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ORIGINAL ARTICLE

The Impact of Chronic Pulmonary Aspergillosis Co-infection on the Health-Related Quality of Life of Patients with Pulmonary Tuberculosis in Uganda

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Abstract

Background Both pulmonary tuberculosis (PTB) and chronic pulmonary aspergillosis (CPA) significantly affect health-related quality of life (HR-QoL). We aimed to determine the impact of CPA co-infection on the HR-QoL of Ugandans with PTB.

Methods We conducted a prospective study as part of a larger study among participants with PTB with persistent pulmonary symptoms after 2 months of anti-TB treatment at Mulago Hospital, Kampala, Uganda between July 2020 and June 2021. HR-QoL was assessed using St. George Respiratory Questionnaire (SGRQ) at enrollment and at the end of PTB treatment (4 months apart). SGRQ scores range from 0 to 100, with higher score representing a poorer HR-QoL.

Results Of the 162 participants enrolled in the larger study, 32 (19.8%) had PTB + CPA and 130 (80.2%) had PTB. The baseline characteristics of the two groups were comparable. Regarding overall health, a higher proportion of the PTB group rated their HR-QoL as "very good" compared to those who had PTB + CPA (68 [54.0%] *versus* 8 [25.8%]). At enrollment, both groups had comparable median SGRQ scores. However, at follow up, the PTB group had statistically significantly better SGRQ scores (interquartile range); symptoms (0 [0–12.4] *versus* 14.4 [0–42.9], $p < 0.001$), activity ((0 [0–17.1] *versus* 12.2 [0–35.5], $p = .03$), impact (0 [0–4.0] *versus* 3.1 [0–22.5], $p = 0.004$), and total scores ((0 [0–8.5] *versus* 7.6[(0–27.4], $p = 0.005$).

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Conclusion CPA co-infection impairs HR-QoL of people with PTB. Active screening and management of CPA in patients with PTB is recommended to improve HR-QoL of these individuals.

Keywords Pulmonary tuberculosis · Persistent symptoms · Chronic pulmonary aspergillosis · Quality of life · St. George Respiratory Questionnaire · Uganda

Introduction

Tuberculosis (TB) is a global public health problem and the leading cause of death from a single infectious agent [1]. Pulmonary TB (PTB) is the most common form, accounting for over 60% of the disease [1]. The hallmark of PTB sequalae is lung impairment through destruction of its architecture, including cavitation, fibrosis and bronchiectasis leading to reduced pulmonary function [2]. An estimated 18–87% of PTB patients may experience lung impairment following post-PTB treatment or microbiological cure [2] and have higher mortality rates of up to threefold higher than in the general population [3].

The true burden of post-TB sequalae in our Ugandan setting is without doubt underreported due to paucity of clinical, research, and advocacy data. Post-TB sequalae may manifest as structural complications including bronchiectasis, bronchitis, residual cavitation, or chronic obstructive pulmonary disease (COPD); infectious complications including chronic pulmonary aspergillosis (CPA), colonization and infection with non-tuberculous mycobacteria, empyema, and TB recurrence; and psychosocial complications [4]. Overall, post-TB complications are diverse with a resultant effect of significant impairment on the health-related quality of life (HR-QoL) [4].

PTB sequalae manifest through a decline in HR-QoL [3]. Studies done in South Africa and Uganda show significant decline in HR- QoL among patients with active PTB [5–7]. It is important to evaluate the psychosocial well-being and HR-QoL of patients [8, 9]. Measurements of HR-QoL are increasingly proving to be key and are important indicators in day-to-day patient care, research, and even in programmatic monitoring and evaluation of populations [8, 9].

Patients with PTB are at an increased risk of CPA [10, 11], and CPA-coinfection may lead to poorer PTB outcomes [11, 12]. Moreover, in Uganda currently, itraconazole, the choice drug for CPA treatment is not on the Ministry of Health's Essential Drugs List and remains mostly unaffordable to the population most likely to get PTB. We sought to investigate and compare HR-QoL of participants treated for PTB and those with PTB + CPA to understand if CPA worsened HR-QoL in this patient population.

Methods

Study Design

This was a nested sub study of a larger previously published study [13]. We conducted a prospective observational study at the National TB control center of Mulago National Referral Hospital (MNRH), Kampala, Uganda between 1st July 2020 and 30th June 2021.

Study Setting

The TB Unit at MNRH serves as the national TB treatment center in Uganda. The unit uses a mixed model of care, whereby, 1) very sick patients are hospitalized at the start of their TB treatment until clinically stable, and 2) outpatient care where patients continue treatment from the community under supervision. The unit manages about 1,500 TB patients annually, making it the largest treatment center in the country.

Study Population

We enrolled all eligible patients 18 years and older with microbiologically confirmed drug sensitive PTB (DS-PTB) using GeneXpert MTB/RIF and persisting pulmonary and/or systemic symptoms despite 2 months of standard anti-TB treatment. Patients on second line anti-TB regimens, pregnant women, critically ill patients, and those with extra-pulmonary TB were excluded.

Study Procedure

HR-QoL was assessed using the St. George Respiratory Questionnaire (SGRQ). QoL data was collected at two time points: time point 1 was enrollment which happened at month 2 of anti-TB therapy and time point 2 was at the end of anti-TB treatment. CPA diagnosis was also established at time point1. The end of anti-TB treatment (time point 2) was 4 months from enrollment.

Diagnosis of Chronic Pulmonary Aspergillosis

CPA was defined as the presence of persistent respiratory symptoms (at least a cough or hemoptysis lasting for 3 months or more), suggestive CXR findings (cavities, pericavitary infiltrates, a fungal ball (intra-cavitary content), pericavitary fibrosis, or pleural thickening), and evidence of *Aspergillus* infection (a positive HVS culture and/or *Aspergillus* IgG/IgM ICT) consistent with the Global Fungal Infection Forum II diagnostic criteria for CPA in resource-limited settings [14]. The data from each patient was carefully evaluated by the lead investigator (MN) who made a provisional diagnosis of CPA. Two trained medical mycologists (FB and RK) experienced in the diagnosis of CPA independently evaluated MN's provisional diagnosis and any discrepancy was resolved by an expert in CPA (DWD).

St. George Respiratory Questionnaire

The SGRQ was the tool used to collect HR-QoL data for this study. The SGRQ is a 50 item survey designed to measure the impact of lung disease on overall mental health and wellbeing. It contains three components: symptoms, activity level, and the impact of lung health on daily life. The total score, calculated for all items, provides a general view of the patient's respiratory health. It is scaled from 0 (optimal) to 100 (worst); responses are used to produce a score for each component and an aggregate score. It has been successfully used previously to evaluate quality of life among pulmonary TB patients [15, 16]. Notably, the SGRQ is validated for CPA [17–19] and validated in Uganda where our study was based [20]. SGRQ HR-QoL measures were interpreted as described in earlier literature [21, 22].

Data Analysis

Baseline characteristics of the study population were summarized using percentages for categorical data and compared using chi square tests and Fisher exact tests. Median and interquartile ranges were calculated for continuous variables. The QoL as measured using the SGRQ was calculated for all participants based on the SGRQ manual [23]. Baseline and follow up median QoL scores were compared using the Wilcoxon rank sum tests in the PTB and PTB + CPA groups. Box plots considering the symptoms, activity, impacts and total scores were drawn for visualization of the data. For all analyses, a P-value of less than or equal to 0.05 was considered as statistically significant. All data analysis was conducted in STATA V.14 (StataCorp, College Station, Texas).

Results

Baseline Clinical Characteristics of the Participants

Of the 162 participants enrolled, 97 (60.0%) were male with a median age of 30 (IQR: 25–40) years for all participants. Forty-eight (29.6%) participants were living with HIV and 15 (9.3%) were previously treated for PTB.

Overall, 32/162 (19.8%) participants had CPA. Of the 32 participants with CPA, 3/32 (9.3%) were commenced on antifungal therapy. This low percentage of antifungal therapy use is because itraconazole is not readily available or affordable to those who need it in Uganda. The antifungal therapy consisted of a standard guideline recommended dose of itraconazole of 200 mg twice daily. The clinical characteristics of patients with PTB and those with PTB + CPA were comparable. However, a slightly higher percentage of those with PTB had chest pain (93.1% versus 90.6%, $p = 0.016$), Table 1.

Overall Self-Rated Health Status

The difference in overall health, both at baseline and follow up between the participants who had PTB + CPA ($p = 0.424$) compared to those who had PTB (0.342) was not statistically significant. However, a higher proportion of participants in the PTB group

Table 1 Baseline clinical characteristics

Characteristics	All, (%)	PTB + CPA *n* = 32	PTB *n* (%) *n* = 130	*P*-value
Shortness of breath	67 (41.4)	10 (27.8)	57 (45.2)	0.061
Weight loss	84 (51.8)	18 (56.3)	66 (50.8)	0.900
Fatigue				
	75 (46.3)	15 (46.9)	60 (46.1)	0.899
Fever				
	31 (19.1)	5 (15.6)	26 (20.0)	0.669
Loss of appetite				
	59 (36.4)	11 (34.4)	48 (36.9)	0.663
Shortness of breath				
	67 (41.4)	9 (28.1)	58 (44.6)	0.061
Hemoptysis				
	20 (12.4)	7 (21.9)	13 (10.0)	0.142
Night sweats				
	105 (64.8)	18(56.3)	87 (66.9)	0.086
Chest pain				
	150 (92.6)	29 (90.6)	121 (93.1)	0.016
Wheezing				
	15 (9.3)	12 (9.2)	3 (9.4)	0.828

reported favorable outcomes in their overall health at follow-up, with 68 (54.0%) participants in the PTB group reporting a "very good" compared to only 8 (25.8%) in the PTB + CPA group, Table 2.

Quality of Life Across Domains of St. George's Respiratory Questionnaire

At enrollment (baseline, 2 months of anti-TB therapy, no antifungal therapy), both groups had comparable median QoL scores; symptoms (55.4 [42.9–66.0] *versus* 53.3 [37.6– 66.8], $p = 0.987$), activity (60.3 [47.7–72.8] *versus* 59.5 [47.5–72.8], $p = 0.542$), impact (43.6 [30.1–6.2] *versus* 46.6 [37.7–56.7], $p = 0.358$), and total scores (51.0 [40.0–3.1] *versus* 51.7 [42.9–62.5], $p = 0.699$), Table 3, Fig. 1.

However, at follow up (end of PTB therapy), participants with PTB compared to those with PTB + CPA had better median (IQR) quality of life scores which was statististically significant; symptoms (0 [0–2.4] *versus* 14.4 [0–42.9], $p < 0.001$), activity (0 [0–17.1] *versus* 12.2 [0–35.5], $p = 0.03$), impact (0 [0–4.0] *versus* 3.1[(0–22.5], $p = 0.004$), and total scores (0 [0–8.5] *versus* 7.6 [0–27.4], $p = 0.005$), Table 4, Fig. 2.

Discussion

In this prospective cohort study, we showed that participants with PTB had better SGRQ scores compared to those with PTB + CPA. Our findings are

Table 2 Comparison of overall health between the PTB group and the PTB + CPA group

Status	PTB + CPA	PTB		
	Baseline n (%)	Follow –up n (%)	Baseline n (%)	Follow –up n (%)
Very good	0 (0)	8 (25.8)	0 (0)	68 (54.0)
Good	6 (18.8)	9 (29.0)	22 (16.9)	41 (32.5)
Fair	21 (65.6)	11 (35.5)	84 (64.6)	11 (8.7)
Poor	5 (15.6)	1(3.2)	23 (17.7)	3(2.4)
Very poor	0(0.0)	2 (6.4)	1 (0.8)	3(2.4)
P-value	0.424		0. 342	

Table 3 Comparing the SGRQ scores according to PTB and PTB + CPA groups, baseline, n = 162

Characteristic	PTB	PTB + CPA,	*P* value*
Symptoms, median, interquartile range	55.37 (42.85–66.03)	53.25(37.62–66.82)	0.987
Activities, median, interquartile range	60.26(47.68–72.82)	59.46 (47.46–72.82)	0.542
Impacts median, interquartile range	43.62(30.08–56.17)	46.61 (37.66–56.73)	0.358
Total score (median, interquartile range)	50.97 (39.9–63.05)	51.65(42.94–62.52)	0.699

*Based on Wilcoxon rank sum test

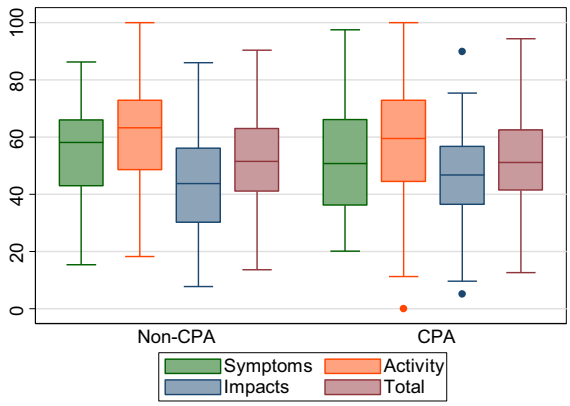

Fig. 1 Box plots of the SGRQ scores by the CPA status. The top and bottom of the boxes represent the 25th and 75th percentile while the horizontal line represents the median and the dots represent the outliers. Baseline scores by CPA status

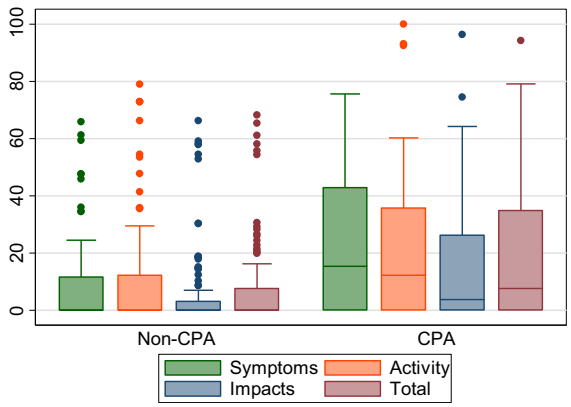

Fig. 2 Box plots of the SGRQ scores by the CPA status. The top and bottom of the boxes represent the 25th and 75th percentile while the horizontal line represents the median and the dots represent the outliers. Follow up scores by CPA status

consistent with previous literature that showed that CPA significantly affects HR-QoL, particularly for those who have not been initiated on anti-fungal therapy [17]. Of the 32 participants with CPA in our study, only 3 received anti-fungal therapy. This could explain the poor HR-QoL experienced by the CPA/PTB group.

The WHO promotes patient involvement in healthcare decisions because this allows them to be more proactive in their management and ultimately more able to adhere with treatment plans [5, 24]. The use of disease-specific health status questionnaires helps to discriminate between different levels of disease severity. Patient experience can be assessed using a patient-reported outcome measure (PROM). The SGRQ as a form of PROM has already been successfully validated in Uganda [20].

At enrollment, we observed that participants were quite ill, and therefore we recorded the highest SGRQ scores at this point of the study. The scores then

Table 4 Comparing the SGRQ scores according to PTB and PTB + CPA groups, follow up, n = 157

Characteristic	PTB	PTB + CPA	*P* value*
Symptoms, median, interquartile range	0 (0–12.39)	14.43 (0–42.85)	< 0.001
Activities, median, interquartile range	0 (0–17.12)	12.17(0–35.47)	0.029
Impacts median, interquartile range	0 (0–3.97)	3.06(0–22.53)	0.004
Total score (median, interquartile range)	0 (0–8.48)	7.57(0–27.43)	0.005

*Based on Wilcoxon rank sum test

improved markedly in the different HR-QoL domains at the follow up visit which coincided with end of anti-TB therapy. This was very likely a reflection of the known efficacy of anti-TB therapy and adherence to this treatment by the participants.

While studies that measured HR-QoL among TB patients are still few in Africa [25], there is some precedence already set by another study similar to the present study that investigated both PTB and CPA and their effects on HR-QoL [26]. Such research will go a long way in improving management and outcomes for these patients.

This observed improvement in HR-QoL due to anti-TB therapy accords with findings from similar studies [27–30]. Thus from a programmatic perspective, ensuring adherence to treatment and retention in care is important for improvement in HR-QoL. For our study, only 9.3% of participants diagnosed with CPA were able to access treatment since itraconazole remains expensive in our setting and is not included on the Ministry of Health's Essential Medicines List.

Both at baseline and follow-up, there were no significant differences ($p = 0.424$, 0.342) in overall health between the group that had PTB and those that had PTB + CPA. This may be explained with the fact that at baseline, both groups were ill, and therefore overall health was poor for both. At follow-up, improvement due to effective anti-TB therapy likely, and temporarily, masked underlying CPA disease (whose genesis is more gradual and insidious) by improving lung inflammation, cavity size, and pleural disease hence giving symptom relief.

In comparing the SGRQ scores by CPA status at baseline, there was no significant difference in scores between the PTB + CPA group versus the PTB group. This would still be explained by illness in both groups at baseline. Conversely, at follow up, a statistically significant difference arises in SGRQ scores between the two groups. This could possibly be due to the persistence of symptoms in the group with PTB + CPA, as has been reported in previous studies [17, 26], and especially so because majority of CPA patients could not afford anti-fungal therapy.

This study had some limitations. This was a single center study, involving mainly patients from the central region of Uganda and may not be representative of other African populations, since social demographics and support systems that could influence HRQoL may differ across sites. Future multicenter studies are recommended.

In conclusion, HR-QoL- based disease appraisals in resource-limited settings are important instruments to grasp health outcomes and provide focused and empirically informed ways to manage care and treatment better [26]. HR-QoL among PTB patients improves with anti-TB therapy, however co-infection with CPA negatively impacts their HR-QoL. Therefore, programmatic approaches to screen, diagnose, and treat CPA co-infection among PTB patients will improve QoL and general well-being in this population.

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Author Contributions All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by MN, FB, and JM. The first draft of the manuscript was written by MN and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Declarations

Conflict of interest There is no conflict of interest to disclose.

Ethics Approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Makerere University School of Biomedical Science Research and Ethics Committee (SBS-795) and the Uganda National Council for Science and Technology (HS739ES)

approved the study protocol. The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to.

Consent to Participate All study participants provided informed written consent.

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