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Factors influencing decline in quality of life in smokers without airflow obstruction: The COPDGene study

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ABSTRACT

Introduction: Current and former smokers with normal spirometry and with Preserved Ratio Impaired Spirometry (PRISm) experience respiratory events similar to chronic obstructive pulmonary disease (COPD) exacerbations. Exacerbations significantly reduce quality of life (QoL) in COPD patients however the effect of respiratory exacerbations on QoL in these groups is unknown. We hypothesized that exacerbations and change in exacerbation status would predict QoL decline among normal spirometry and PRISm participants in COPDGene.

Methods: COPDGene is a multicenter, longitudinal study in the U.S. designed to identify genetic determinants of COPD. We enrolled study subjects in Phase 1 of COPDGene and performed multivariable logistic regression models to determine independent predictors of decline in quality of life [>4 points on the St George's Respiratory Questionnaire (SGRQ)]. Separate analyses were performed for current and former smokers with normal spirometry and PRISm. Frequent exacerbator status was defined by > 2 moderate or >1 severe exacerbations in the year prior to the baseline and year 5 follow-up visits.

Results: Independent predictors of QoL deterioration included current smoking, higher exacerbation frequency, and a change from infrequent to frequent exacerbation status (REF: infrequent to infrequent exacerbation status) in both groups [PRISm (OR = 3.15,95%CI, 1.67–5.94), normal spirometry (OR = 4.72,95%CI, 3.25–6.86)]. A change from frequent to infrequent exacerbation status did not lower the odds of QoL decline in either cohort.

Conclusion: Continued smoking and the onset of frequent exacerbations were predictors of QoL decline in smokers with normal spirometry and PRISm. Further studies are needed to identify modifiable factors associated with decline in QoL in smokers.

1. Introduction

Quality of life (QoL) refers to an individual's self-assessment of their physical, social, and mental state [1]. QoL metrics are now regularly incorporated into clinical practice and clinical trials and may arguably be the most important outcome of interest for patients. In patients with chronic obstructive pulmonary disease (COPD), increased frequency of exacerbations has a clear association with QoL decline [2] [3] [4], findings which have prompted the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines to recommend regular assessments of QoL in addition to lung function testing in all COPD patients [5]. Former and current smokers who do not meet the spirometric criteria for COPD or who have a preserved ratio but impaired spirometry (PRISm: Forced expiratory volume in first second: forced vital capacity (FEV_1/FVC)≥0.70; FEV_1<80% predicted) experience respiratory symptoms that prompt the prescription and use of steroids or antibiotics, or a visit to clinic, emergency room, or hospitalization, and are similar to COPD exacerbations. Symptomatic current and former smokers with preserved lung function have been shown to have increased frequency of

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Abbreviations

BMI	body mass index
COPD	chronic obstructive pulmonary disease
FEV_1	forced expiratory value in first second
F–F	frequent to frequent
F–I	frequent to infrequent
FVC	forced vital capacity
I–F	infrequent to frequent
I–I	infrequent to infrequent
MCID	minimal clinically important difference
MMRC	Modified Medical Research Council
PRISm	preserved ratio impaired spirometry
QOL	quality of life
SGRQ	St George's Respiratory Questionnaire

exacerbations, a shorter 6-min walk test, and increased airway wall thickening compared to those without symptoms [6]. A prior analysis of COPDGene has shown that participants with PRISm also had more frequent and more severe exacerbations compared to those with mild COPD (GOLD 1) [7]. However, information regarding the frequency and severity of these exacerbations and the impact of exacerbations over time (exacerbations status) on QoLin these cohorts is limited.

Existing literature on the association between QoL and exacerbations has been focused mostly on COPD. Esteban et al. evaluated the decline in QoL over 5 years in COPD participants and found that those who were hospitalized ≥3 times had a 13.6 point increase in St. George's Respiratory Questionnaire (SGRQ) score at follow-up compared to those hospitalized less frequently [8]. Miravitlles et al. conducted an observational study over a 2-year period and found that frequent exacerbations increased the total SGRQ score by approximately 2 points per year greater than infrequent exacerbations in moderate COPD after adjusting for baseline characteristics [9]. A major limitation of both of these studies is that over 97% of their cohort was male and all had COPD, limiting the generalizability of their results to women, who experience worse QoL [10,11], and to smokers without COPD who have normal spirometry or PRISm. These studies also failed to account for changes in exacerbation status (frequent to infrequent; infrequent to frequent), evidence that may inform our understanding of the effectiveness of exacerbation reduction on QoL in smokers.

COPDGene is a multicenter, longitudinal study that enrolled over 10,000 participants with a smoking history and provides a robust database to evaluate longitudinal patterns of QoL. In the current study, we hypothesized that frequency of exacerbations and change in exacerbation status would predict longitudinal decline in QoL in smokers with spirometry that was normal at baseline or classified as PRISm.

2. Methods

2.1. Study design, setting, and participants

Participants were included from the COPDGene Study, a longitudinal study that recruited 10,371 participants aged 45–80 years old with a ≥10 pack year smoking history. Individuals were not eligible to enroll in COPDGene if they had an active lung disease other than asthma or COPD. The detailed objectives and methods of COPDGene have been previously published [12]. Subjects were included in our analysis if they 1) self-identified as an "ever smoker" answering "yes" to "have you ever smoked cigarettes?"; 2) had PRISm or baseline normal spirometry; and 3) had QoL data at two time points (Phase 1 and Phase 2) as measured by the SGRQ. Phase 1 data was collected at initial enrollment (2008–2011) and Phase 2 data was collected approximately five years later (2012–2016). Longitudinal follow up data was collected on a yearly basis and extends past Phase 2 until July 2017. The Institutional Review Board (IRB) for National Jewish Health and each participating clinical center approved the COPDGene research protocol (HS-2778). The study met ethical guidelines according to the Belmont Report and the World Medical Association Declaration of Helsinki [13, 14].

2.2. Variables

Demographic characteristics in the analysis included age at study enrollment, race, sex, and level of education. Level of education was categorized as less than high school (includes 8th grade or less and some high school), high school graduate (includes high school graduate or General Education Diploma), or more than high school (includes some college or technical school, college graduate, master's or doctoral degree). Smoking history was self-reported and included current smoking status ("Do you now smoke cigarettes, as of one month ago?"), age of smoking initiation, and pack-years smoked. Body mass index (BMI) was calculated from height and weight obtained from baseline assessment. Comorbidities were self-reported as physician diagnosed at study enrollment (Phase 1). Comorbidity count was calculated by the addition of comorbidities present [15]. The modified Medical Research Council dyspnea scale (MMRC) was used to assess level of dyspnea with a higher score [range 0–4] indicating more severe dyspnea [16]. Distance walked was measured by a standardized 6-min walk test at baseline assessment. Subjects had spirometric testing before and after bronchodilator treatment according to American Thoracic Society guidelines [17]. Post-bronchodilator measurements were used in the analysis and patients were categorized into PRISm ($FEV_1/FVC \geq 0.70$; $FEV_1 < 80\%$ predicted) and normal ($FEV_1/FEV \geq 0.70$; $FEV_1 \geq 80\%$) groups. Exacerbation in the prior 12 months was assessed through interview ("Have you had a flare up of chest troubles in the past 12 months?"). Moderate exacerbation was defined as an exacerbation that was treated in an outpatient setting. Severe exacerbation was defined as having an exacerbation in the prior 12 months that led to a hospitalization. Yearly exacerbation frequency was defined as the number of exacerbations that occurred on average during the number of years the participant had longitudinal follow up (range of follow up: 0–9.5 years). Participants were categorized into two groups based on exacerbation status ("frequent exacerbators" or "infrequent exacerbators") using baseline data. Frequent exacerbators had either 1 severe or 2 or more moderate exacerbations in the 12 months prior to the Phase 1 visit [5]. Infrequent exacerbators had no severe exacerbations and less than 2 moderate exacerbations in 12 months prior to the Phase 1 visit. Exacerbation status was also assessed using these same criteria as reported for the 12 months prior to visit 2. Participants were then classified into 4 mutually exclusive categories based on their exacerbation status at each visit: frequent to frequent (F–F), frequent to infrequent (F–I), infrequent to infrequent (I–I), and infrequent to frequent (I–F)]. QoL was assessed using St. George's Respiratory Questionnaire (SGRQ), a 50-item instrument with a score range of 0–100 and a minimal clinically important difference (MCID) of 4. Higher scores on the SGRQ indicate worse QOL (survey instrument not modified) [18] [17].

2.3. Statistical methods

All analyses were stratified to allow for separate evaluations of subjects with normal spirometry and PRISm. Baseline comparisons for categorical and continuous variables were assessed using chi-squared and one-way ANOVA analyses, respectively. Linear regression models were performed to assess predictors of baseline SGRQ score with a beta of 4 considered clinically significant based on the MCID for the measure [19]. Separate multivariable logistic regression models were used to predict declines in quality of life, as measured by 4-point (MCID) and 8-point increases in SGRQ (associated with moderate clinically important difference [20]) within each pre-specified category with exacerbation status as the predictor of interest. Other variables included in the

models were those factors known to affect quality of life in COPD, including age, race, sex, FEV_1 percent predicted, education, MMRC, smoking status, comorbidities, and pack years at Phase 1. We chose to include race as it has been previously shown to influence QOL decline in participants who have experienced severe exacerbations. Specifically, black participants had a 4.2 higher adjusted SGRQ score for a hospitalized exacerbation compared to white participants [21]. Black participants may also experience racial discrimination as well as have differences in health behaviors including delays in seeking mental health treatment that may affect quality of life [22, 23]. Exacerbation status is reflective of only two points in time; therefore we also performed multivariable logistic regression models for QoL decline with yearly exacerbation frequency as the predictor of interest. All analyses were performed with IBM SPSS version 24.0. A two-sided alpha level of 0.05 was considered statistically significant for all analyses.

3. Results

Out of the 10,371 participants in COPDGene, 3435 were included in the current study. Table 1 displays the baseline characteristics of the study participants by spirometric cohorts and Supplemental Table 1 displays the baseline comorbidities. The PRISm cohort was more often female with a higher number of current smokers and pack years compared to the subjects with normal spirometry. Subjects with PRISm had a higher mean MMRC score, lower FEV1%, and shorter distance walked. They also had a higher number of comorbidities, participants who experienced severe exacerbations and used supplemental oxygen, and participants with "frequent exacerbation" status at baseline compared to subjects with normal spirometry. PRISm participants had higher mean SGRQ scores at baseline while approximately 30% of both cohorts experienced a 4-point increase in SGRQ score between Phase 1 and Phase 2.

Table 2 displays the linear regression model for baseline SGRQ scores in both cohorts. Factors that were associated with a SGRQ MCID of 4 included level of dyspnea and exacerbation in the year prior to visit 1 across both cohorts. Current smoking was associated with a 4.95 higher SGRQ score for PRISm participants. Smoking was also associated with higher scores for subjects with normal spirometry but the increase was less than the MCID.

Results of the multivariable logistic regression models for a 4-point increase in SGRQ score from Phase 1 to Phase 2 are shown in Table 3. Higher baseline SGRQ was associated with lower odds of decline. In the PRISm cohort, MMRC of 2 or 4 (ref: MMRC 0), current smoker status (ref: former smoker), and persistent frequent exacerbation (F–F) status or change from infrequent to frequent exacerbation status (I–F) (ref: infrequent to infrequent exacerbation status, I–I) was associated with a higher odds of an increase in SGRQ. In subjects with normal spirometry, MMRC of 2 (ref: MMRC 0), current smoker status, higher comorbidity count, and I–F change in exacerbation status was associated with an increased odds of a 4-point SGRQ increase while higher education (ref: less than high school), and white race (ref: black race) were associated with a lower odds of a 4 point increase. In both subsets of subjects, F–I exacerbation status was not associated with protection from a decline in QoL.

Results of the logistic regression model for an 8-point increase in SGRQ are shown in Supplemental Table 2. In both subsets of subjects, F–F and I–F exacerbation status (ref: I–I) were associated with higher odds of an 8-point increase. Yearly exacerbation frequency was also associated with increased odds of a 4-point SGRQ increase [PRISm (OR = 2.11, 95%CI, 1.60–2.80); normal spirometry (OR = 2.16, 95% CI, 1.73–2.71)]. These associations remained significant for an 8-point SGRQ increase (data not shown).

4. Discussion

Our study demonstrates that over a period of approximately 5 years,

Table 1
Baseline characteristics of cohort.

Variable	PRISm N = 720	Normal Spirometry N = 2715	P-value
Demographics			
Age, mean (SD)	58.0 (8.4)	57.8 (8.4)	0.5
Male sex, N (%)	314 (43.6)	1322 (48.7)	0.02
Race, N (%)			0.09
Non-Hispanic White	444 (61.7)	1768 (65.1)	
African-American	276 (38.3)	947 (34.9)	
Education, N (%)			<0.001
Less than HS	107 (9.3)	252 (9.3)	
Graduated HS	184 (25.6)	607 (22.4)	
More than HS	429 (59.6)	1856 (68.4)	
Smoking History			
Current Tobacco Use, N (%)	402 (55.8)	1381 (50.9)	0.02
Age started smoking, mean (SD)	16.9 (4.7)	17.2 (4.5)	0.1
Pack years, mean (SD)	41.3 (22.7)	36.9 (20.4)	<0.001
Clinical Characteristics			
FEV1%, mean (SD)	70.3 (8.2)	97.3 (11.4)	<0.001
FVC%, mean (SD)	71.6 (9.0)	96.3 (11.8)	<0.001
TLC, race adjusted, L, mean (SD)	5.7 (1.1)	5.7 (1.1)	0.3
Supplemental O2, N (%)	21 (2.9)	26 (1.0)	<0.001
Comorbidity count, mean (SD)	3.7 (2.4)	2.8 (2.2)	<0.001
MMRC score, mean (SD)	1.4 (1.4)	0.7 (1.1)	<0.001
Distance walked, feet, mean (SD)	1306 (251)	1518 (351)	<0.001
BMI, mean (SD)	32.3 (7.3)	29.1 (5.8)	<0.001
Exacerbation in prior 12 months, N (%)	174 (24.2)	349 (12.9)	<0.001
Severe exacerbations, N (%)	68 (9.4)	94 (3.5)	<0.001
Yearly exacerbation frequency, mean (SD)	0.3 (0.7)	0.2 (0.5)	<0.001
Frequent Exacerbation status, baseline, N (%)	95 (13.2)	137 (5.0)	<0.001
SGRQ Total Score, mean (SD)	27.6 (22.5)	15.3 (16.9)	<0.001
SGRQ 4 Point Increase, N (%)	218 (30.3)	823 (30.3)	1.0
SGRQ 8 Point Increase, N (%)	163 (22.6)	548 (20.2)	0.1

Table 2
Linear regression for baseline quality of life.

Variable	PRISm N = 720; R2 = 0.67		Normal Spirometry N = 2713; R2 = 0.62	
	Beta (SE)	P-value	Beta (SE)	P-value
Male	−0.06 (1.00)	1.0	0.52 (0.41)	0.2
Race				
Black	REF	–	REF	–
White	−0.40 (1.21)	0.7	−1.29 (0.54)	0.02
Age	−0.25 (0.07)	0.001	−0.12 (0.03)	<0.001
Comorbidity count	1.53 (0.22)	<0.001	0.95 (0.10)	<0.001
MMRC				
0	REF	–	REF	–
1	9.50 (1.52)	<0.001	9.23 (0.60)	<0.001
2	10.80 (0.75)	<0.001	9.07 (0.37)	<0.001
3	9.39 (0.48)	<0.001	9.11 (0.26)	<0.001
4	10.18 (0.48)	<0.001	9.38 (0.32)	<0.001
Current smoker	4.95 (1.21)	<0.001	3.87 (0.51)	<0.001
Education				
Less than HS	REF	–	REF	–
Graduated HS	−2.71 (1.63)	0.1	0.29 (0.81)	0.7
More than HS	−1.59 (1.59)	0.04	−0.52 (0.38)	0.1
Pack years	0.09 (0.02)	<0.001	0.04 (0.01)	<0.001
FEV1% predicted	−0.20 (0.06)	0.001	−0.03 (0.02)	<0.001
Exacerbation in prior 12 months	7.51 (1.24)	<0.001	8.38 (0.63)	<0.001

Table 3
Adjusted odds of decline in QoL (SGRQ 4 point increase).

Variable	PRISm N = 720		Normal Spirometry N = 2713	
	OR (95% CI)	P value	OR (95% CI)	P value
Male	1.18 (0.83–1.66)	0.4	0.87 (0.73–1.04)	0.1
Race				
Black	REF	–	REF	–
White	0.72 (0.47–1.09)	0.1	0.79 (0.63–0.99)	0.04
Age	1.00 (1.00–1.17)	0.7	1.00 (0.98–1.01)	0.6
Comorbidity Count	1.09 (1.00–1.18)	0.04	1.09 (1.04–1.13)	<0.001
MMRC				
0	REF	–	REF	–
1	1.28 (0.75–2.17)	0.4	1.23 (0.94–1.60)	0.1
2	1.89 (1.04–3.45)	0.04	1.51 (1.06–2.13)	0.02
3	1.83 (0.96–3.48)	0.07	1.38 (0.92–2.07)	0.1
4	2.82 (1.16–6.89)	0.02	1.45 (0.76–2.74)	0.3
Current smoker	1.59 (1.04–2.43)	0.03	1.42 (1.15–1.77)	0.001
Education				
Less than HS	REF	–	REF	–
Graduated HS	0.78 (0.44–1.38)	0.4	0.67 (0.48–0.93)	0.02
More than HS	0.92 (0.54–1.58)	0.8	0.66 (0.48–0.90)	0.01
Pack years	1.01 (1.00–1.02)	0.01	1.01 (1.00–1.01)	0.001
FEV1% predicted	0.98 (0.96–1.01)	0.1	0.99 (0.98–1.00)	0.01
Baseline SGRQ Total Score	0.95 (0.94–0.97)	<0.001	0.97 (0.96–0.97)	<0.001
Exacerbation Status				
I→ I	REF	–	REF	–
F→ F	2.75 (1.16–6.49)	0.02	2.02 (0.97–4.25)	0.06
F→I	1.50 (0.77–2.91)	0.2	0.84 (0.50–1.41)	0.5
I→ F	3.15 (1.67–5.94)	<0.001	4.72 (3.25–6.86)	<0.001

transitioning from infrequent to frequent exacerbation status, higher yearly exacerbation frequency, and baseline current smoking are each associated with a clinically significant reduction in quality of life in smokers with normal spirometry or PRISm. However, stabilization of exacerbation status (F–I) was not associated with protection from a decline in QoL.

Smokers without COPD experience increases in respiratory symptoms that are clinically similar to exacerbations that occur in those with spirometrically confirmed COPD [24] [25] [26]. A prior COPDGene study found that these exacerbations occur without the loss of lung function [7], however the effect of exacerbations on decline in QoL in PRISm and smokers without COPD is less clear. In our study, subjects with PRISm were similar to typical COPD patients with higher exacerbation frequency, higher comorbidity count, more symptoms, and worse baseline QoL compared to participants that had no airflow obstruction at baseline. Other studies have reported an increase in BMI [27], morbidity [28], increased airway wall thickness [29] and mortality [30] [31] in patients with restrictive spirometry compared to those with no lung disease. Prior data published from COPDGene has also shown that 25% of PRISm individuals developed obstruction between Phase 1 and Phase 2 follow up (31), highlighting the heterogenous nature of this group as well as the potential benefit of routine spirometry in these groups to detect early COPD. In both regression models of a 4-point and 8-point increase in SGRQ, normal spirometry and PRISm subjects had higher odds of QoL decline if they experienced a deterioration in exacerbation status (I–F). This is clinically important as the impact of exacerbations on QoL and health care costs is not exclusive to COPD patients. Smokers with normal spirometry and PRISm who exacerbate may also benefit from recommendations to prevent exacerbations as well as deterioration in QoL.

Our study also showed that smoking was a predictor of QoL decline in smokers without COPD. These results confirm prior observations and emphasize the need for smoking cessation. A quality of life-adjusted expectancy (QALE) analysis from the 2009 Behavioral Risk Factor Surveillance system found that smoking accounted for 11 years of QALE loss for smokers, 4 of which were due to deteriorations in QoL [32]. In our study, 56% of PRISm and 51% of subjects with normal spirometry were current smokers. In a review evaluating the relationship between QoL and smoking, active smoking was associated with a reduced QoL in 32 out of 33 studies, with the number of cigarettes smoked inversely proportional to the measurement of QoL [33]. Cessation efforts result in an improvement in quality of life [34] [35] however only half of current smokers receive advice from their primary care physician to quit [36]. In an analysis of the 2010 National Health Interview Survey, those who are young, male, from the southern U.S., and Hispanic or Latino were less likely to be counseled on tobacco cessation. While education and income did not affect counseling delivery, only 41% of uninsured smokers was advised to quit by a healthcare professional [36].

We expected participants with a decrease in exacerbation frequency (F–I status) to have lower odds of QoL decline, however this was not observed in either subjects with normal spirometry or PRISm. The Towards a Revolution in COPD Health (TORCH) study found that patients with no exacerbations had an improvement in SGRQ total scores (−2.6 (95% CI -3.5 to −1.7) units/year) over a 3 year follow up period [37]. Results from the ISOLDE study similarly suggested that fluticasone administration was associated with a slowing of QoL decline due to a decrease in exacerbation frequency [38] [39]. While these randomized controlled trials included repeated assessments of QoL, the results may not be generalizable to a real world population as they underrepresent the elderly, those with multiple comorbidities [40], and, specifically in these studies, women (approximately 75% male study populations) [37] (38). Other cohort studies have raised questions about the relationship between exacerbation status and changes in QoL. Yoo et all evaluated QoL trajectories in the Korean Obstructive Lung Disease population-based cohort and found that BODE (body mass index, airflow obstruction, dyspnea, exercise capacity) index, respiratory symptoms and depression were predictors of QoL trajectory while recent exacerbations had no association [41]. Instead of focusing on stabilizing exacerbation frequency, it may be beneficial to patients if we focus on stabilizing health status, which may in turn improve health outcomes. The Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study demonstrated this effect as participants who had an improvement in health status at one-year follow up had a lower risk of future exacerbations and mortality in the following two years [42].

Our study adds to the literature by showing an association of deteriorating quality of life and exacerbation frequency in smokers without COPD. We also show that stabilization of disease in patients who are previously frequent exacerbators may not improve quality of life. Our results should be interpreted in light of several limitations. Our cohort only included participants who had completed baseline and follow up QoL data, a selection bias that may have influenced our results as those with very poor quality of life are more likely to forgo follow up and also may have died prior to the Phase 2 study visit. The presence of anxiety and depression are known to affect QoL [43] however were not assessed at baseline and therefore were not included in our analysis. We also did not adjust for medication use or compliance with preventive care including vaccinations which may have affected exacerbation rate.

5. Conclusion

In summary, our study showed that a change in exacerbation status from an infrequent to a frequent exacerbator, higher yearly exacerbation frequency, and continued smoking predicted a decline in QoL in subjects with normal spirometry and PRISm. Stabilization of disease was not protective against a QoL decline in either cohort. Further studies regarding the efficacy of bronchodilator therapy and novel tobacco smoking cessation interventions as well as identification of modifiable causes of QoL deterioration in those not meeting current spirometric criteria for COPD are warranted.

Author's potential conflicts of interest

DLD has received grants from the NIH and consulting fees from Novartis in the last three years. ALC reports research support from Boehringer Ingelheim and consulting fees from AstraZeneca and Novo Nordisk. MTD reports grants from NIH involving the work under consideration for publication, grants from the Department of Defense outside the submitted work, contracted clinical trial support from AstraZeneca, Boehringer Ingeheim, Boston Scientific, GlaxoSmithKline, Novartis, PneumRxBTG, Pulmonx, and Yungjin outside the submitted work, and consulting fees from AstraZeneca, GlaxoSmithKline, and PneumRxBTG outside the submitted work. MKH reports consulting for GSK, AZ and BI. She also has received research support from Novartis and Sunovion. TMP, ASI, AL, YK, EAR, SB have no conflicts to report.

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Notation of prior abstract publication/presentation

This work has been submitted as an abstract proposal for the American Thoracic Society Conference 2019 in Dallas, Texas.

Authors' contributions

Study design: TMP, SB, AC, YK, AL, ASI, EZR, DLD, MH, MTD.

Acquisition of data: TMP, MTD, ASI, EZR, DLD, MH, MTD.

Data analysis and interpretation: TMP, DLD, YK, SB, AL, AC, MTD.

Manuscript writing: TMP, MTD.

Critical review of the manuscript for important intellectual content: TMP, SB, AC, YK, AL, ASI, EZR, DLD, MH, MTD.

Approved final version for publication: TMP, SB, AC, YK, AL, ASI, EZR, DLD, MH, MTD.

Guarantor statement

TMP had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis and content of the manuscript.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2019.105820.

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