Health-Related Quality of Life in Fabry Disease: A Cross-sectional International Multicenter Study

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Abstract

Background

Fabry disease (FD) is a rare X-linked lysosomal storage disorder caused by α-galactosidase A (α-Gal A) deficiency. The progressive accumulation of globotriaosylceramide results in life-threatening complications, including renal, cardiac, and cerebrovascular diseases. In order to improve health care of FD-patients, knowledge of its predictors is important. The aim of our study was to evaluate health-related quality of life (HrQol) in FD and to identify its independent determinants by exploring a wide range of demographic, social and clinical parameters.

Results

In this cross-sectional multicenter study, 124 adult patients with FD were recruited at three specialized European centers in Germany and Switzerland. Demographics, social status and clinical parameters as well as data on HrQol (EQ5D, EQVAS) and depression were collected by means of self-reporting questionnaires. HrQol and its predictors were evaluated by univariate and multivariate regression analyses.

Study population consisted of 72 female and 52 male FD patients (median age 48yrs) of whom 87.9% (N=109) were on enzyme replacement therapy (ERT) (68.8% [N= 75] were on agalsidase α and 31.2% [N=34] on agalsidase β). Univariate analysis revealed various factors reducing HrQol, such as age>40 years, classic phenotype, organ involvement (kidney and heart disease, stroke/ transient ischemic attack, gastrointestinal disturbances), depression, and burning limb pain. However, only the following factors were identified as independent predictors of decreased HrQol: classic phenotype, kidney and heart disease, stroke/TIA, depression, and burning limb pain. ERT was an independent determinant of increased HrQol.

Conclusions

Modifiable factors, such as burning limb pain and depression identified as independent predictors of HrQol-deterioration should be addressed in programs aiming to improve HrQol in FD. A multidisciplinary approach is essential in FD-patients since diverse organ involvement prominently compromises HrQol in affected patients. Our findings that the classic phenotype is a strong predictor of HrQol worsening.

Introduction

Fabry disease (FD) is a rare lysosomal storage disorder due to mutations in the GLA-gene which account for reduced or absent activity of α-galactosidase A (α-Gal A). Deficiency of α-Gal A causes accumulation of glycosingolipids, particularly globotriasylceramide (Gb3) and globotriasylsphingosine (Lyso-Gb3), in the lysosomes of all cells throughout the body as well as in body fluids [1]. The disease is inherited as an X-linked trait, with an estimated incidence of ~1 in 3,100 Caucasian males [2]. There are two major
phenotypes: classic and later-onset [3]. Males with the classic phenotype have very low enzymatic activity and, consequently, suffer from acroparaesthesia, hypohidrosis, cold and hot intolerance, abdominal cramping, which severely reduces their quality of life [4]. They develop skin angiokeratoma and corneal opacities already during childhood. With advancing age, progressive Fabry-nephropathy and cardiomyopathy as well as early-onset strokes contribute to the early demise of these patients [1]. In contrast, males with the later-onset phenotype have a significant residual α-Gal A activity and, therefore, lack the early childhood manifestations but experience a normal childhood [5]. However, they develop either Fabry-cardiomyopathy [6] or, less frequently, Fabry-nephropathy [7], which can be as severe as in the classic phenotype. For both phenotypes, heterozygous female patients are generally more mildly afflicted because of their random X-chromosomal inactivation, although their phenotypes can vary widely, from asymptomatic to manifestations as severe as those seen in their male family members [8].

Previous studies reported a markedly reduced quality of life (QoL) in FD patients, particularly in conjunction with pains [9], fatigue [10], depression [11], obstructive sleep apnea [12], hearing loss [13], and gastrointestinal symptoms [4]. In this relatively large patients group, we added data such as demographics, social status, clinical parameters, in addition to these manifestations. These evaluations are useful to find independent factors to modulate HrQoL of Fabry patients. Knowledge of the independent determinants of health-related quality of life (HrQoL) could facilitate early identification of patients who need more intense psychological support and care, increased monitoring, specifically targeted adjunctive treatment such as pain medication or antidepressants, and, most importantly, might trigger preventive strategies, best managed by a multidisciplinary team. In a retrospective analysis of medical records, Arends and colleagues found that reduced HrQoL in patients with FD was related to the phenotype, age, pain, and disease severity. The authors encouraged further studies to identify independent parameters influencing QoL in order to improve patients’ care [14]. Neto and colleagues emphasize that patient-reported outcomes reflecting physical and mental health should be considered as key aspects of health monitoring and indicators of therapeutic requirements [11]. Since the knowledge on HrQoL-deteriorating or improving variables may advance the goal-oriented support and treatment of FD patients and, thus, to improve their well-being, we designed a multicentre study analysing the self-perceived HrQoL dimensions in Fabry patients in order to identify independent HrQoL predictors.

**Results**

**Demographics and clinical parameters**

124 patients (72 females and 52 males) (68 from Zurich, Switzerland, 47 from Mainz and 9 Münster, Germany), participated in the study (Table 1). The GLA genotype and phenotype of Zurich patients are shown in Table A1 of the Additional file 1. The median age was 49 years for males, 48 years for females. Male patients had a tendency of an earlier median age of symptoms onset (9 years) than female patients (15 years), but this difference was not statistically significant (p=0.23).
65.3\% (N=81) of patients reported pain. Burning pain in hands was found in 13.7\% (N=17), painful feet were present in 22.6\% (N=28) of patients. 87.9\% (N=109) of patients received enzyme replacement therapy (ERT). Of those, 68.8\% (N= 75) were on agalsidase alfa and 31.2\% (N=34) were on agalsidase beta.

**Table 1.** Clinical parameters and HrQoL of males and females with Fabry disease.
|                          | Males (n=52) | Females (n=72) |
|--------------------------|--------------|---------------|
| Age in years, median (range) | 49 (25-75)   | 48 (18-78)    |
| Year of FD diagnosis, median (range) | 2008 (1975-2015) | 2007 (1978-2018) |
| Age of symptom onset, median (range) | 9 (5-60)     | 15 (4-47)     |
| Marital status, n of patients who gave information | 48           | 56            |
| Single n (%)             | 15 (31)      | 13 (23)       |
| Married n (%)            | 29 (60)      | 34 (61)       |
| In partnership n (%)     | 4 (9)        | 7 (13)        |
| Separated or divorced n (%) | 0 (0)       | 2 (3)         |
| BMI in kg/m², median (range) | 26 (19-46)  | 24 (17-53)    |
| On specific therapy n (%) |             |               |
| Agalsidase α             | 39 (75)      | 39 (54)       |
| Agalsidase β             | 7 (13)       | 15 (21)       |
| Neuropathic pain         | 33 (63)      | 48 (67)       |
| Gastrointestinal symptoms | 29 (56)    | 33 (46)       |
| Heat intolerance         | 36 (69)      | 45 (63)       |
| Cold intolerance         | 25 (48)      | 27 (38)       |
| Sweating problems        | 28 (54)      | 29 (40)       |
| Kidney disease           | 24 (46)      | 22 (31)       |
| On chronic RRT           | 7* (13)      | 3**(0.5)      |
| Heart disease            | 26 (50)      | 27 (38)       |
| Chest pain               | 7 (13)       | 7 (10)        |
| Arrhythmias              | 17 (33)      | 15 (21)       |
| Stroke or TIA            | 27 (52)      | 30 (42)       |
| Hypacusis                | 23 (44)      | 29 (40)       |
| Depression               |              |               |
| BDI median (range)       | 7 (0-57)     | 10 (0-36)     |

Abbreviations: BDI, Beck Depression Inventory; RRT, Renal replacement therapy; TIA, transient ischemic attack; BMI, body mass index
* 5 FD patients were kidney transplanted, 2 FD patients were on chronic dialysis

** 2 FD patients were kidney transplanted, 1 FD patient was on chronic dialysis

Health-related quality of life

There was a slight trend of showing a worse HrQoL in men than in women, which, however, did not reach statistical significance (EQ-5D-index: 0.74±0.21 vs. 0.76±0.20, p=0.62; EQ VAS: 69.7±18.9 vs. 75.8±19.6, p=0.09). Patients below the age of 41 years had higher HrQol values than those above the age of 40. HrQoL values were significantly lower in patients with organ involvement, such as kidney disease, heart involvement, and stroke/TIA, than in those without clinically manifest organ involvement (Table 2). Other clinical conditions impairing HrQoL in FD patients were burning pain in hands and feet and depression. They lowered HrQoL-values by 25%, 30%, and 15% respectively (p<0.01). Gastrointestinal problems showed a minor trend towards decreased HrQoL-values (FD patients with GI symptoms vs FD patients: EQ-5D-index: 0.71±0.21 vs. 0.78±0.20, p=0.17; EQ VAS: 70.1±21.6 vs. 77.7±19.4, p<0.01 (Table 2). The body-mass-index (BMI) did not influence HrQoL-values. Marital status also had no influence on HrQoL values.

Table 2. EQ-5D-Index and EQ VAS according to clinical and social parameters
|                          | EQ-5D-Index Mean±SD | P value | EQ VAS Mean±SD | P value |
|--------------------------|---------------------|---------|----------------|---------|
| Males                    | 0.74±0.21           | 0.62    | 69.7±18.91     | 0.09    |
| Females                  | 0.76±0.20           |         | 75.8±19.61     |         |
| Age >40 years            | 0.72±0.21           | 0.04    | 68.69±19.07    | <0.01   |
| ≤40 years                | 0.72±0.21           |         | 82.34±17.01    |         |
| Marital status alone     | 0.70±0.20           | 0.09    | 72.45±19.06    | 0.79    |
| with partner             | 0.78±0.20           |         | 73.32±19.34    |         |
| BMI >25kg/m²             | 0.74±0.19           | 0.54    | 72.15±19.08    | 0.55    |
| ≤25kg/m²                 | 0.76±0.22           |         | 74.19±19.80    |         |
| No therapy               | 0.68±0.18           | <0.01   | 69.14±17.99    | <0.01   |
| Agalsidase α             | 0.77±0.20           |         | 77.51±19.10    |         |
| Agalsidase β             | 0.81±0.21           |         | 82.31±15.08    |         |
| Phenotype Classic        | 0.68±0.20           | <0.01   | 69.05±22.02    | <0.01   |
| Later-onset              | 0.82±0.18           |         | 81.71±17.95    |         |
| Burning limb pain        | 0.51±0.17           | <0.01   | 55.75±19.38    | <0.01   |
| No burning limb pain     | 0.77±0.18           |         | 76.87±14.44    |         |
| Gastrointestinal problems| 0.71±0.21           | 0.17    | 70.1±21.6      | <0.01   |
| No gastrointestinal problems | 0.78±0.20     |         | 77.7±19.4      |         |
| Heat intolerance         | 0.72±0.18           | 0.01    | 73.63±19.02    | 0.02    |
| No heat intolerance      | 0.80±0.19           |         | 81.78±16.74    |         |
| Cold intolerance         | 0.73±0.20           | 0.04    | 68.87±19.22    | 0.04    |
| No cold intolerance      | 0.82±0.23           |         | 78.74±17.57    |         |
| Hypacusus                | 0.79±0.19           | 0.04    | 67.90±20.08    | 0.03    |
| No hypacusus             | 0.71±0.21           |         | 78.23±17.07    |         |
| Kidney disease           | 0.69±0.21           | 0.02    | 65.30±21.61    | <0.01   |
| No kidney disease        | 0.79±0.20           |         | 80.01±17.53    |         |
| Heart disease            | 0.69±0.21           | 0.01    | 62.76±20.25    | <0.01   |
| No heart disease         | 0.81±0.21           |         | 82.74±16.47    |         |
Stroke/TIA in the past  | 0.80±0.21 | <0.01 | 68.27±19.27 | <0.01
No stroke/TIA in the past | 0.69±0.19 | 81.75±16.48
Depression  BDI<14 | 0.84±0.16 | <0.01 | 81.47±16.43 | <0.01
BDI≥14 | 0.63±0.19 | 62.85±18.05

Abbreviations: BDI, Beck Depression Inventory; BMI, body mass index; SD, standard deviation; TIA, transient ischemic attack.

Parameters identified by multivariate regression analysis as independent determinants of decreased HrQol-values in FD patients are shown in Table 3 and include classic phenotype, kidney involvement, heart involvement, stroke/TIA, burning limb pain and depressive symptoms. In contrast, ERT with agalsidase alfa or agalsidase beta was identified as an independent determinant of increased HrQol-values.

These identified predictors of HrQol could explain 53.1% of the variability of the EQ-5D index scores and 45.8% of the variability of the values on the EQ VAS.

Table 3. Independent determinants of HrQol in multiple regression analysis

|                        | EQ5D Index |                     |                     | EQ VAS |                     |                     |
|------------------------|------------|----------------------|----------------------|--------|----------------------|----------------------|
|                        | B          | 95% CI               | p-value              | B      | 95% CI               | p-value              |
| Constant               | 1.17       | 0.93; 1.22           | 0.0                  | 109.31 | 93.11; 121.34        | 0.0                  |
| Classic phenotype      | -0.14      | -0.22; -0.04         | <0.01                | -12.51 | -21.12; -5.92        | <0.01                |
| Kidney disease         | -0.06      | -0.22; -0.03         | 0.03                 | -6.79  | -14.12; -2.77        | 0.04                 |
| Heart involvement      | -0.17      | -0.29; -0.05         | <0.01                | -20.03 | -28.50; -11.08       | <0.01                |
| Stroke/TIA             | -0.07      | -0.17; -0.04         | 0.03                 | -4.91  | -7.01; -1.05         | 0.04                 |
| Burning limb pain      | -0.14      | -0.27; -0.08         | 0.04                 | -7.95  | -17.23; -2.89        | 0.03                 |
| Depression (BDI)       | -0.04      | -0.18; -0.02         | <0.01                | -0.89  | -2.01; -0.53         | <0.01                |
| Agalsidase α           | 0.04       | 0.01; 0.12           | 0.04                 | 3.92   | 0.51; 7.27           | 0.04                 |
| Agalsidase β           | 0.11       | 0.04; 0.29           | 0.02                 | 15.88  | 5.69; 28.03          | 0.01                 |
| Adjusted R²*           | 0.531      |                      |                      | 0.458  |                      |                      |

* Total adjusted R² for each model
Abbreviations: HrQol, health-related quality of life; B, regression coefficient; BDI, Beck Depression Inventory, TIA, transient ischemic attack

**Discussion**

Our study investigated HrQol in FD patients from two European countries. The sample size of our patient cohort was rather large with respect to the low prevalence of this orphan disease. Previous studies also evaluated associations between HrQol and single symptoms of FD, such as pain [9], fatigue [10], depressive symptoms [11]. Along these lines, Gold et al studied 200 untreated male FD patients and found renal involvement, cardiac complications, stroke and pain to be significantly related to HrQol [15]. Wagner et al 2014 found impaired renal function and pain as the major contributing factors for reduced HrQol [16]. These and other studies on HrQol in FD are summarized by Arends et all in a systematic review concluding that pain, objective renal disease, phenotype, age and gender are some of the major contributors to reduced HrQol if FD [17]. Our study corroborates and extends previous works, analysing potential impact of a wide spectrum of factors associated with FD, also including social life and demographic data on their HrQol.

The analyses show that the HrQol of FD patients is mainly influenced by clinical symptoms rather than demographic or social parameters. Among all demographic and social parameters, only younger age (<40 years) was associated with higher HrQol-values in the univariate analysis. Similarly, Arends et al found that higher age was a negative predicting factor for the HrQol in FD patients [14]. However, the multivariate analysis of our data did not identify any of the demographic or social factors as independent predictors of deteriorated or improved HrQol. Surprisingly, there was no significant relation between male or female gender and HrQoL-values, although FD is an X-linked disease and considered to manifest more prominently in male patients [18]. This result supports the conclusions of our previous study that FD manifestations have a greater influence on the health status than the sex of the patient [19]. The result also supports the conclusion that heterozygous females, like male FD patients, need targeted support.

Although disease-specific therapies such as ERT [20] and pharmacological chaperone treatment [21] are available for FD patients, and have been reported to improve neuropathic pain [22], persistent pain still is a therapeutic challenge and compromises HrQol [14] [23]. Morand et al reported a prominent reduction in the QoL of FD patients who experience pain and gastrointestinal disturbances [4]. In our study, the presence of burning limb pain reduced the patients’ HrQol-values by approximately 30%. Indeed, burning limb pain is a modifiable factor and should be more carefully addressed in the treatment programs of Fabry patients in order to improve their HrQol. In Fabry disease, pain is a highly relevant clinical aspect that afflicts both sexes and manifests with complex presentations [9]. Similar to the findings of a large German study on pain in FD [9], our patients reported that their hands and feet were the body parts most affected by pain. In patients with the classic phenotype, pain can be burning, stabbing, tingling, or shooting, with the punctum maximum in the distal extremities, radiating towards proximal regions, and it can be permanent, chronic-intermittent, or, sometimes, critically excruciating [9, 24]. Since improved pain control quite likely enhances HrQoL, pain needs to be carefully evaluated in every patient and treatment
options must be addressed in face-to-face communications between the patient and the treating specialist. Pain intensity and location should be carefully determined using disease-specific tools, such as FabryScan [25], Fabry-specific Pediatric Health and Pain Questionnaire [26], or Wurzburg Fabry Pain Questionnaire [27], in addition general pain scales such as the Brief Pain Inventory [11], Short-Form McGill Pain Questionnaire [24] may complement the clinical description of pain. Furthermore, the SF-36 health-related quality of life assessment may add to better defining the patient's current condition [11]. Unfortunately, there are so far no controlled prospective interventional trials that evaluated adjunctive pain therapies.

Gastrointestinal disturbances had a moderate influence on the HrQol and reduced EQ VAS values by 10%. In fact, the multivariate analysis did not identify gastrointestinal symptoms as one of the independent predictors of HrQol-deterioration, although, it is of course clinically relevant to alleviate gastrointestinal complaints. Previous studies showed that disease-specific therapy is associated with gastrointestinal improvement but does not abolish gastrointestinal disturbances [21] [28]. So far, there are no interventional clinical studies that identified adjunctive therapies, such as analgesics or smooth muscle relaxants, as effective in the improvement of abdominal pain and cramping. Yet, recently a promising approach to supplement alpha-galactosidase orally has been reported [29]. However, further studies should be encouraged to improve neuropathic limb and gastrointestinal pains in order to increase HrQoL.

Depressive symptoms have been shown to be an important HrQol-reducing factor in patients with FD [4]. Our data support these findings. The presence of depressive symptoms reduced EQ VAS values by 23% and EQ5D Index values by 25% as demonstrated in the univariate analysis. In addition, the multivariate analysis identified depression as one of the modifiable factors that independently affect HrQol-values. Similarly to pain assessment and therapy, screening for and specific treatment of depression should therefore be an integral part of health-care programs for FD patients.

Other important factors independently influencing the HrQol in patients with FD were kidney and heart disease, and the history of stroke/TIA. These findings confirm the fact that the management of FD patients requires a multidisciplinary approach with the exchange of views between nephrologists, cardiologists, and neurologists.

The classic phenotype was identified as an unmodifiable independent predictor of reduced HrQol in FD. It is known that classic patients are prone to develop more complications during the course of the disease [4]. Our results were in line with the data of Arends et al who showed a faster decline of HrQol in classic patients than in later-onset patients [14].

Our study has several limitations. We only included patients from two European countries. Consequently, our results might not be representative on a broader scale as the health-care situation differs in other European or non-European countries. However, there are established, internationally known guidelines for the treatment of FD patients. Therefore, treatment patterns should not differ too much between various countries. Second, there were no patients with oral chaperone therapy available at the time of patient
recruitment. Therefore, we could not include this treatment option in the current analysis. Third, symptoms and events included in the study were reported by patients instead of retrieving data from medical records. On one hand, associating subjective health, reflected by self-reported kidney and heart disease and history of stroke, may not be the most frequently used way to assess the impact of disease complications on quality of life. On the other hand, focusing on subjective health may represent a patients-centred approach helping to search for important clinical manifestations from the patients` view. An interesting approach in a next study would be to compare patient-reported kidney and heart disease with objective parameters such as proteinuria, significantly impaired renal function, diastolic and systolic left ventricular function, arrhythmias etc. in order to analyse their correlation.

Finally, we cannot rule out the presence of further confounders due to variables not assessed in this study, such as the economic situation of patients and their families, in multivariate regression analysis of HrQoL-determinants. Still, this study confirmed the negative impact of pain, depression, gastrointestinal symptoms, kidney and heart disease, and the history of stroke/TIA, and the classic phenotype on the HrQol while sex surprisingly had no significant effect but ERT had a beneficial effect on HrQol.

**Method**

**Study design and clinical evaluation**

This is a cross-sectional multicentre study including adult Fabry patients from three specialized German speaking Fabry centers: University Hospital Zurich Switzerland, University Medical Center of the Johannes Gutenberg University Mainz and Interdisciplinary Fabry Center (IFAZ) at the University Hospital Münster, Germany.

Patients (N = 124) treated in these centers completed questionnaires, which were distributed during the routine clinical examinations or by regular mail.

The questionnaires consisted mainly of quantitative, closed questions with pre-defined response options. All patients were asked to report their demographic and clinical parameters including their treatment status, symptoms as well as cardiac, renal, and cerebrovascular FD complications, as perceived and known by the patients. In addition, the treating physician of all patients from Zurich provided information regarding the patients` mutations.

**Phenotyping**

All mutations in the Zurich patients have been classified as coding for the classic or later-onset phenotype based on genotype and residual α-Gal A activity in males and are published in the International Fabry Disease Genotype/Phenotype Database (www.dbFGP.org) as well as in previous studies [30-34]. Nonsense, frameshift, consensus splice site and some missense mutations encode for 0% to 2% residual α-Gal A activity and lead to the classic phenotype in males. Alternative splicing mutations and certain other missense mutations encode for >2% of mean normal α-Gal A activity and
cause the later-onset phenotype in males. All phenotypic assignments of the mutations are supported by the clinical manifestations in males and the age of symptom onset.

**Evaluation of HrQoL and depressive symptoms**

We evaluated HrQoL by using the German version of generic EuroQol® questionnaire, a validated, non-disease-specific, tool [35] suited to reliably assess QoL in Fabry disease [17, 36]. This HrQoL questionnaire consists of a five-dimensional self-classifier (EQ-5D®) and a visual analogue scale (EQ-VAS). The EQ-5D® covers the five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [35]. Each dimension can be described by three levels of severity (1 = no problem, 2 = moderate problem, 3 = severe problem). Based on the results of the EQ-5D®, we calculated an index score using a regression algorithm developed by Greiner et al [37]. The second part of the EuroQol® is a visual analogue scale (EQ VAS) ‘similar to a thermometer’ ranging from 0 (worst imaginable health state) to 100 (best imaginable health state).

We used the second version of Beck Depression Inventory (BDI) in our study [38]. The cutoff value for mild or more severe depressive symptoms was ≥14.

**Statistics**

The statistical data analysis was performed using IBM SPSS Statistics Version 23.0 (IBM Corp., Armonk, NY, USA). All clinical and quality of life data are presented as mean with standard deviation (SD). The Kolmogorov-Smirnov test was used to test data for normal distribution. The t-test was used to compare normally distributed data. The Mann-Whitney U test was applied to compare not normally distributed data. Statistical significance was assumed for p<0.05. Independent predictors of HrQoL were estimated using multivariate regression analysis with forward selection (p<0.1) while the following assumptions were met: linear relationship between outcome and independent variables, residuals were normally distributed, no multi-collinearity was allowed and the variance of error terms were similar across the values of independent variables. The fraction of explained variability was calculated for each prediction model based on the R² method, as appropriate [39].

**Declarations**

**Ethics approval and consent to participate**

The study was approved by local ethic committees of University Hospital Zurich Switzerland, University Medical Center of the Johannes Gutenberg University Mainz and University Hospital Münster, Germany. All participants have signed a written informed consent.

**Availability of data and materials**

The dataset supporting the conclusions of this article is included within the article and its additional file.
**Competing interests**

YW reports honoraria for educational presentations and consultations from Arvelle Therapeutics, Bayer AG, BIAL, Bioprojet Pharma, Eisai, Eythpharm GmbH, LivaNova, Novartis and UCB Pharma, which were not related to the topic of this study. AN received speaker honoraria and research grants from Amicus, Shire/Takeda and Sanofi Genzyme. ML received research grants and speaker honoraria from Amicus Therapeutics, Sanofi Genzyme and Shire/Takeda and consultation honoraria from Avrobio. EB received research grants and speaker honoraria from Amicus Therapeutics, Sanofi Genzyme, Shire/Takeda as well as honoraria for educational presentations and consultations from Chiesi and Greenovation/Eleva.

**Consent for publication**

Not applicable

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**Authors’ contributions**

Design of the study: AN, MH, FB, ES, ML, EB, JBH, YW. Statistical analysis and first draft: AN, YW. Wrote the manuscript: AN, YW. In addition, all authors participated in analysis and interpretation of data and provided critical revisions to the manuscript drafts. All authors read and approved the final manuscript.

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