. Recognizing this diversity is crucial for clinical reasoning and designing studies to develop more effective treatment strategies.

5. Study Limitations

This study had several important limitations. First, it utilized a retrospective design, meaning clinical evaluations were not conducted

in a blinded or controlled manner. Additionally, it was not feasible to control for all potential confounding variables, such as medication adjustments, motor phenotype, and comorbid conditions that may influence fatigue and other non-motor symptoms. Specifically, we were unable to account for the use of medications such as amantadine and selegiline, which have potential fatigue-reducing effects.

Our analysis of fatigue relied solely on item 1.13 of the MDS-UPDRS-I, as the dataset did not include any fatigue-specific scales. While previous studies [34] have found a strong correlation between item 1.13 of the MDS-UPDRS and the Parkinson Fatigue Scale (PFS) scores—emphasizing the importance of further investigating fatigue when identified through the MDS-UPDRS—we acknowledge that this approach may oversimplify the multifaceted nature of fatigue. As a result, the prevalence and contributing factors may have been underestimated or mischaracterized. Furthermore, a proportion of patients were lost to follow-up over time, resulting in unequal sample sizes at specific time points, which may have impacted the interpretation of our findings.

6. Author roles

1) Research project: A. Conception, B. Organization, C. Execution;
2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
3) Manuscript Preparation: A. Writing of the first draft, B. Review and Critique;
FS: 1A, 1B, 1C, 2A, 2B, 2C, 3A, 3B.
GL: 1B, 1C, 2B, 3A.
VSL: 1C.
ASM: 1C.
JMRD: 1C.
QY: 1C.
AEMN: 2C,3B.
JC: 2C, 3B.
KAJ: 2C, 3B.
CH: 2C, 3B.
JKW: 1A, 1B, 1C, 2A, 2B, 2C, 3A, 3B.

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CRediT authorship contribution statement

Filipe Sarmento: Writing – review & editing, Writing – original draft, Resources, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Griffin Lamp:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Formal analysis, Data curation. **Venkat Srikar Lavu:** Methodology, Data curation. **Achyutha S. Madamangalam:** Writing – original draft. **Jagan Mohan Reddy Dwarampudi:** Data curation. **Qingqi Yuan:** Data curation. **Alfonso Enrique Martinez-Nunes:** Writing – review & editing. **Julia Choi:** Writing – review & editing, Supervision. **Kara A Johnson:** Writing – review & editing, Supervision. **Coralie de Hemptinne:** Writing – review & editing, Supervision. **Joshua K. Wong:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Data curation, Conceptualization.

Ethics approval

Informed patient consent was not necessary for this work. This study was approved by the University of Florida (UF) Institutional Review Board (IRB), IRB202301783. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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