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Uphill both ways: Fatigue and quality of life in valley fever

Ashley L. Garrett[1], Yu-Hui H. Chang[2], Kathleen Ganley[3] and Janis E. Blair[4,*]

[1]Department of Internal Medicine, Mayo Clinic, Scottsdale, Arizona, [2]Department of Biostatistics, Mayo Clinic, Scottsdale, Arizona, [3]Department of Physical Therapy and Athletic Training, Northern Arizona University, Phoenix, Arizona and [4]Division of Infectious Diseases, Mayo Clinic Hospital, Phoenix, Arizona

*To whom correspondence should be addressed: Janis E. Blair, Division of Infectious Diseases, Mayo Clinic Hospital, 5777 E Mayo Blvd, Phoenix, AZ 85054. Tel: +480-342-0115; Fax: +480-342-0689; E-mail: blair.janis@mayo.edu.

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Abstract

Primary pulmonary coccidioidomycosis is characterized by prolonged respiratory and systemic symptoms and fatigue. We prospectively administered the fatigue severity scale (FSS) and Short Form-36 Health Status Questionnaire (SF-36) to patients with proven or probable primary pulmonary coccidioidomycosis to quantify disease effect on quality of life (QOL). The 24-week observational study did not specify whether antifungal treatment would be provided; the treating physician made treatment decisions. FSS and SF-36 were completed at 4-week intervals. Thirty-six patients participated, of whom 20 received antifungal treatment. At onset of coccidioidal illness, mean FSS score was higher (ie, more fatigue) in the treatment group. However, in early illness, both groups had higher fatigue levels than reference populations with other diseases (eg, multiple sclerosis). FSS scores gradually improved, and scores in each group were below the *severe fatigue* level at week 12 and week 16 in the nontreatment and treatment groups, respectively. By week 24, mean FSS score of the nontreatment group equaled the general population. SF-36 component and profile scores were lower (with more symptoms) in the treatment group at each time point than the nontreatment group; both groups showed similar improvement. Mental and emotional health SF-36 scores were not as severely affected as physical scores. Most patients reached a physical functioning level similar to the general population at week 12. Pulmonary coccidioidomycosis causes severe fatigue and substantially affects physical abilities. Fatigue was found to be prolonged, with gradual improvement in QOL, regardless of antifungal administration.

Key words: coccidioidomycosis, fatigue, health-related quality of life, valley fever.

Introduction

Primary pulmonary coccidioidomycosis (colloquially known as *valley fever*) is a common cause of community-acquired pneumonia in the US Southwest.[1,2] The dimorphic fungi *Coccidioides immitis* and *Coccidioides posadasii* live in the desert soil as filamentous moulds and

produce arthroconidia that can act like spores, becoming aerosolized and then inhaled. Thereafter a cascade of inflammatory responses occurs, with manifestations ranging from asymptomatic or mild respiratory illness to severe coccidioidal infection requiring hospitalization.[3,4] Characteristics of primary pulmonary coccidioidomycosis include cough, fever, night sweats, chest pain, arthralgia, rash, and severe prolonged fatigue.[5] Most symptoms resolve within several weeks to a few months, but for many patients, fatigue persists for several months, making it a characteristic feature of the disease.[5,6] In 1 study, 84% of patients with coccidioidomycosis reported fatigue that manifested in inability to perform usual activities of daily living for a mean of 96 days after illness onset.[7]

The first study of fatigue in coccidioidomycosis assessed a cohort with pulmonary and extrapulmonary infection, the duration of which ranged from a few days to a few years.[6] The investigators demonstrated that fatigue levels declined over the course of months and inversely correlated with body mass index. Building on this work, we sought to measure the severity and duration of fatigue, its disruption to quality of life (QOL), and the possible effect of antifungal treatment on otherwise healthy patients with primary pulmonary coccidioidomycosis during the first 6 months of illness.

Methods

We conducted a 24-week prospective observational study to thoroughly describe the clinical course of primary pulmonary coccidioidomycosis. We have previously described the clinical course of all the patients in the present study with respect to the time course of respiratory and systemic symptoms and the effect of antifungal treatment on the clinical illness.[5] We used 2 standardized, validated scoring systems to assess individual participant QOL: Short Form-36 Health Status Questionnaire (SF-36)[8,9] and fatigue severity scale (FSS).[10]

The Mayo Clinic Institutional Review Board approved the study. Participants with acute symptomatic, mild-to-moderate pulmonary coccidioidomycosis were recruited and signed informed consent for participation at the Mayo Clinic campus in Phoenix, Arizona, from March 1, 2010, through October 31, 2012. No financial compensation or other incentive was provided to research participants.

Patients eligible to participate had symptomatic, proven, or probable (as defined by European Organisation for Research and Treatment of Cancer clinical criteria[11]) primary pulmonary coccidioidomycosis for less than 2 months. *Proven coccidioidomycosis* was defined as a case showing positive histologic or culture results. *Probable coccid-*

ioidomycosis was defined as the combination of the following characteristics:

1) Positive results on serologic testing with immunoglobulin G antibodies to *Coccidioides* species with enzyme immunoassay, immunodiffusion, or complement fixation or with immunoglobulin M antibodies by immunodiffusion;
2) Characteristic radiographic findings;[12]
3) Characteristic symptoms.

At least 2 symptoms were required for study eligibility (eg, fever, night sweats, myalgias, pleuritic chest pain, rash, dyspnea, fatigue, headache). Since patients with acute pulmonary coccidioidomycosis can need several weeks for seroconversion from seronegativity to study-eligible seropositivity, we also enrolled patients who otherwise met inclusion criteria but had isolated enzyme immunoassay immunoglobulin M seropositivity. Such patients were withdrawn from study later if they did not meet the serologic criteria for the study by 2 months after symptom onset. Participants were required to be ≥18 years of age.

Participants were excluded if they had any of the following characteristics: 1) severe pulmonary coccidioidal disease, evidenced by miliary pulmonary distribution, >50% involvement of lung parenchyma, or large pleural effusion on radiographic imaging; 2) symptomatic illness requiring hospitalization; 3) extrapulmonary coccidioidomycosis; 4) receipt of immunosuppressive therapies, with the exception of topical or short course of oral corticosteroids (<5 days); 5) presence of another medical condition that potentially could predispose to severe or disseminated coccidioidomycosis (eg, hematologic malignancy, human immunodeficiency virus infection, diabetes mellitus, receipt of hematologic or solid organ transplant); or 6) comorbid conditions that potentially could influence coccidioidal illness (eg, liver disease, chronic kidney disease stages 4 and 5, cardiomyopathy, chronic pulmonary disease).

Physician investigators monitored participants prospectively for 24 weeks. At the initial clinic visit, each patient underwent laboratory evaluation with complete blood cell count, complete metabolic panel and serologic testing for antibodies against *Coccidioides*, and chest radiograph. Patients returned for clinical, serologic, and radiographic testing at 4, 12, and 24 weeks after enrollment. The SF-36 and FSS tools were assessed at the initial visit and readministered every 4 weeks for 6 months. All recorded times were normalized to the time of symptom onset, not study enrollment.

FSS is a 9-item self-administered questionnaire used to assess fatigue in the clinical setting.[10,13] A Likert-like scale of 1 to 7 is used for each item, with 1 corresponding to strong disagreement and 7 to strong agreement with the statement. Higher FSS scores correlate with more severe

fatigue. The score can be reported either as a sum of the 9 questions (eg, the study by Muir Bowers et al.[6]) or as divided by the total number of items to yield a mean score (eg, the study by Krupp et al.[10]). SF-36 is a 36-item self-administered questionnaire that has been well validated and used for many medical conditions to describe the impact of disease on health-related QOL.[8,9,13] The items are divided into 8 subscales: "general health," "physical functioning," "role physical," "bodily pain," "vitality," "social functioning," "role emotional," and "mental health." The subscales are used to calculate a "physical component score" and a "mental component score," each reported in the range of 0 to 100. A general population score is scaled to 50 using norm-based scoring, and a score <50 corresponds to QOL less than the general population.[9]

The decision to administer antifungal treatment often was made by a health care provider before study enrollment. However, antifungal therapy could be initiated, held, or continued at the discretion of a study physician investigator and on evaluation of each case. Patients who received antifungal treatment during or at any time before the study were included in the treatment group.

Patient characteristics were summarized as percentage or median (interquartile range) and compared using the χ^2 test or Wilcoxon rank sum test. The mean (SD) for the FSS mean score and SF-36 (subscales and summary scales) were reported by group and by weeks from onset (4, 8, 12, 16, 20, and 24 weeks), and the 95% confidence interval (CI) of the point estimate was computed. The 2-sided P values were reported. All statistical analysis was performed with statistical software (SAS version 9.4; SAS Institute Inc).

Results

From March 1, 2010, through October 31, 2012, a total of 45 patients with acute symptomatic pulmonary coccidioidomycosis met inclusion criteria and agreed to participate in the present study. Nine patients later withdrew from the study, for a total enrollment of 36 patients. The primary reason for the 9 patient withdrawals was failure to have seroconversion. Of the 36 remaining patients, 20 (56%) received antifungal treatment (Figure 1). Twenty-seven patients (75%) completed the full 24-week observation period. The median time from symptom onset to study enrollment was 33 days. Table 1 summarizes the demographic characteristics of the 36 participants. The symptoms and course of illness of all 36 patients were fully described previously.[5]

Figure 2 summarizes the temporal relations of the FSS in the treatment and nontreatment groups. FSS scores improved in both groups during the study's 24 weeks ($P < .001$) (Table 2). The mean (SD) FSS scores progres-
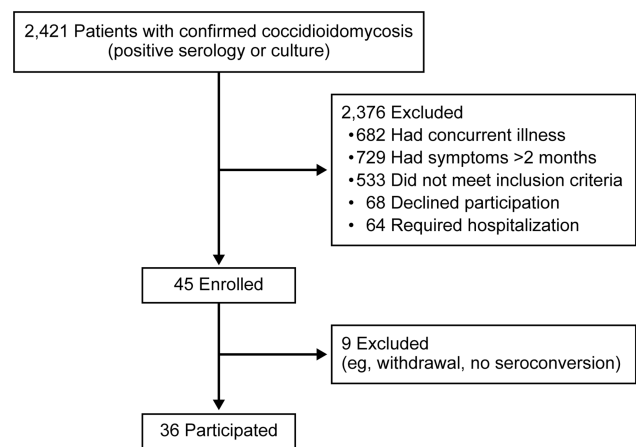

Figure 1. Flow Diagram of Patient Enrollment from March 1, 2010, to October 31, 2012.

sively decreased—the illness became less symptomatic—from week 4 (5.89 [1.3] and 5.28 [1.4] for the treatment and nontreatment groups) to week 24 (3.59 [2.1] and 2.21 [1.8], respectively). However, the difference in FSS scores between the 2 groups over the 24 weeks was not statistically significant ($P = .11$).

The SF-36 score and component score relations are depicted in Figure 3. Although not statistically significant ($P = .20$), the mean standardized physical component scores were lower (ie, indicated more severe symptoms) in the treatment group than the nontreatment group at 4 weeks. There was no significant difference in standardized mental component scores between the treatment and the nontreatment groups during the 24 weeks ($P = .08$). The component scores in both groups improved over the disease course ("physical component" score, $P<.001$; "mental component" score, $P = .003$), with the highest scores (least severe symptoms) obtained at week 24.

When the individual domains of the SF-36 (Table 3) were examined, those less severely affected were "mental health," "general health perceptions," and "role emotional" scores, with scores near or greater than 50 at enrollment. However, the "role physical," "vitality," and "social functioning" scores were diminished at enrollment (mean score, <38) and showed improvement toward the values expected of the general population (mean score, 50) between week 12 and week 16 in treated and nontreated groups. The mean "physical functioning" score (ie, physical abilities such as walking and climbing stairs) was >50 for both groups at all time points; however, at enrollment, the mean (SD) "role physical" scores (completion of and performance at work) were 3.1 (8.8) and 5.0 (10.5) in the treatment and nontreatment groups, respectively.

Laboratory parameters, including coccidioidal serologic results, serum hemoglobin, white blood cell count, and

Table 1. Demographic Characteristics of 36 Participants in Treatment and Nontreatment Groups.

Baseline Characteristic	Total (N = 36)	Treatment (n = 20)	Nontreatment (n = 16)	P Value
Age, median, (range), y	53 (21–79)	52 (28–79)	53 (21–68)	.15[a]
Sex, no. (%)				
Male	16 (44)	11 (55)	5 (31)	.15[b]
Female	20 (56)	9 (45)	11 (69)	.15[b]
Race/ethnicity, no. (%)				.65[b]
White	33 (92)	18 (90)	15 (94)	
Hispanic	1 (3)	1 (5)	0 (0)	
Asian	2 (6)	1 (5)	1 (6)	
Employed at time of diagnosis, no. (%)	22 (61)	14 (70)	8 (50)	.22[b]
Illness resulted in work absences, no./total (%)	18/22 (82)	12/14 (86)	6/8 (75)	.53[b]
Work missed, median, no. (IQR), (range), d	10 (5–14) (1–28)	10 (5–15) (2–28)	7 (4–12) (1–13)	.32[a]
Attending school at time of diagnosis, no. (%)	3 (8)	2 (10)	1 (6)	.68
Illness resulted in school absences, no./total (%)	1/3 (33)	0 (0)	1/1 (100)	.08
Positivity on serologic test at study enrollment, no./total (%)				
EIA IgM	34/35 (97)	18/19 (95)	16/16 (100)	.35[b]
EIA IgG	26/35 (74)	12/19 (63)	14/16 (88)	.10[b]
Immunodiffusion IgM	14/36 (39)	7/20 (35)	7/16 (44)	.59[b]
Immunodiffusion IgG	19/35 (53)	10/20 (50)	9/16 (56)	.71[b]
CF IgG	12/32 (38)	6/16 (38)	6/16 (38)	>.99[b]

Abbreviations: CF, complement fixation; EIA, enzyme immunoassay; IgG, immunoglobulin G; IgM, immunoglobulin M; IQR, interquartile range.

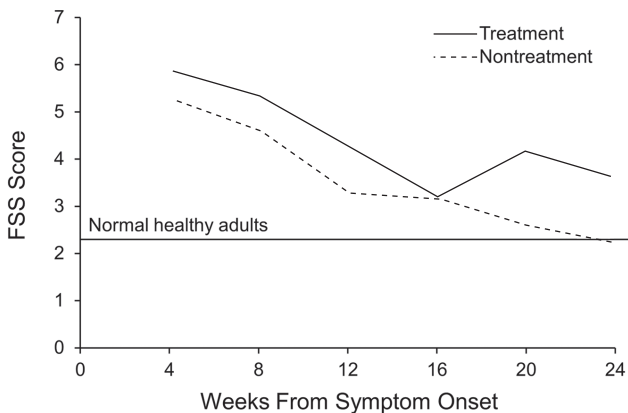[a]By Wilcoxon ranksum test.

[b]By χ^2 test.

Figure 2. FSS Scores of Treatment Group vs Nontreatment Group. Scores are from time of symptom onset through the study's 24 weeks of March 1, 2010, to October 31, 2012. FSS indicates fatigue severity scale.

albumin level, did not correlate with fatigue or SF-36 measurements (data not shown).

Discussion

Primary pulmonary coccidioidomycosis is a fungal infection native to the US Southwest and is known to cause multiple symptoms, including fever, chills, cough, arthralgias, and fatigue. The fatigue of primary coccidioidomycosis can last for months before resolution.[5,6] Clinically important fatigue has been described as a principal symptom

in many other infectious and autoimmune diseases, including systemic lupus erythematosus, rheumatoid arthritis, and chronic hepatitis C.[10,14]

Measuring fatigue in clinical research is difficult.[15] Various tools have been developed, and one of the most frequently used is FSS.[10] In addition to quantifying fatigue, this tool is important for understanding the effect of an illness on health-related QOL. The SF-36 survey is commonly used to determine the effect of a disease state on physical and mental QOL.[9]

In the present study, we used FSS and SF-36 to quantify fatigue and health-related QOL of patients with primary pulmonary coccidioidomycosis. FSS is typically expressed as a mean of the answers to its 9 questions. Less commonly, FSS is reported as a sum of the responses. The mean FSS score for the general healthy population has been reported as 2.3 to 3.0.[10,16] The FSS scale has been used for patients with chronic progressive multiple sclerosis, systemic lupus erythematosus, and chronic hepatitis C whose fatigue level was quantified with mean (SD) scores of 4.7 (1.5) and 4.8 (1.3), and a mean (SE) score of 3.37 (.08), respectively.[10,17] The threshold FSS score for defining severe fatigue has been described previously as ≥4.[17] At the onset of our study, the treated and nontreated groups had a mean (SD) fatigue level above this threshold (5.89 [1.3] and 5.28 [1.4]). The scores gradually decreased over time to <4 at week 12 and at week 16 in the nontreatment and treatment groups, respectively.

Table 2. The Fatigue Severity Scale Scores Measured for Treatment and Nontreatment Groups Over 24 Weeks.

Weeks From Onset	Treatment			Nontreatment		
	No.	Mean (SD)	Median (95% CI)	No.	Mean (SD)	Median (95% CI)
4	10	5.89 (1.3)	6.39 (4.9–6.8)	10	5.28 (1.4)	5.39 (4.3–6.3)
8	20	5.31 (1.5)	5.72 (4.6–6.0)	16	4.57 (1.7)	4.83 (3.7–5.5)
12	19	4.33 (1.8)	4.89 (3.5–5.2)	15	3.29 (2.3)	3.00 (2.0–4.6)
16	18	3.20 (1.7)	3.39 (2.4–4.1)	13	3.15 (2.3)	2.00 (1.8–4.5)
20	9	4.15 (1.9)	3.89 (2.7–5.6)	12	2.60 (2.1)	1.11 (1.2–4.0)
24	13	3.59 (2.1)	3.89 (2.4–4.8)	14	2.21 (1.8)	1.44 (1.2–3.3)

The only other study addressing fatigue in coccidioidomycosis[6] included 48 patients with either pulmonary disease or disseminated infection. The investigators compared patients with acute and chronic (both treated and not treated) coccidioidomycosis vs controls with various underlying medical problems but without symptomatic coccidioidomycosis or other acute illness. Patients with underlying disease, including diabetes mellitus and congestive heart failure, were included in both the coccidioidal group and the control group. Patients were monitored prospectively and completed the FSS at enrollment and at 2 and 4 months. Baseline median FSS sum was 53 (corresponding to a calculated mean of 5.89 when divided by 9 questions of the FSS), which declined to 48 (calculated mean, 5.33) at 2 months and 41 (calculated mean, 4.56) at 4 months ($P = .023$). In that study,[6] a threshold for severe fatigue was defined as ≥ 41 (calculated mean, 4.56).

In comparing the results of the present study with the study by Muir Bower et al.,[6] we assumed the equivalence of the time points of 8 and 16 weeks to 2 and 4 months, respectively. At enrollment and at 4 weeks of study, we found the levels of fatigue to be similar to the findings of Muir Bower et al. (5.89 vs 5.89, respectively). Both studies showed improvement in the patient fatigue level between week 8 (mean, 5.31 vs 5.33) and week 16 (3.20 vs 4.56). However, in the study by Muir Bower et al., fatigue levels stayed "severe" through the 16 weeks. Possible reasons for this apparent increased improvement rate in our study population are 1) less severe coccidioidal disease than the population of Muir Bower et al. (which included patients with pulmonary and disseminated coccidioidal infections) and 2) no important comorbid illnesses vs the study population of Muir Bower et al., which included patients with multiple medical comorbidities. Although the fatigue levels at enrollment and 8 weeks were similar in the 2 studies, the similarity may represent a limitation of the FSS to discriminate high levels of fatigue.

We used SF-36 scores to measure the effect of fatigue and other coccidioidomycosis-related symptoms on QOL. The SF-36 questionnaire is designed to inform functioning in several domains (Table 3). Although the terminology seems similar, the "physical functioning" domain involves questions regarding specific activities, such as carrying groceries, climbing stairs, and walking a mile, whereas the "role physical" domain involves amount of time spent on work and ability to accomplish work. Although summary scores showed gradual improvement over the study, some subscale scores were more adversely affected than others.

Primary pulmonary coccidioidomycosis markedly reduced the "role physical" ("work") scores (mean [SD], 3.1 [8.8] and 5.0 [10.5] in treatment group vs nontreatment group) at 4 weeks. In contrast, the "physical functioning" scores that represent responses to questions about specific activities, such as dressing and bending, stayed >50 (ie, at a normal level) throughout the 6 months. The difference in these scores likely represents coccidioidomycosis-related fatigue that interferes with the ability to sustain physical activity as required for work, in contrast to brief periods required for walking or carrying groceries. In real-world terms, 82% of this cohort missed work because of coccidioidal illness (median, 10 working days). The median time to full-time employment was 8.4 and 5.7 weeks in the treatment and nontreatment groups, respectively.[5] Our data suggest that the patients' perception of physical limitations lasts for 12 to 16 weeks. However, unless arthralgias are a prominent disease manifestation, we have not observed that pulmonary coccidioidomycosis causes the type of physical pain that limits brief activities such as bending or kneeling.

The SF-36 "vitality" and "social functioning" scores also were markedly affected for our patients with mild to moderate primary pulmonary coccidioidomycosis, with mean values less than 38 at enrollment in both groups. These domains showed a positive trend of improvement, increasing to the level of the general population (ie, 50) between week 12 and week 16. This finding likely highlights (once again) the effect of illness-related fatigue on physical endurance because patients are unable to sustain the energy level required to participate socially. The "mental health," "role emotional," and "general health perceptions" scores remained near or greater than those of the general
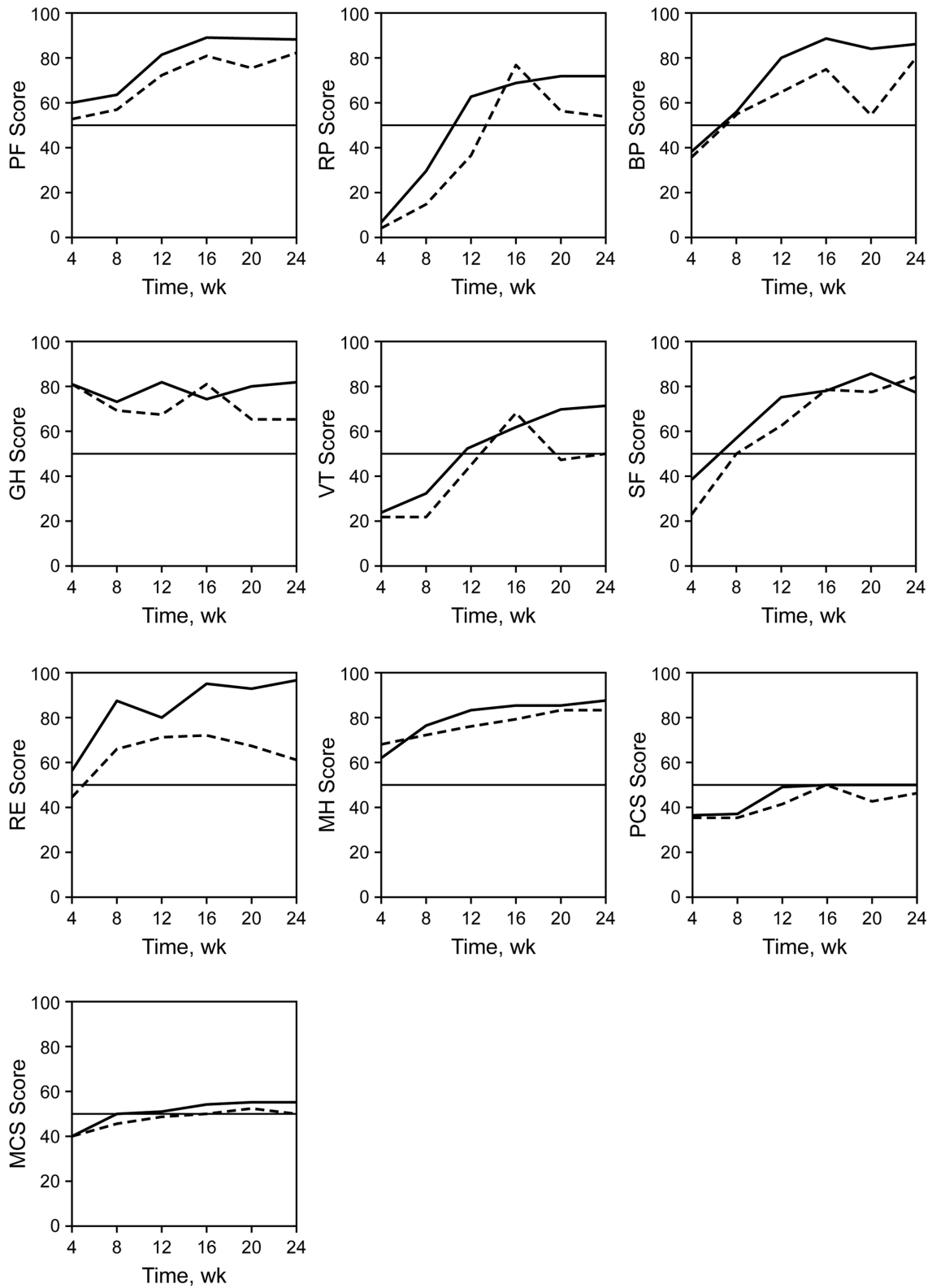
Figure 3. Short Form-36 Health Status Questionnaire Scores of Treatment Group vs Nontreatment Group. Scores are from time of symptom onset through the study's 24 weeks of March 1, 2010, to October 31, 2012. Treatment group is shown with dashed line; nontreatment group, with solid line. Solid line at 50 indicates the score of the general population. BP indicates bodily pain; GH, general health perceptions; MCS, mental component scale; MH, mental health; PCS, physical component scale; PF, physical functioning; RE, role emotional; RP, role physical; SF, social functioning; VT, vitality.

Table 3. Short Form-36 Health Status Questionnaire Subscale Domains and Examples of Activities Addressed by Questions Used in Calculating the Score for That Domain.

Subscale Domain	Example of Areas Assessed
Physical functioning	Activities such as carrying groceries, climbing stairs, walking a mile
Role physical	Ability to perform, accomplish, and complete work
Bodily pain	Intensity of pain and limitations due to pain
General health	Overall perception and rating of health
Vitality	Amount of energy and feeling tired or worn out
Social functioning	Extent and time of limitations in social activities
Role emotional	Difficulty with work or daily activities due to emotional limitations
Mental health	Feeling nervous or "down in the dumps"

population throughout the study period, showing that 1) the study participants likely did not have underlying emotional or mental health disturbances that result in physical limitations and 2) the illness presentation is primarily physical.

In this study, as well as the previously published report involving the same cohort of patients,[5] a bimodal curve of symptoms and QOL measures was observed in the treated cohort. This curve is as yet unexplained. The bimodal pattern was not only seen in symptoms, but also in fatigue and QOL. Whether this curve reflects an immunologic effect following resolution of infection or a medication effect is not known but could be further studied in future work.

We did not observe a difference in the trajectory of improvement of fatigue or QOL when we compared the patient groups. Throughout the observation period, patients who received antifungal treatment had a lower median QOL score and more severe fatigue than their counterparts who did not receive antifungal treatment; yet, these differences were not statistically different. We surmise that the patients with more severe disease were more likely to receive antifungal treatment and that antifungal therapy itself may cause measurable fatigue. However, the equal trajectory in both groups likely represents the true disease trajectory and the course of fatigue resolution.

Given the absence of measureable effect of antifungal therapy on QOL measures, the factors that may help these patients overcome such a severe limitation is important. Persistent fatigue is a common feature of cancer, and recommendations for management of cancer-related fatigue may represent a template for fatigue associated with coccidioidomycosis. Current treatment recommendations include education about disease-related fatigue, management of potential contributing factors, and guidance on the self-monitoring of fatigue and physical activity levels.[18,19] Similar interventions are recommended for the management of fatigue associated with other conditions, such as rheumatoid arthritis[20] and chronic fatigue or myalgic encephalomyelitis.[21] Exercise testing and individualized exercise prescription may be most appropriately administered by physical therapists or other exercise specialists.[22] Decreasing fatigue by increasing exercise tolerance, muscle strength, and overall endurance may lead to increased ability to perform work and achieve QOL. However, the efficacy and cost-effectiveness of such interventions in pulmonary coccidioidomycosis require further research.

Limitations of this study include the small sample size of 36 patients who met eligibility criteria, of whom 75% stayed through the follow-up period. The patients were not randomly assigned to treatment and nontreatment groups but were placed in these groups on the basis of the decisions of treating physicians. The nonrandomization of antifungal treatment likely biased the more symptomatic patients to being in the treatment group. Yet, when QOL and fatigue scores were analyzed for both groups, no significant difference existed between them. However, the study was not designed or powered to compare treatment and nontreatment groups. A control group of patients without pulmonary coccidioidomycosis was not included in the study. The difficulty in diagnosing this illness with characteristic radiologic or laboratory markers likely led to delayed coccidioidal diagnosis and study enrollment.

In conclusion, mild-to-moderate primary pulmonary coccidioidomycosis is a common cause of community-acquired pneumonia among residents of the US Southwest's desert climates and is commonly associated with prolonged fatigue. Our study quantified the severity of this fatigue, as well as the disease impact on other aspects of QOL. Compared with healthy adults, the fatigue and QOL of persons with mild-to-moderate primary pulmonary coccidioidomycosis gradually improve but remain abnormal for a prolonged period of time.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and the writing of the paper.

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