

Fibromyalgia and Its Consequent Disability

Maytal Ben-Yosef^{1,4}, Galia Tanai^{1,4}, Dan Buskila MD², Daniela Amital MD MHA^{3,4} and Howard Amital MD MHA^{1,4}

¹Department of Medicine B and Center of Autoimmune Diseases, Sheba Medical Center, Tel Hashomer, Israel

²Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel

³Ness-Ziona, Mental Health Center, Beer-Yaakov, Israel

⁴Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

ABSTRACT Fibromyalgia is a common pain syndrome treated by physicians of many disciplines and presents with many co-morbidities. The authors reviewed the complexities in assessing disabilities in fibromyalgia patients and the complex interrelationships between patients, their working places, and the medical community regarding preserving productivity. Flexibility is essential to keep the patients functional and productive. Job loss is costly to both society and patients and joint measures are needed to prevent unemployment.

IMAJ 2020; 22: 446–450

KEY WORDS: disability, fibromyalgia, pain, performance, work loss

Fibromyalgia is a rheumatic disorder characterized by chronic widespread pain and is primarily associated with symptoms of fatigue, unrefreshing sleep, and cognitive impairment [1]. Fibromyalgia is considered the second most common rheumatic disorder after osteoarthritis with an estimated prevalence of 2–4% worldwide and a female to male ratio of 3–9:1 [2]. Fibromyalgia can cause a negative impact on most elements of the life of a patient, causing extensive functional disability, difficulties performing daily and work related activities [3]. Disability status is dependent on complex interactions of various personal, social, and environmental factors significantly affecting the life of a patient. These impairments may disrupt the normal coping of a patient often following medical, physical and psychological traumatic events [4].

The international classification of functioning, disability and health defines disability as an end result of impairments (physical and/or mental function abnormality or loss), activity limitations (difficulties in conducting different activities), and participation restrictions (difficulties in social life) [5–8]. However the employment ability of a patient is not as easily defined. There is no absolute definition of work ability. The assessment is relative and is a balance between personal resources and the workplace demands. Moreover, the ability to work involves physical, mental, and social conditions, which are all influenced by environmental factors that change over time.

The impact of fibromyalgia on the quality of life, functionality, and employment ability can be determined by clinical assessments and self-reported questionnaires such as the commonly used 36-Item Short-Form Health Survey, Health Assessment Questionnaire (HAQ), Fibromyalgia Impact Questionnaire (FIQ), and Revised Fibromyalgia Impact Questionnaire. The complexity and multi-symptomatic nature of fibromyalgia, requires a multidimensional assessment to evaluate different aspects of the life of a patient. For example, pain intensity impacts the physical, emotional, social and work functionality, and rates of unemployment [9–12].

As shown in a number of studies, the rate of employment among patients with fibromyalgia varies with location, ranging from 34% to 77% [13]. This wide range reflects both differences in the social beneficiary systems, labor market demands of different countries, and the varying definitions of work [3]. An epidemiological survey of people with fibromyalgia in Spain found that 11% were on sick-leave, and 23% had permanent work disability pension due to fibromyalgia [12], whereas in Australia, Canada, and the United States, one-third of the women with fibromyalgia received financial support relating to work disability [14,15].

However it seems that throughout the world the fibromyalgia-related disability rate, averaging 35%, is constantly growing and should concern not only practitioners but also health organizations at large, underlining the importance of preserving the patients in the work force. This review provides a brief overview of fibromyalgia related disability. Worldwide epidemiological trends in fibromyalgia associated burdens are discussed as well as possible solutions.

Work disability and fibromyalgia

It is well established that musculoskeletal disorders are responsible for a significant portion of the costs for work disability [16]. For example, Yelin et al. [16] studied the risk of work disability in relation to disease progression among patients with rheumatoid arthritis and showed that erosions of joints negatively impacts the ability to work. In contrast, the mechanisms that cause disabilities in fibromyalgia are both obscure and complex and are difficult to measure and target. The trig-

gers that lead to fibromyalgia are diverse and the disease expression differs among patients. Many clinicians believe it is unreliable and sometimes even unprofessional to base clinical judgment on an individual's subjective experience of widespread pain and fatigue. This often leads many clinicians to stereotype and label patients with fibromyalgia as secondary gain seekers and as malingers.

Other triggers that lead to disability arise from more objective reasons such as the nature of the vocation, the working environment, and the failure of modalities of therapy. There is a female predominance in fibromyalgia. In the 25 occupations where the risk of musculoskeletal disorders is most frequent, women are overrepresented in 18, including cleaning, food processing work, manufacturing and construction, and packing and storage work. While it is evident that the majority of women participate in the labor market females more often report the occurrence of pain [17]. In a longitudinal pilot study of 94 young women who were newly diagnosed with fibromyalgia in the United States and Sweden, a rapid process of employment loss was observed within the first year after being diagnosed with fibromyalgia [18]. The results showed that the percentage of women being employed had decreased from 60% at time of diagnosis to 41% one year after the observation point. Symptom severity was found to be a predictor for employment loss. Interestingly, ratings of pain and fatigue as well as activity limitations have been found to be less severe in working than in non-working women with fibromyalgia. Many other studies demonstrated that working women with fibromyalgia have reported a better health status than non-working women with fibromyalgia related to symptoms of pain and fatigue, health related quality of life, and disease specific health status [13,18-20]. This finding is of major importance for considerations in the management plan of fibromyalgia patients and reinforces the importance of adding physical and occupational therapy to pain killers and anti-depressive drugs. It seems reasonable to assume that employment may be a major protective health factor in patients with fibromyalgia. In general, employed women are not only healthier, but their health status declines more slowly compared with women who are not employed. Reisine et al. [19], completed a 5-year follow-up of women with fibromyalgia. At the beginning of the study the health status of employed women was better compared to unemployed women with fibromyalgia, and this was maintained over 5 years. In a Swedish study that analyzed the health status of working and non-working women with fibromyalgia, symptom ratings of pain and fatigue as well as activity limitations were found to be less severe in the working than in the non-working women [21-23].

Addressing function and treating disabilities should be one of the main goals medical staff if possible. Several stud-

ies showed that among workers with fibromyalgia, less severe symptom ratings, better physical function in physical tests and less activity limitations were observed in the group of workers with no temporary work disability. In France and Germany fibromyalgia severity was significantly associated with increased costs of productivity loss [24,25].

Effects of symptoms and co-morbidities on working ability

Despite the connection between working and better prognosis of fibromyalgia it is clear that initial symptom severity of fibromyalgia is in itself a predictor of future employment loss [18]. Moreover, Guymer et al. [26] examined the correlation between fibromyalgia onset and work ability, and found that in 287 Australians with fibromyalgia, the rate of full-time workers decreased from 54% at time of diagnosis to 16% at the time of the survey. Al-Allaf and colleagues [27] conducted a case-control study comparing work disability in outpatients with fibromyalgia with other patients attending non-rheumatology outpatient clinics in Eastern Scotland, and found that work loss due to fibromyalgia was significantly more common compared to the other patients in the study (46.8% vs. 14.1%, $P < 0.00001$).

Musculoskeletal disorders, and fibromyalgia in particular, are the cause for a significant portion of the costs for work disability

In a different study, work productivity was compared between workers with fibromyalgia and workers without musculoskeletal pain. As expected, work productivity loss was significantly greater in workers with fibromyalgia [14]. In that study, the percentage of work time missed because of health issues in the week prior to the study served as a tool for measuring productivity. The authors found that work time missed (absenteeism) was three times higher in fibromyalgia workers than among workers without musculoskeletal pain. The authors also studied "presenteeism," i.e., the percentage of performance impairment while at work owing to health issues in the prior seven days. They concluded that presenteeism constituted 45% of the working time of workers with fibromyalgia. Comparison of productivity loss and health benefit claims between patients with fibromyalgia and patients with osteoarthritis showed no significant difference with similar burdens and costs to employers [15].

Fitzcharles et al. [28] conducted a tertiary care cohort study of 248 patients with fibromyalgia. The cohort included three groups: 90 patients were employed, 81 were unemployed and not receiving disability payments, and 77 were unemployed and received disability payments because of fibromyalgia. The group was demographically homogenous. This study showed that all measurements for disease severity (excluding measurements of anxiety and depression) differed significantly among the groups. Patients with severe disease were more disabled, used more medications, and were much less active physically. It is important to note that the authors contended that disabled patients were more likely to be previously employed in manual

industrial professions, while employed patients were more commonly working in non-manual positions ($P = 0.005$). Such an association clearly implies that the type of vocation is linked to the emergence of fibromyalgia and its severity.

Wolfe and colleagues [29] summarized the predictors for social security work disability (SSD) in patients with fibromyalgia from the United States. They reported that overall, a total of 34.8% of the patients with fibromyalgia were defined with SSD. The annual incidence of SSD in fibromyalgia was 3.4%.

The probability of receiving disability corresponded to the level of the poly-symptomatic distress index (derived from the American College of Radiology criteria). According to their report the impact of co-morbid fibromyalgia was highly significant, and among rheumatoid arthritis or osteoarthritis patients who also had fibromyalgia 56% and 42.4% respectively, received SSD. Significantly, the authors found that the strongest predictor of SSD was functional status as measured by the HAQ [29].

Kassam et al. [30] studied the impact of depression in co-morbid patients on labor force participation. In this study based on of the Canadian Community Health Survey data, fibromyalgia patients had a higher incidence of major depression when compared to those without fibromyalgia, 22.2% vs. 7.2%, ($P < 0.05$) respectively. In their analysis, a logistic regression model incorporating both major depression and fibromyalgia as predictors of labor force participation did not identify any interaction between these two variables, suggesting an independent multiplicative contribution to the outcome of both parameters. Moreover, work disability occurred in 5.9% of patients with fibromyalgia without major depression and the percentage rose to 23% in patients with both conditions.

Perspectives of patients and the working place regarding work ability

Since work ability seems to be a favorable factor in fibromyalgia, information gained from the perspective of the patients could help understand what measures are to be taken in order to increase their involvement in the working environment. When working and non-working fibromyalgia patients were compared, the working group was found to be more highly educated than the non-working group [31]. Moreover, the authors found that flexibility and resourcefulness were major factors in the ability to maintain work. The working group with fibromyalgia was not only better educated but also proactive. Of the working patients, 66% had modified their work environment and 33% had changed their occupation to maintain their working capability [31].

Concurrent depression may amplify the effect of fibromyalgia on loss of work and should be appropriately addressed

Lower education levels correlate with less adaptable jobs, which usually require more physical activity. A study showed that previous employment in physically demanding jobs was found to be a facilitator of work disability in female fibromyalgia patients [20]. Another study focusing on healthcare workers showed that the mean ratings of perceived exertions at work was a risk factor for long-term sickness absence [32].

A local Swedish qualitative study that focused on women with fibromyalgia, reported that they expressed increased need

for rest and claimed it was crucial for managing physical work, and for maintaining their work role [21]. Another study reported that working women with fibromyalgia described concern regarding future employment [33]. An American study analyzed assessment centers evaluating patients with chronic pain at their workplace. The results of the study showed that the performance-based functional assessments focused merely on the physical factors and ignored the more comprehensive integrative social, spiritual, and biological well-being of these individuals. Obviously by doing so employers decrease the potential for adjusting the work environment to the changing health status of their employees and as a consequence risk losing working position and experiencing a socio-economic decline [34]. Liedberg et al. [35] compared working women with fibromyalgia with non-working women with fibromyalgia and concluded that the social support received by colleagues and employers was found to be of greater importance for work ability than symptom severity. This means that using local resources at working places may prevent subsequent job loss.

Are fibromyalgia patients malingerers?

Claims of work disability may be motivated by possible secondary gain. Since fibromyalgia is still a type of subjective illness, often dependent on personal resilience to negative life events, many challenges stand in the way of a practitioner's ability to conduct evidence-based diagnosis, leading to suspicion of simulation or malingering. Yet in studies assessing this, clinicians were able to identify simulators and to differentiate them from patients with fibromyalgia, reaching a diagnostic accuracy of

80% in distinguishing fibromyalgia patients from simulators and normal controls [36].

Belenguer-Prieto and colleagues [37] analyzed the specificity and sensitivity of objective tests aimed at detect-

Patients, working places, and social frames with the ability to modify working conditions and adjust the vocational environment, are able to prevent job loss and dependence on social welfare

ing the possibility of malingering in fibromyalgia. In their observational case-control study of 211 Spanish fibromyalgia patients, the profile of the patient simulating symptoms was based on the proposed criteria for evaluating disability related to the simulation of pain. In their study the two groups were easily dis-

tinguished The malingers and real patients had an almost similar number of tender point counts, however, the malingers had striking scores on every parameter that measured pain or disability such as the FIQ scores (89.8 vs. 68.8, $P < 0.001$), shorter distances in the 6-minute walk tests (231.0 vs. 356.3 meters, $P < 0.001$) and appearance of allodynia at lower thresholds (159.8 vs. 229.9 mmHg, $P < 0.001$).

Conclusions

The major problem of assessing work disability in fibromyalgia patients is the difficulty of diagnosing fibromyalgia. The diagnosis remains purely clinical and based on subjective inputs of data gathered by the patients. The evaluation of clinical physical examination or any laboratory test cannot validate the diagnosis. The degree of disability cannot be measured objectively and therefore assessments of impairments are based on the clinician's understanding of the patient's world, concepts, function, resilience, and resources.

Psychological factors such as personality traits, concomitant depression and anxiety, sense for catastrophizing, a poor internal locus of control, social isolation, and financial difficulties may also contribute to the augmentation of disability. Classical fibromyalgic characteristics such as loss of physical capacity and fatigue, impaired concentration and memory which lead to conflicts with employers and workmates turns makes the workplace so difficult. The disinclination to understand and sympathize with fibromyalgia symptoms combined with the lack of objective measures are major reasons for rejecting fibromyalgia claims.

On the basis of the studies reviewed in this article, it is clear that patients with fibromyalgia who manage to keep their job for as long as possible have a better prognosis [21,27-29,33]. Yet only patients whose symptoms are not particularly debilitating can continue working with reasonable productivity. Patients, working places and social frames that are able to modify working conditions and adjust the vocational environment are able to prevent patients from leaving work and becoming dependent on social welfare [23,34]. Malingering, which is seen to be a threat to the maintenance of social beneficiary systems, can be excluded in patients who receive aggressive treatment, in the presence of collateral corroboration of the complaints by family members, and in view of the significant financial losses that concur with the disability. Determining the lifestyle and behavior of the patients can be helpful to determine the validity of the complaints; however it should be remembered that this may be misleading given the fluctuations in fibromyalgia symptoms, especially in environments which are perceived by the patient to be more secure and relaxing.

Stressful and negative life events seem to precede the onset of pain by many years as only 4% of Canadian patients identified a traumatic event in the same year in which fibromyalgia symptoms appeared [38,39]. Analysis of the medical records of the Maccabi

health maintenance organization in Israel found that the time from the onset of symptoms of fibromyalgia until the confirmation of the diagnosis of fibromyalgia by a rheumatologist is 5 years [40]. Therefore, rejecting fibromyalgia claims on the grounds there was no immediate relation between traumatic events and proper establishment of the diagnosis of fibromyalgia is incorrect.

A necessary therapeutic approach addressing the interdisciplinary needs of patients with fibromyalgia is definitely warranted. It will improve conditions and outcomes, and prevent loss of work. Unfortunately such an attitude is nearly never adopted by care givers who find it easier and more economical to follow the misconception that active intervention in fibromyalgia is futile. Patients must be encouraged to continue working and working places should be compensated for adjusting to accommodate the special needs of disabled employees. This holistic approach is perhaps the best strategy to keep fibromyalgia patients as active and productive citizens.

Correspondence

Dr. H. Amital

Head, Dept. of Medicine B, Sheba Medical Center, Tel Hashomer 52621, Israel

Phone: (972-3) 530-2652

Fax: (972-3) 535-4796

email: howard.amital@sheba.health.gov.il

References

1. Amital H, Ablin J, Aloush V, Häuser W, Buskila D. The first Israeli fibromyalgia congress, February 2013. *IMAJ* 2013; 15 (12): 789-92.
2. Clauw DJ. Fibromyalgia: a clinical review. *JAMA* 2014; 311 (15): 1547-55.
3. Schweiger V, Del Balzo G, Raniero D, et al. Current trends in disability claims due to fibromyalgia syndrome. *Clin Exp Rheumatol* 2017; 35 (105 Suppl 3): 119-26.
4. Yavne Y, Amital D, Watad A, Tiosano S, Amital H. A systematic review of precipitating physical and psychological traumatic events in the development of fibromyalgia. *Semin Arthritis Rheum* 2018; 48 (1): 121-33.
5. Hieblinger R, Coenen M, Stucki G, Winkelmann A, Cieza A. Validation of the international classification of functioning, disability and health core set for chronic widespread pain from the perspective of fibromyalgia patients. *Arthritis Res Ther* 2009; 11 (3): R67.
6. Offenbächer M, Cieza A, Brockow T, et al. Are the contents of treatment outcomes in fibromyalgia trials represented in the international classification of functioning, disability, and health? *Clin J Pain* 2007; 23 (8): 691-701.
7. Prodinge B, Cieza A, Williams DA, et al. Measuring health in patients with fibromyalgia: content comparison of questionnaires based on the International Classification of Functioning, Disability and Health. *Arthritis Rheum* 2008; 59 (5): 650-8.
8. Prodinge B, Salzberger T, Stucki G, Stamm T, Cieza A. Measuring functioning in people with fibromyalgia (FM) based on the international classification of functioning, disability and health (ICF)--a psychometric analysis. *Pain Pract* 2012; 12 (4): 255-65.
9. Chiusalupi M, Crupi M, Rustici R, Ciarabella A. How does yoga work on pain dimensions? An integrated perspective in two individuals with fibromyalgia. *Adv Mind Body Med* 2018; 32 (4): 4-8.
10. Grape HE, Solbrække KN, Kirkevold M, Mengshoel AM. Staying healthy from fibromyalgia is ongoing hard work. *Qual Health Res* 2015; 25 (5): 679-88.
11. Pyles DA, Coldren WH, Eder GM, Hadad CM, McGrier PL. Mechanistic investigations into the cyclization and crystallization of benzobisoxazole-linked two-dimensional covalent organic frameworks. *Chem Sci* 2018; 9 (30): 6417-23.

12. Collado A, Gomez E, Coscolla R, et al. Work, family and social environment in patients with fibromyalgia in Spain: an epidemiological study: EPIFFAC study. *BMC Health Serv Res* 2014; 14: 513.
13. Henriksson CM, Liedberg GM, Gerdle B. Women with fibromyalgia: work and rehabilitation. *Disabil Rehabil* 2005; 27 (12): 685-94.
14. McDonald M, DiBonaventura M daCosta, Ullman S. Musculoskeletal pain in the workforce: the effects of back, arthritis, and fibromyalgia pain on quality of life and work productivity. *J Occup Environ Med* 2011; 53 (7): 765-70.
15. Kleinman N, Harnett J, Melkonian A, Lynch W, Kaplan-Machlis B, Silverman SL. Burden of fibromyalgia and comparisons with osteoarthritis in the workforce. *J Occup Environ Med* 2009; 51 (12): 1384-93.
16. Yelin E, Henke C, Epstein W. The work dynamics of the person with rheumatoid arthritis. *Arthritis Rheum* 1987; 30 (5): 507-12.
17. Bingefors K, Isacson D. Epidemiology, co-morbidity, and impact on health-related quality of life of self-reported headache and musculoskeletal pain—a gender perspective. *Eur J Pain* 2004; 8 (5): 435-50.
18. Burckhardt C, Liedberg G, Henriksson C, Kendall S. The impact of fibromyalgia on employment status of newly-diagnosed young women: a pilot study. *J Musculoskelet Pain* 2010; 13: 31-41.
19. Reisine S, Fifield J, Walsh SJ, Feinn R. Do employment and family work affect the health status of women with fibromyalgia? *J Rheumatol* 2003; 30 (9): 2045-53.
20. Palstam A, Bjersing JL, Mannerkorpi K. Which aspects of health differ between working and nonworking women with fibromyalgia? A cross-sectional study of work status and health. *BMC Public Health* 2012; 12: 1076.
21. Liedberg GM, Henriksson CM. Factors of importance for work disability in women with fibromyalgia: an interview study. *Arthritis Rheum* 2002; 47 (3): 266-74.
22. Liedberg GM, Björk M, Börsbo B. Self-reported nonrestorative sleep in fibromyalgia - relationship to impairments of body functions, personal function factors, and quality of life. *J Pain Res* 2015; 8: 499-505.
23. Henriksson CM, Liedberg GM, Gerdle B. Women with fibromyalgia: work and rehabilitation. *Disabil Rehabil* 2005; 27 (12): 685-94.
24. Perrot S, Winkelmann A, Dukes E, et al. Characteristics of patients with fibromyalgia in France and Germany. *Int J Clin Pract* 2010; 64 (8): 1100-8.
25. Winkelmann A, Perrot S, Schaefer C, et al. Impact of fibromyalgia severity on health economic costs: results from a European cross-sectional study. *Appl Health Econ Health Policy* 2011; 9 (2): 125-36.
26. Guymer EK, Littlejohn GO, Brand CK, Kwiatek RA. Fibromyalgia onset has a high impact on work ability in Australians. *Intern Med J* 2016; 46 (9): 1069-74.
27. Al-Allaf AW. Work disability and health system utilization in patients with fibromyalgia syndrome. *J Clin Rheumatol* 2007; 13 (4): 199-201.
28. Fitzcharles MA, Ste-Marie PA, Rampakakis E, Sampalis JS, Shir Y. Disability in fibromyalgia associates with symptom severity and occupation characteristics. *J Rheumatol* 2016; 43 (5): 931-6.
29. Wolfe F, Walitt BT, Katz RS, Häuser W. Social security work disability and its predictors in patients with fibromyalgia. *Arthritis Care Res (Hoboken)* 2014; 66 (9): 1354-63.
30. Kassam A, Patten SB. Major depression, fibromyalgia and labour force participation: a population-based cross-sectional study. *BMC Musculoskelet Disord* 2006; 7: 4.
31. Rakovski C, Zettel-Watson L, Rutledge D. Association of employment and working conditions with physical and mental health symptoms for people with fibromyalgia. *Disabil Rehabil* 2012; 34 (15): 1277-83.
32. Andersen LL, Clausen T, Persson R, Holtermann A. Dose-response relation between perceived physical exertion during healthcare work and risk of long-term sickness absence. *Scand J Work Environ Health* 2012; 38 (6): 582-9.
33. Sallinen M, Kukkurainen ML, Peltokallio L, Mikkelsen M. Women's narratives on experiences of work ability and functioning in fibromyalgia. *Musculoskeletal Care* 2010; 8 (1): 18-26.
34. Strong S, Baptiste S, Cole D, et al. Functional assessment of injured workers: a profile of assessor practices. *Can J Occup Ther* 2004; 71 (1): 13-23.
35. Liedberg GM, Björk M. Symptoms of subordinated importance in fibromyalgia when differentiating working from non-working women. *Work* 2014; 48 (2): 155-64.
36. Mannerkorpi K, Gard G. Hinders for continued work among persons with fibromyalgia. *BMC Musculoskelet Disord* 2012; 13: 96.
37. Belenguer-Prieto R, Morales-Espinoza EM, et al. Specificity and sensitivity of objective tests to detect possible malingering in fibromyalgia: a case-control study in 211 Spanish patients. *Clin Exp Rheumatol* 2013; 31 (6 Suppl 79): S86-93.
38. Häuser W, Fitzcharles MA. Facts and myths pertaining to fibromyalgia. *Dialogues Clin Neurosci* 2018; 20 (1): 53-62.
39. Fitzcharles M-A, Ste-Marie PA, Mailis A, Shir Y. Adjudication of fibromyalgia syndrome: challenges in the medicolegal arena. *Pain Res Manag* 2014; 19 (6): 287-92.
40. Gendelman O, Amital H, Bar-On Y, et al. Time to diagnosis of fibromyalgia and factors associated with delayed diagnosis in primary care. *Best Pract Res Clin Rheumatol* 2018; 32 (4): 489-99.

Capsule

Observational study of hydroxychloroquine in hospitalized patients with COVID-19

Hydroxychloroquine has been widely administered to patients with COVID-19 without robust evidence supporting its use. **Geleris** and co-authors examined the association between hydroxychloroquine use and intubation or death at a large medical center in New York City. Data were obtained regarding consecutive patients hospitalized with COVID-19, excluding those who were intubated, died, or discharged within 24 hours after presentation to the emergency department (study baseline). The primary end point was a composite of intubation or death in a time-to-event analysis. Of 1446 consecutive patients, 70 patients were intubated, died, or discharged within 24 hours after presentation and were excluded from the analysis. Of the remaining 1376 patients, during a median follow-up of 22.5 days, 811 (58.9%) received hydroxychloroquine (600 mg twice on day 1, then 400 mg daily for a median

of 5 days); 45.8% of the patients were treated within 24 hours after presentation to the emergency department, and 85.9% within 48 hours. Hydroxychloroquine-treated patients were more severely ill at baseline than those who did not receive hydroxychloroquine (median ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen, 223 vs. 360). Overall, 346 patients (25.1%) had a primary end-point event (180 patients were intubated, of whom 66 subsequently died, and 166 died without intubation). In the main analysis, there was no significant association between hydroxychloroquine use and intubation or death (hazard ratio, 1.04, 95% confidence interval, 0.82 to 1.32). Results were similar in multiple sensitivity analyses.

NEJM 2020; 10.1056/NEJMoa2012410

Eitan Israeli