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Not All That Hurts Is Fibromyalgia: The Challenges of Differential Diagnosis of Patients Referred to a Tertiary Care Center

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Abstract

Background/Objectives: Fibromyalgia (FM) is a complex and disabling condition characterized by chronic widespread pain, fatigue and multiple somatic symptoms, often overlapping with rheumatic (RMD) and non-rheumatic diseases. Since objective biomarkers are lacking, diagnosis relies on validated criteria and careful clinical assessment. This study aimed to describe a referral cohort including patients with either a previous diagnosis or suspicion of FM and to identify the proportion of patients fulfilling FM criteria, the severity of their FM, and to identify alternative or associated conditions. **Methods:** A prospective cohort of consecutive patients referred to our Center between June 2023 and October 2025 was assessed according to the 2016 American College of Rheumatology (ACR) diagnostic criteria for FM. Demographic data, medical history, and clinical findings were collected. Additional laboratory or imaging investigations were performed when clinically indicated. FM severity was evaluated using validated tools included in the 2016 ACR diagnostic criteria. **Results:** Overall, 247 patients were enrolled: 44 with a certified previous FM diagnosis, 145 referred by physicians for suspected FM and 58 self-referred. Among patients without a previous certified diagnosis, FM was newly diagnosed in 75% of physician-referred and 77% of self-referred patients. A substantial proportion was also diagnosed with an RMD. Longer symptom duration, higher fatigue and worse global health were associated with FM. **Conclusions:** Among patients who reached our referral center because of suspected FM, a high proportion fulfilled the 2016 ACR criteria. Careful application of FM criteria and evaluation of coexisting conditions may improve timely diagnosis and management.

Keywords: fibromyalgia; chronic pain; widespread pain; fatigue; differential diagnosis

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Academic Editor: Liangjing Lu

Received: 25 August 2026
Revised: 4 November 2026
Accepted: 6 November 2026
Published: 11 November 2026

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1. Introduction

Fibromyalgia (FM) is a common disabling disease whose heterogeneous clinical picture is characterized by chronic and widespread pain (CWP), fatigue, sleep disorders, cognitive dysfunction, mood changes and various symptoms and signs of autonomic dysfunction [1]. Pain in FM is typically classified as nociplastic, according to the definition formulated by the International Association for the Study of Pain in 2017, as "pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage

causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain" [2]. However, many patients may also experience other types of pain due to coexisting conditions. Over the past few decades, several sets of diagnostic/classification criteria have been proposed, and FM prevalence may vary, ranging between 2 and 4% according to the different sets of criteria [3–5]. FM may occur alone but is often associated with other diseases. For example, over 20% of patients with inflammatory arthritis may display concomitant FM [6,7]. FM pathophysiology is still unknown, and therapeutic strategies are often unsuccessful [8,9]. The heterogeneity of FM clinical pictures may suggest that different pathophysiological mechanisms are involved, including immune and inflammatory factors, neuroinflammation, infections, endocrine disorders, small fiber impairment, central and peripheral sensitization phenomena, somatic and psychological aspects, psychiatric comorbidities [10–15]. Finally, also environmental factors, including climatic variations, air pollution, electromagnetic field exposure, physical and emotional traumas, dietary patterns, and infections, may also have a role in the manifestation and intensity of symptoms related to FM [13,14].

FM lacks specific biomarkers and laboratory tests [5]. This may lead to a variety of caveats such as variability of assessment by clinicians, over/underestimation of self-reported symptoms, and failure to capture the symptom modification over time. In addition, the coexistence of other diseases whose symptoms may overlap with those of FM adds a layer of complexity to this matter, requiring a detailed evaluation of medical history and clinical examination and the use of additional analyses, tests, and imaging. In fact, FM may often coexist with other conditions such as rheumatic and musculoskeletal diseases (RMDs), neuromuscular diseases and psychiatric diseases, to cite a few. Hence, clinicians should identify whether diagnostic criteria are fulfilled, assess for other conditions that may coexist, and investigate alternative explanations when clinically indicated

Based on this background, the aim of this study was to evaluate the proportion of patients fulfilling FM criteria, the severity of their FM and/or alternative or associated conditions in patients referred for the first time to our Center due to either a previous FM diagnosis or clinical suspicion of FM.

2. Materials and Methods

2.1. The Patient Cohort

We enrolled a prospective cohort of consecutive patients referred to our Center between June 2023 and October 2025 with a previous diagnosis or a clinical suspicion of FM and evaluated them according to the 2016 American College of Rheumatology (ACR) diagnostic criteria [4]. The inclusion criteria were as follows: patients aged ≥ 18 years who agreed to participate in the study, could read and write Italian, and had the physical and cognitive ability to communicate. Patients with cognitive impairment preventing them from comprehending written or spoken Italian, those with terminal illnesses and those declining to participate in the study were excluded. At the time of the first consultation, patients were divided into 3 groups: group 1, patients with a previous diagnosis of FM, certified by a medical report; group 2, patients referred by other physicians with a clinical suspicion of FM; group 3, patients who spontaneously believed to be affected by FM. Demographic data, including age and biological sex, medical history, including comorbidities, and physical examination, including body mass index (BMI), were evaluated. Further investigations, such as laboratory and imaging tests, were required according to the clinical features to obtain a final diagnosis (Supplementary Table S1). The primary study endpoint was to evaluate the proportion of patients fulfilling FM criteria within this referral cohort, the severity of their FM and/or alternative or associated conditions in patients referred for the first time to our Center due to either a previous FM diagnosis or clinical suspicion of FM.

Patients with generalized pain, defined as pain in at least 4 of 5 regions, symptoms present at a similar level for at least 3 months, a Widespread Pain Index (WPI) of ≥7 and a Symptom Severity Scale (SSS) of ≥5 or a WPI of 4–6 and a SSS score of ≥9, were diagnosed as having FM, according to the 2016 ACR diagnostic criteria [4]. Notably, an FM diagnosis was valid irrespective of other diagnoses and an FM diagnosis does not exclude the presence of other clinically important illnesses. At the end of this diagnostic assessment, patients were divided in 9 groups (A-I groups): group A: only FM (new diagnosis); group B: only RMDs (new diagnosis); group C: FM and RMDs (new diagnoses); group D: neither FM nor RMDs (new alternative diagnosis); group E only FM (confirmed pre-existing diagnosis); group F: only RMDs (confirmed pre-existing diagnosis); group G: FM and RMDs (confirmed pre-existing diagnoses); group H: FM (new diagnosis) and RMDs (confirmed pre-existing diagnosis); group I: FM (confirmed pre-existing diagnosis) and RMDs (new diagnosis). The secondary endpoints were: i. comprehensive description of the impact of symptoms using the revised version of Fibromyalgia Impact Questionnaire (FIQR) [16], as well as the Polysymptomatic Distress scale (PSD) [17], the Patient-Acceptable Symptom State (PASS; a single dichotomously answered question (yes/no) about how satisfied the patient is with the severity of symptoms) [18], a 0–10 numerical rating scale for fatigue (with 10 being the "worst"), and global health was assessed on a 5-point Likert scale answering the question "In general, would you say your health is 1 = excellent, 2 = very good, 3 = good, 4 = fair, 5 = poor"; ii. investigation of clinical differences between study groups. In detail, FIQR consists of twenty-one 0–10 numerical rating scales (with 10 being the "worst") that investigate three main health domains, which are, respectively, function, overall impact, and symptoms, and refer to the previous seven days. The final score ranges between 0 and 100, while PSD is the sum of WPI and SSS. Following the coordinated severity categories validated by Salaffi et al. [17] the proposed cutoff points for FIQR disease severity are: 0–23 for remission, 24–40 for mild disease, 41–63 for moderate disease, 64–82 for severe disease, and 83–100 for very severe disease, while PSD severity cutoff points include: 0–5 for remission, 6–15 for mild disease, 16–20 for moderate disease, 21–25 for severe disease, and 26–31 for very severe disease. All the methods were carried out in accordance with the Good Clinical Practice guidelines, and all the patients provided written informed consent in accordance with the Declaration of Helsinki. Ethical review and approval (by the internal review board of the University of L'Aquila) were obtained in accordance with local legislation and institutional requirements. Generative artificial intelligence (GenAI) has not been used in this paper.

2.2. Statistical Analysis

The data were analyzed with IBM SPSS v28.0 software. Explorative analysis of the variables was performed using the chi-square test, the Mann–Whitney U test or the Kruskal–Wallis test with multiple post hoc comparisons. Univariable and multivariable binary logistic regression was also performed. The binary outcome variable was diagnosed, or not, with fibromyalgia after consultation at our Center. All the tests were two-tailed, and values of $p < 0.05$ were considered significant.

3. Results

A total of 247 patients were enrolled, of which 44 had a previous diagnosis of FM (Group 1), 145 were referred by other physicians with a clinical suspicion of FM (Group 2) and 58 self-referred for suspicion of FM (Group 3). Table 1 summarizes the demographic and clinical assessment at first consultation of the three groups.

Table 1. Demographic and clinical characteristics of the patient cohort according to the type of referral (group 1, patients with a previous diagnosis of FM, certified by a medical report; group 2, patients referred by other physicians with a clinical suspicion of FM; group 3, patients who spontaneously believed to be affected by FM). The analysis was performed with either the Mann–Whitney U test or the Chi square test to compare Group 2 and Group 3.

	N = 44		**N = 145**		**N = 58**		
	GROUP 1		**GROUP 2**		**GROUP 3**		
	N	%	N	%	N	%	*p* value Group 2 vs. Group 3 *
Female sex	42	95	137	94	50	86	0.09
Previous diagnosis of RMD	13	29	43	30	4	7	**0.0005**
	Median	**IQR**	**Median**	**IQR**	**Median**	**IQR**	***p* value Group 2 vs. Group 3 #**
Age, years	59	52–63	58	52–67	39	34–49	**<0.0001**
BMI, kg/m^2	28	25–30	25	22–29	24	21–28	0.472
Symptom duration, years	10	7–15	5	3–10	3	2–5	**<0.0001**
Total WPI	12	8–14	11	8–15	9	6–13	**<0.0001**
SSS	9	7–10	8	5–10	8	6–10	0.824
WPI + SSS	20	17–23	20	14–24	17	13–21	0.055
Total FIQR	67	45–82	61	40–77	53	41–68	0.238
FIQR physical function	20	12–25	15	8–22	14	10–21	0.943
FIQR overall impact	13	8–18	11	5–16	10	4–16	0.422
FIQR symptoms	38	26–41	33	24–41	31	21–38	0.272
0–10 VAS fatigue	8	7–10	8	5–9	8	6–9	0.949
Global health (5-items Likert scale)	4	4–5	4	4–5	4	3–5	**0.03**
N. of comorbidities	3	2–6	3	2–5	2	0–4	**<0.0001**

* Calculated with Chi square test; # calculated with Mann–Whitney U test. FM, fibromyalgia, BMI, body mass index; WPI, widespread pain index; SSS, symptom severity score; FIQR, fibromyalgia impact questionnaire revised; VAS, visual analog scale; SD, standard deviation; N, number; IQR, interquartile range.

3.1. Self-Referred Patients with a Clinical Suspicion of FM

Self-referred patients were significantly younger, with a shorter symptom duration and a lower number of comorbidities, and they were less likely to have a previous diagnosis of RMD as compared to patients referred by a physician (Supplementary Table S2). Of interest, although at the time of first consultation the total WPI of self-referred patients was significantly lower than that of those referred by a physician, the SSS and WPI + SSS were comparable in the two groups (Table 1). Table 2 shows the patient regrouping after the first consultation. A new diagnosis of FM was made in 109/145 (75%) patients referred by another physician (Group 2) and in 45/58 (77%) self-referred patients (Group 3). Among these, 49/109 (45%) and 11/45 (24%) patients also received the diagnosis of a coexisting RMD. In 12 (8%) patients from Group 2 and in 10 (17%) patients from Group 3, neither FM nor an RMD was diagnosed, and an alternative diagnosis was identified. (Table 3).

Table 2. Post-referral reclassification of the patient cohort reflecting new diagnosis and old diagnosis that were confirmed.

	Reason For Referral					
	Previous Diagnosis of FM, Certified by a Medical Report with or Without an RMD		**Referred by Other Physicians with a Clinical Suspicion of FM with or Without an RMD**		**Self-Referred for Suspicion of FM with or Without an RMD**	
	GROUP 1		GROUP 2		GROUP 3	
POST-REFERRAL CLASSIFICATION	N	%	N	%	N	%

Table 2. *Cont.*

	Reason For Referral					
	Previous Diagnosis of FM, Certified by a Medical Report with or Without an RMD		**Referred by Other Physicians with a Clinical Suspicion of FM with or Without an RMD**		**Self-Referred for Suspicion of FM with or Without an RMD**	
group A: only FM (new diagnosis)	na	na	33	23	31	53
group B: only RMDs (new diagnosis)	1	2	17	12	3	5
group C: FM and RMDs (new diagnoses)	0	0	49	34	11	19
group D: neither FM nor RMDs (new alternative diagnosis)	3	7	12	8	10	17
group E only FM (confirmed pre-existing diagnosis)	17	39	na	na	na	na
group F: only RMDs (confirmed pre-existing diagnosis)	0	0	7	5	0	0
group G: FM and RMDs (confirmed pre-existing diagnoses)	12	27	0	0	0	0
group H: FM (new diagnosis) and RMDs (confirmed pre-existing diagnosis)	0	0	27	19	3	5
group I: FM (confirmed pre-existing diagnosis) and RMDs (new diagnosis).	11	25	0	0	0	0

FM, fibromyalgia; RMD, rheumatic and musculoskeletal disease; N, number.

Table 3. Distribution of post-referral diagnosis of rheumatic and musculoskeletal diseases or other diseases.

POST REFERRAL GROUP	**Pre-Referral Group**			
	Referred by Other Physicians		**Self-Referred**	
	GROUP 2		**GROUP 3**	
GROUP B: only RMDs (new diagnosis)	N = 17		N = 3	
	N	%	N	%
Rheumatoid arthritis	1	6	0	0
Psoriatic arthritis	3	18	0	0
Spondyloarthritis (SpA)	0	0	1	33
Osteoarthritis	6	35	0	0
Sjogren disease	1	6	0	0
Undifferentiated connective tissue disease	1	6	2	67
Undifferentiated SpA	3	18	0	0
Undifferentiated arthritis	2	12	0	0
GROUP C: FM and RMDs (new diagnoses)	**N = 49**		**N = 11**	
	N	**%**	**N**	**%**
Rheumatoid arthritis	1	2	1	9
Psoriatic arthritis	5	10	0	0
Spondyloarthritis	7	14	2	18
Osteoarthritis	16	33	1	9
Sjogren disease	3	6	1	9
Undifferentiated connective tissue disease	7	14	0	0
Undifferentiated SpA	4	8	6	55
Undifferentiated arthritis	0	0	0	0

Table 3. *Cont.*

POST REFERRAL GROUP	Pre-Referral Group			
	Referred by Other Physicians		Self-Referred	
	GROUP 2		GROUP 3	
Polymialgia rheumatica	3	6	0	0
Calcium pyrophosphate deposition disease	1	2	0	0
Tietze Syndrome	1	2	0	0
Leukocytoclastic vasculitis	1	2	0	0
GROUP D: neither FM nor RMDs (new alternative diagnosis)	**N =12**		**N = 10**	
	N	%	N	%
HBV-related arthritis	1	8	0	0
Drug induced muscular damage *	1	8	0	0
Autoimmune thyroiditis	2	17	0	0
Multiple chemical sensitivity	2	17	0	0
Primary chronic widespread pain	1	8	0	0
Septic arthritis	1	8	0	0
Major depressive disorder	1	8	1	10
Peripheral neuropathy	1	8	0	0
Hypovitaminosis D	1	8	0	0
Generalized anxiety disorder	0	0	2	20
Long COVID	0	0	3	30
Myofascial pain syndrome	0	0	1	10
Lumbar disc protrusion	0	0	1	10
Post-infectious arthritis	0	0	1	10

* Increased CK and myalgias due to statins.

We then sought to clarify whether any demographic or clinical variable was associated with a subsequent diagnosis of FM in groups 2 and 3. Overall, patients with a new diagnosis of FM (regardless of the type of referral) had a longer symptom duration, a higher visual analog scale (VAS) fatigue and worse global health (Supplementary Table S3) as compared to patients in whom an FM diagnosis was ruled out. Conversely, age and BMI were comparable in the 2 groups. Since the total WPI score is a criterion for FM diagnosis we focused on individual items to explore whether any of them were more specific to FM.

We performed univariable analysis and, as expected, most of the WPI items taken individually were associated with FM diagnosis. At multivariable analysis, the only variables that remained significantly associated with an FM diagnosis were lower arm, buttock, and jaw (Supplementary Table S4). Jaw pain was the item with the highest odds ratio at multivariable analysis.

At univariate analysis, a higher VAS fatigue was associated with a new FM diagnosis (OR = 2.0; 95% confidence interval (CI) 1.6–2.4), and when we added, as a covariate, a coexisting RMD the association remained significant.

Finally, for explorative purposes, we built binary logistic regression models aimed to explore the resulting ORs of the combination of different variables that were statistically significant at univariate analysis. We built a first binary logistic regression model, which included FM diagnosis as the binary outcome and the coexistence of VAS fatigue equal to 5 or higher and jaw pain as the covariate. This model resulted in an OR of 35.8 (95% CI 4.8–267.4).

We then built a second model, which included FM diagnosis as a binary outcome and the coexistence of VAS fatigue equal to 5 or higher and lower arm pain. This second model yielded an OR of 18.3 (95% CI 6.8–49.7).

In the last model, which included FM diagnosis as a binary outcome we combined all the 3 features mentioned above, namely, as a covariate, the coexistence of a VAS fatigue of 5 or higher, jaw pain and lower arm pain (which was observed in over 50 patients). In this scenario the OR increased to 49.9 (95% CI 3.0–826.9).

3.2. Patients Referred with a Previous Diagnosis of FM, Certified by a Medical Report

Forty-four patients had a previous FM diagnosis certified by a medical report but 4 (9%) of these did not fulfill the ACR diagnostic criteria at first consultation. When revising the clinical records of these 4 patients, established previous misdiagnosis was identified. Hence, an alternative diagnosis was made: one patient suffered from severe osteoarthritis, one patient had drug-induced muscular damage (increased CK and myalgias due to statins), one patient had cervical and lumbar discal protrusion with compressive peripheral neuropathy, and one patient had major depressive disorder. After the first consultation, 11/44 patients received a new diagnosis of a coexisting RMD.

4. Discussion

FM is a chronic disabling disease whose leading symptom is CWP, and that can occur alone or in combination with RMDs or other pain conditions [1]. Over the last 35 years, new diagnostic criteria have been developed seeking to provide guidance to physicians in properly identifying FM [4,19–22]. However, the lack of objective diagnostic markers has hampered the accurate identification and management of this condition.

Our study demonstrated that, in general, among patients who reached our referral center because of suspected FM (either referred by a physician or self-referred), a high proportion fulfilled the 2016 ACR criteria [4]. These new criteria defined some parameters that are essential for a diagnosis, such as CWP, WPI and SSS. However, although they show improved diagnostic accuracy, they require a comprehensive understanding of individual presentations. In fact, not all cases of FM fulfill the diagnostic criteria, and some authors suggested distinguishing these borderline cases by re-introducing the concept of incomplete FM (IFM) [23,24]. In line with this, patients diagnosed with FM using older versions of diagnostic criteria may not fulfill the revised, more recent versions [25]. In our cohort, about 10% of the 44 patients who had a previous FM diagnosis certified by a medical report did not fulfill the 2016 diagnostic criteria at first consultation in our Center due to a previous misdiagnosis. Cassisi et al. found that only 53.5% of the patients with previously diagnosed FM had diagnoses confirmed based on the 2016 ACR criteria, 22.3% were classified as having IFM, and 24% were diagnosed as not having FM [24]. This diagnostic error was less frequent among rheumatologists (20%) than among other physicians (37.5%). Such evidence confirms the intrinsic limitations of any diagnostic criteria for FM due to the heterogeneity of the clinical picture, its evolution over time, and the possible biases related to coexisting diseases [26].

As mentioned above, the total WPI score is a criterion for FM diagnosis. This assessment encompasses numerous sites, allowing the patient to pause, reflect on their pain and map it, thereby providing the physician with a comprehensive picture of their symptoms. We therefore performed an exploratory analysis to find out the association between individual WPI sites and FM. Multivariable analysis showed that lower arm, buttock, and jaw pain showed the highest ORs. Besides pain, fatigue is another hallmark of FM as well as of several RMDs, and we observed that higher VAS fatigue, regardless of a coexisting RMD, was

associated with a new FM diagnosis. Furthermore, higher values of fatigue in association with pain in the above-mentioned sites achieved higher ORs.

Of interest, 40% of the patients referred to our Center, who fulfilled the 2016 ACR criteria for FM, also received the diagnosis of a coexisting RMD. Our findings fit with the hypothesis that FM is often only one facet of the clinical scenario and that other diseases should still be confirmed or ruled out during the diagnostic process. Previous studies, including cohorts of patients with inflammatory and/or immune-mediated conditions, such as inflammatory bowel disease, multiple sclerosis and RMDs, described self-reporting as being disproportionate according to disease activity. Such pain often persisted even when clinical, biochemical and imaging evidence of inflammation had resolved [27]. This out-of-proportion pain is often labeled non-inflammatory, and there is a growing recognition that inflammatory and non-inflammatory pain phenotypes can coexist. Several findings, including data from animal models, suggest that mechanisms other than inflammation can contribute to nociplastic pain [28,29]. A significant contributor to non-inflammatory pain is the presence of concurrent FM. A systematic review has shown that FM is common in inflammatory arthritis, affecting approximately one in every five patients [30], and its presence is associated with elevated disease activity scores and patient global assessment scores. Likewise, a recent systematic review of 11 studies [31] has found that the concomitant diagnosis of FM and connective tissue disorders is very frequent, sharing joint pain, joint swelling, muscle weakness, and dysautonomia. In particular, the prevalence of concomitant diagnosis of hypermobile Ehlers–Danlos syndrome/hypermobility spectrum disorders and FMS ranged from 68 and 88.9% and from 8.0 to 64.2% for generalized joint hypermobility and FMS. Therefore, people with RMDs and concomitant FM often struggle to achieve treatment targets and frequently require switching to several alternative disease-modifying medications. Hence, an FM diagnosis should always be ruled out when dealing with difficult-to-treat RMD patients [32,33].

Among autoimmune non-rheumatic conditions, thyroid diseases and celiac disease deserve to be discussed. A recent systematic review and meta-analysis found that FM is associated with the increased presence of thyroid autoimmunity, especially among women with postmenopausal status [34]. This piece of evidence, together with the observed high frequency of thyroid autoimmunity in patients with FM [35], points to a relationship, albeit still unclear, between the two diseases.

Celiac disease and non-celiac gluten sensitivity, a syndrome characterized by a cohort of symptoms related to the ingestion of gluten-containing food in subjects who are not affected by celiac disease or wheat allergy, have a high prevalence in FM patients [36–38]. At the same time, the presence of clinical extraintestinal manifestations in patients with celiac disease or non-celiac gluten sensitivity should lead clinicians to consider FM as a possible diagnosis. Although in patients with FM plus celiac disease or non-celiac gluten sensitivity, the treatment with gluten-free diet has been shown to improve symptoms, including musculoskeletal pain and fatigue [39], a gluten-free diet cannot be systematically recommended to all patients with FM [40]. Moreover, several FM patients have gastrointestinal symptoms due to the high degree of association of FM with irritable bowel syndrome [39,41]. All these data suggest that searching for celiac disease or non-celiac gluten sensitivity in FM patients is not cost-effective and that this workup should be reserved only for those with any other clue to these gastrointestinal diseases

Non-rheumatic conditions that share symptoms with FM add a layer of complexity to the already complex scenario of differential diagnosis.

Our study displays some limitations that deserve to be discussed. A single-center design, self-selection among Group 3, absence of a population-based comparison group, heterogeneous diagnostic workup, lack of standardized diagnostic verification for all alter-

native diagnoses and lack of external validation may affect the interpretation. In addition, we acknowledge that our analysis may be subject to risk of incorporation bias/circular reasoning since the painful sites are part of the WPI. A similar issue of criterion contamination/incorporation bias may exist regarding fatigue that is also incorporated into the broader symptom framework used in the 2016 ACR criteria. Hence, although our findings are exploratory and hypothesis-generating and require to be externally validated in a separate cohort, we believe that they may set the stage for future research in the field.

Secondly, our results may be affected by referral bias since the study population consists of patients referred to a tertiary center focused on the care of RMDs; hence, the observed frequency of coexisting RMDs cannot be generalized to the general FM population, primary care populations or community-based cohorts.

Another limitation of our study is related to the fact that due to the limited number of patients with coexisting FM and RMDs, further analysis dividing patients according to the RMD type (e.g., connective tissue diseases vs. chronic inflammatory arthritis vs. osteoarthritis) was not performed. We acknowledge that the umbrella term RMD encompasses very different disorders with profoundly different pathophysiology, diagnostic certainty, and relationships with FM and that future studies enrolling larger cohorts should explore this aspect.

5. Conclusions

FM is a complex disabling disease, and the diagnostic process requires careful application of diagnostic criteria and a thorough assessment to identify potential coexisting diseases contributing to the clinical picture. Awareness of primary care physicians about the multifaceted clinical picture of FM may facilitate referral and ensure timely diagnosis of FM and any associated diseases.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/diagnostics16223719/s1, Table S1. Laboratory and imaging investigations performed according to medical history and physical examination to obtain a final diagnosis. Not all patients underwent all assessments and this was guided by clinical judgement. Table S2. Distribution of pre-referral diagnosis of rheumatic and musculoskeletal diseases. Table S3. Demographic and clinical characteristics of patients according to the diagnosis (or lack thereof) of fibromyalgia. Table S4. Univariable and multivariable analysis to evaluate the association between WPI individual items and an fibromyalgia diagnosis. (OR, odds ratio; 95% CI, confidence interval).

Author Contributions: Conceptualization, F.C. and A.A.; methodology, F.C., A.A. and C.F.; validation P.A., M.E.C. and D.C.; formal analysis A.A. and F.C.; investigation D.C., M.L. and A.P.; resources F.C. and C.F.; data curation F.C., A.A., P.A., M.E.C. and M.L.; writing—original draft preparation F.C. and A.A., writing—review and editing F.C., A.A., P.A., M.E.C., D.C., M.L., A.P. and C.F.; supervision C.F. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Ethical review and approval were obtained in accordance with local legislation and institutional requirements by the IRB of the University of L'Aquila on 27 October 2020 (code 49/2020/2021).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: All relevant data are included in the manuscript.

Acknowledgments: The Authors are grateful to Dania Di Fabio and the Abruzzo branch of the Italian Patient Association for Fibromyalgia Syndrome (AISF ODV).

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

ACR	American College of Rheumatology
BMI	Body mass index
CI	Confidence interval
CK	Creatine kinase
COVID	Coronavirus disease
CWP	Chronic widespread pain
FIQR	Revised Fibromyalgia Impact Questionnaire
FM	Fibromyalgia
FMS	Fibromyalgia syndrome
GenAI	Generative artificial intelligence
IBM	International Business Machines
IFM	Incomplete fibromyalgia
IgG	Immunoglobulin G
OR	Odds ratio
PASS	Patient-Acceptable Symptom State
PSD	Polysymptomatic Distress scale
RMDs	Rheumatic and musculoskeletal diseases
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SPSS	Statistical Package for the Social Sciences
SSS	Symptom Severity Scale
VAS	Visual analog scale
WPI	Widespread Pain Index

References

1. Williams, D.A.; Clauw, D.J. Fibromyalgia. *N. Engl. J. Med.* **2026**, *395*, 267–277. [CrossRef] [PubMed]
2. Kosek, E.; Cohen, M.; Baron, R.; Gebhart, G.F.; Mico, J.A.; Rice, A.S.C.; Rief, W.; Sluka, A.K. Do We Need a Third Mechanistic Descriptor for Chronic Pain States? *Pain* **2016**, *157*, 1382–1386. [CrossRef] [PubMed]
3. Wolfe, F.; Ross, K.; Anderson, J.; Russell, I.J.; Hebert, L. The Prevalence and Characteristics of Fibromyalgia in the General Population. *Arthritis Rheum.* **1995**, *38*, 19–28. [CrossRef] [PubMed]
4. Wolfe, F.; Clauw, D.J.; Fitzcharles, M.A.; Goldenberg, D.L.; Häuser, W.; Katz, R.L.; Mease, P.J.; Russell, A.S.; Russell, I.J.; Walitt, B. 2016 Revisions to the 2010/2011 Fibromyalgia Diagnostic Criteria. *Semin. Arthritis Rheum.* **2016**, *46*, 319–329. [CrossRef] [PubMed]
5. Sarzi-Puttini, P.; Giorgi, V.; Marotto, D.; Atzeni, F. Fibromyalgia: An Update on Clinical Characteristics, Aetiopathogenesis and Treatment. *Nat. Rev. Rheumatol.* **2020**, *16*, 645–660. [CrossRef] [PubMed]
6. Falasinnu, T.; Nguyen, T.; Jiang, T.E.; Chaichian, Y.; Rector, A.; Darnall, B.D.; Mackey, S.; Simard, J.F. The Problem of Pain in Rheumatology: Clinical Profiles Associated with Concomitant Diagnoses with Chronic Overlapping Pain Conditions. *ACR Open Rheumatol.* **2022**, *4*, 890–896. [CrossRef] [PubMed]
7. Di Carlo, M.; Farah, S.; Atzeni, F.; Alciati, A.; Di Franco, M.; Iannuccelli, C.; Bazzichi, L.; Bianchi, G.; Giovale, M.; Tirri, R.; et al. Geographical Disparities in Fibromyalgia Severity: An Italian Study. *Eur. J. Pain* **2025**, *29*, e4735. [CrossRef] [PubMed]
8. Macfarlane, G.J.; Kronisch, C.; Dean, L.E.; Atzeni, F.; Häuser, W.; Fluß, E.; Choy, E.; Kosek, E.; Amris, K.; Branco, J.; et al. EULAR Revised Recommendations for the Management of Fibromyalgia. *Ann. Rheum. Dis.* **2017**, *76*, 318–328. [CrossRef] [PubMed]
9. Bazzichi, L.; Di Carlo, M.; Salaffi, F.; Farah, S.; Porta, F.; Ablin, J.N.; Varrassi, G.; Galli, F.; Fornasari, D.; Carotti, M.; et al. Pain Study Group of the Italian Society of Rheumatology (SIR). Therapeutic Advances in Fibromyalgia: One Year in Review 2026. *Clin. Exp. Rheumatol.* **2026**, *44*, 1069–1081. [CrossRef] [PubMed]
10. García-Domínguez, M. Fibromyalgia and Inflammation: Unrevealing the Connection. *Cells* **2025**, *14*, 271. [CrossRef] [PubMed]
11. Filipovic, T.; Filipović, A.; Nikolic, D.; Gimigliano, F.; Stevanov, J.; Hrkovic, M.; Bosanac, I. Fibromyalgia: Understanding, Diagnosis and Modern Approaches to Treatment. *J. Clin. Med.* **2025**, *14*, 955. [CrossRef] [PubMed]
12. Goebel, A.; Krock, E.; Gentry, C.; Israel, M.R.; Jurczak, A.; Urbina, C.M.; Sandor, K.; Vastani, N.; Maurer, M.; Cuhadar, U.; et al. Passive Transfer of Fibromyalgia Symptoms from Patients to Mice. *J. Clin. Invest.* **2021**, *131*, e144201. [CrossRef] [PubMed]
13. Bazzichi, L.; Giorgi, V.; Di Franco, M.; Iannuccelli, C.; Bongiovanni, S.; Batticciotto, A.; Pellegrino, G.; Sarzi-Puttini, P. Environmental Factors and Fibromyalgia Syndrome: A Narrative Review. *Clin. Exp. Rheumatol.* **2024**, *42*, 1240–1247. [CrossRef] [PubMed]
14. Di Carlo, M.; Farah, S.; Di Franco, M.; Iannuccelli, C.; Capacci, A.; Guiducci, S.; Biasi, G.; Giacomelli, R.; Bazzichi, L.; Atzeni, F.; et al. Seasonal Variation Influences Fibromyalgia Severity in Terms of Widespread Pain among Female Patients: Data from a Large National Registry. *Clin. Rheumatol.* **2025**, *44*, 4671–4679. [CrossRef] [PubMed]

15. Treister-Goltzman, Y.; Peleg, R. Fibromyalgia and Mortality: A Systematic Review and Meta-Analysis. *RMD Open* **2023**, *9*, e003005. [CrossRef] [PubMed]
16. Bennett, R.M.; Friend, R.; Jones, K.D.; Ward, R.; Han, B.K.; Ross, R.L. The Revised Fibromyalgia Impact Questionnaire (FIQR): Validation and Psychometric Properties. *Arthritis Res. Ther.* **2009**, *11*, R120. [CrossRef] [PubMed]
17. Salaffi, F.; Di Carlo, M.; Bazzichi, L.; Atzeni, F.; Govoni, M.; Biasi, G.; Di Franco, M.; Mozzani, F.; Gremese, E.; Dagna, L.; et al. Definition of Fibromyalgia Severity: Findings from a Cross-Sectional Survey of 2339 Italian Patients. *Rheumatology* **2021**, *60*, 728–736. [CrossRef] [PubMed]
18. Salaffi, F.; Di Carlo, M.; Di Franco, M.; Bianchi, G.; Bazzichi, L.; Tirri, R.; Guiducci, S.; Gorla, R.; Atzeni, F.; Giacomelli, R.; et al. Determining the PASS Cut-Off Points for the FIQR, FASmod and PSD in Patients with Fibromyalgia: A Registry-Based Study. *Clin. Exp. Rheumatol.* **2023**, *41*, 1275–1282. [CrossRef] [PubMed]
19. Wolfe, F.; Smythe, H.A.; Yunus, M.B.; Bennett, R.M.; Bombardier, C.; Goldenberg, D.L.; Tugwell, P.; Campbell, S.M.; Abeles, M.; Clark, P.; et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. *Arthritis Rheum.* **1990**, *33*, 160–172. [CrossRef] [PubMed]
20. Wolfe, F.; Clauw, D.J.; Fitzcharles, M.A.; Goldenberg, D.L.; Katz, R.S.; Mease, P.; Russell, A.S.; Russell, I.J.; Winfield, J.B.; Yunus, M.B. The American College of Rheumatology Preliminary Diagnostic Criteria for Fibromyalgia and Measurement of Symptom Severity. *Arthritis Care Res.* **2010**, *62*, 600–610. [CrossRef] [PubMed]
21. Wolfe, F.; Clauw, D.J.; Fitzcharles, M.A.; Goldenberg, D.L.; Häuser, W.; Katz, R.S.; Mease, P.; Russell, A.S.; Russell, I.J.; Winfield, J.B. Fibromyalgia Criteria and Severity Scales for Clinical and Epidemiological Studies: A Modification of the ACR Preliminary Diagnostic Criteria for Fibromyalgia. *J. Rheumatol.* **2011**, *38*, 1113–1122. [CrossRef] [PubMed]
22. Arnold, L.M.; Bennett, R.M.; Crofford, L.J.; Dean, L.E.; Clauw, D.J.; Goldenberg, D.L.; Fitzcharles, M.A.; Paiva, E.S.; Staud, R.; Sarzi-Puttini, P.; et al. AAPT Diagnostic Criteria for Fibromyalgia. *J. Pain* **2019**, *20*, 611–628. [CrossRef] [PubMed]
23. Yunus, M.B.; Aldag, J.C. The Concept of Incomplete Fibromyalgia Syndrome: Comparison of Incomplete Fibromyalgia Syndrome with Fibromyalgia Syndrome by 1990 ACR Classification Criteria and Its Implications for Newer Criteria and Clinical Practice. *J. Clin. Rheumatol.* **2012**, *18*, 71–75. [CrossRef] [PubMed]
24. Cassisi, G.; Sarzi-Puttini, P. Consistency between the 2016 ACR Criteria and a Previous Diagnosis or Hypothesis of Fibromyalgia in a Specialised Referral Clinic. *Clin. Exp. Rheumatol.* **2023**, *41*, 1283–1291. [CrossRef] [PubMed]
25. Walitt, B.; Katz, R.S.; Bergman, M.J.; Wolfe, F. Three-Quarters of Persons in the US Population Reporting a Clinical Diagnosis of Fibromyalgia Do Not Satisfy Fibromyalgia Criteria: The 2012 National Health Interview Survey. *PLoS ONE* **2016**, *11*, e0157235. [CrossRef] [PubMed]
26. Goldenberg, D.L. Diagnosing Fibromyalgia as a Disease, an Illness, a State, or a Trait? *Arthritis Care Res.* **2019**, *71*, 334–336. [CrossRef] [PubMed]
27. Khot, S.; Tackley, G.; Choy, E. How to Distinguish Non-Inflammatory from Inflammatory Pain in RA? *Curr. Rheumatol. Rep.* **2024**, *26*, 403–413. [CrossRef] [PubMed]
28. Clark, A.K.; Grist, J.; Al-Kashi, A.; Perretti, M.; Malcangio, M. Spinal Cathepsin S and Fractalkine Contribute to Chronic Pain in the Collagen-Induced Arthritis Model. *Arthritis Rheum.* **2012**, *64*, 2038–2047. [CrossRef] [PubMed]
29. Nieto, F.R.; Clark, A.K.; Grist, J.; Chapman, V.; Malcangio, M. Calcitonin Gene-Related Peptide–Expressing Sensory Neurons and Spinal Microglial Reactivity Contribute to Pain States in Collagen-Induced Arthritis. *Arthritis Rheum.* **2015**, *67*, 1668–1677. [CrossRef] [PubMed]
30. Duffield, S.J.; Miller, N.; Zhao, S.; Goodson, N.J. Concomitant Fibromyalgia Complicating Chronic Inflammatory Arthritis: A Systematic Review and Meta-Analysis. *Rheumatology* **2018**, *57*, 1453–1460. [CrossRef] [PubMed]
31. Alsiri, N.; Alhadhoud, M.; Alkatefi, T.; Palmer, S. The Concomitant Diagnosis of Fibromyalgia and Connective Tissue Disorders: A Systematic Review. *Semin. Arthritis Rheum.* **2023**, *58*, 152127. [CrossRef] [PubMed]
32. Alunno, A.; Carubbi, F.; Stones, S.; Gerli, R.; Giacomelli, R.; Baraliakos, X. The Impact of Fibromyalgia in Spondyloarthritis: From Classification Criteria to Outcome Measures. *Front. Med.* **2018**, *5*, 290. [CrossRef] [PubMed]
33. Iannuccelli, C.; Favretti, M.; Bianchi, B.; Dolcini, G.; Cauli, C.; Ferraro, V.; Gioia, C.; Bazzichi, L.; Atzeni, F.; Batticciotto, A.; et al. Pain Study Group of the Italian Society of Rheumatology (SIR). Pathogenetic and Clinical Aspects of Fibromyalgia: One Year in Review 2026. *Clin. Exp. Rheumatol.* **2026**, *44*, 1057–1068. [CrossRef] [PubMed]
34. Park, S.; Kwon, J.S.; Park, Y.B.; Park, J.W. Is Thyroid Autoimmunity a Predisposing Factor for Fibromyalgia? A Systematic Review and Meta-Analysis. *Clin. Exp. Rheumatol.* **2022**, *40*, 1210–1220. [CrossRef] [PubMed]
35. Pamuk, O.N.; Cakir, N. The Frequency of Thyroid Antibodies in Fibromyalgia Patients and Their Relationship with Symptoms. *Clin. Rheumatol.* **2007**, *26*, 55–59. [CrossRef] [PubMed]
36. García-Leiva, J.M.; Carrasco, J.L.; Slim, M.; Calandre, E.P. Celiac Symptoms in Patients with Fibromyalgia: A Cross-Sectional Study. *Rheumatol. Int.* **2015**, *35*, 561–567. [CrossRef] [PubMed]
37. Losurdo, G.; Principi, M.; Iannone, A.; Amoruso, A.; Ierardi, E.; Di Leo, A.; Barone, M. Extra-Intestinal Manifestations of Non-Celiac Gluten Sensitivity: An Expanding Paradigm. *World J. Gastroenterol.* **2018**, *24*, 1521–1530. [CrossRef] [PubMed]

38. Kılıçoğlu, M.S.; Sayılır, S.; Yurdakul, O.V.; Aydin, T.; Koçhan, K.; Basaranoglu, M.; Kucukakkas, O. Association between Celiac Disease and Fibromyalgia and Their Severity: A Cross-Sectional Study. *PeerJ* **2024**, *12*, e17949. [CrossRef] [PubMed]
39. Rodrigo, L.; Blanco, I.; Bobes, J.; Carmen de Serres, F.J. Remarkable Prevalence of Celiac Disease in Patients with Irritable Bowel Syndrome plus Fibromyalgia in Comparison with Those with Isolated Irritable Bowel Syndrome: A Case-Finding Study. *Arthritis Res. Ther.* **2013**, *15*, R201. [CrossRef] [PubMed]
40. Almirall, M.; Casellas, F.; Dot, J.; de Torres, I.; Segurola, H.; Marsal, S. Prevalence of Non-Coeliac Gluten Sensitivity and Assessment of the Response to Gluten-Free Diet in a Cohort of Patients with Fibromyalgia. *Rheumatology* **2023**, *62*, 1069–1077. [CrossRef] [PubMed]
41. Erdrich, S.; Harnett, J.E. Fibromyalgia Severity and Symptoms Are Associated with the Disorders of Gut-Brain Interaction. *Eur. J. Pain* **2025**, *29*, e4766. [CrossRef] [PubMed]

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