Understanding the clinical profile of patients with frozen shoulder: a longitudinal multicentre observational study

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ABSTRACT

Introduction There is a large diversity in the clinical presentation of frozen shoulder (FS) and the clinical outcome is not always satisfactory. The aim of the current study was to examine to what extent range of motion (ROM) limitation, metabolic factors (diabetes mellitus and thyroid disorders), autonomic symptoms and pain sensitivity may contribute to the prognosis in terms of shoulder pain and disability and quality of life in patients with FS.

Methods Patients with stage 1 or 2 FS were longitudinally followed-up during 9 months after baseline assessment. They completed six questionnaires and underwent quantitative sensory testing (pressure pain thresholds, temporal summation and conditioned pain modulation) and ROM assessment.

Results One hundred and forty-nine patients with FS were initially recruited and 121 completed at least one follow-up measurement. Shoulder pain and disability improved over time and diabetes mellitus was found to be a prognostic factor for final outcome. Several domains of quality of life also improved over time and external rotation ROM, diabetes mellitus, thyroid disorder and autonomic symptoms were found to be prognostic factors for final outcome. These prognostic factors explained 2.5%–6.3% of the final outcome of shoulder pain and disability and quality of life.

Discussion and conclusion In patients with FS, prognostic variables were able to predict different outcomes, indicating that outcomes in this population can be variable-dependent. Other variables not explored in this study might contribute to the prognosis of patients with FS, which should be investigated in future research. In clinical practice, baseline assessment of prognostic factors and focusing on a more holistic approach might be useful to inform healthcare practitioners about progression of patients with FS during a 9-month period.

INTRODUCTION

Frozen shoulder (FS) is a medical enigma, which is difficult to understand and manage. It is characterised by spontaneous onset of shoulder pain and a gradual decrease of both active and passive shoulder range of motion (ROM). The prevalence of primary FS in the general population is 2%–5%. No intervention has demonstrated superior efficacy for FS and disease duration does not appear to be influenced by any treatment. The natural history varies between 1 and 3 years, although there is an incomplete recovery in 7%–50% of patients, who maintain a slightly painful and restricted shoulder at long-term follow-ups. Indeed, 6% of patients with FS still have severe symptoms at more than 7 years. An explanation for this large variety in disease duration might be related to an incomplete understanding of both the most effective treatment and natural history of FS as well as no proper formulation of treatment success criteria. Another possible explanation might be that existing research is more focused on population and intervention averages rather than the experience of individual patients. For instance, a slight improvement for the majority of patients after a treatment could be judged as ineffective, while being beneficial for a small group of patients. Contrary, a treatment could be judged effective while it can have adverse
effects for example, activating the inflammatory reaction, further decreasing ROM, for a small group of patients.15

From other pathologies, such as fibromyalgia, low back pain and musculoskeletal pain, it is known that there are subgroups of patients with different characteristics or clinical profiles.16–23 This knowledge about subgroups has changed the treatment approach of several pathologies, resulting in a more effective, patient-tailored approach.24–28 In FS, some studies are already advising the use of interventions based on subgroups as well, thus increasing the likelihood of more efficient treatment approaches.24–28 Massive mobility deficits, muscle weakness, presence of comorbidities and unbearable symptoms during the first 6 months after onset predicted a worse prognosis in patients with FS.4 30 31

Since there is a large diversity in the clinical presentation of an individual patient with FS and the clinical outcome is not always satisfactory, identification of factors that might predict outcome would be beneficial to tailor treatment. In a previously published review, some prognostic factors were proposed.32 In particular, patients with diabetes mellitus (DM) or thyroid disorders have a 5–7 times higher risk of developing FS.33 Indeed, the prevalence of DM and thyroid disorders in patients with FS ranges from 3% to 41%.34–37 Furthermore, the prevalence of FS increases up to 40% in patients with DM36 38 39 and 10.9% in patients with thyroid disorders.40 However, it is unclear what the effect is of DM in the prognosis of treatment outcome in patients with FS, with few studies demonstrating conflicting results.41–43

Furthermore, chronic low-grade inflammation seems to play an important role in the pathophysiology of FS. It is suggested that the nervous, endocrine and immune system function interdependently and that a disturbance in one system disturbs another system.44 As chronic low-grade inflammation might disturb the immune system, the nervous system could be disturbed as well. The autonomic nervous system is at least partially involved in the release of proinflammatory and anti-inflammatory cytokines45 and might therefore be involved with chronic inflammation. Proinflammatory cytokines, which are released during an inflammatory state, are able to stimulate the vagal nerve and cholinergic anti-inflammatory pathway, resulting in an increase of hyperalgesia in the central nervous system (CNS).46 Therefore, inflammation would interact with both dysautonomia (a condition in which the autonomic nervous system does not work properly)47 48 and CNS dysfunction49 and these dysfunctions might be present in patients with FS. Dysautonomia may result in altered cardiorespiratory, thermoregulatory, gastrointestinal and bladder function.49 Altered central pain processing is reflected by a hypersensitivity (or amplification response) to sensory input (eg, innocuous, noxious or repeated stimuli) and changes in CNS function (ie, glial activation).50 51 Another factor favouring altered central pain processing is persistent nociceptive input,52 53 which might be the case in patients with FS.

Identifying prognostic factors might contribute to the reformation of current treatment strategies to improve patients’ outcomes. Consequently, a patient-tailored approach could result in a better prognosis. Therefore, the aim of this study was to determine to what extent local (shoulder ROM), metabolic (DM and thyroid), autonomic and central pain processing (hyperalgesia and endogenous function) factors might predict prognosis in patients with FS.

In summary, metabolic factors (DM and thyroid disorder), autonomic dysfunction and/or altered central pain processing may play a more dominant role in patients with FS than currently thought, although this hypothesis needs to be tested. Therefore, we hypothesise that patients with smaller shoulder ROM limitations, absence of DM, thyroid disorders and/or self-reported autonomic symptoms and/or normal central pain processing at baseline will have a better prognosis for shoulder pain and disability and quality of life over 9 months follow-up.

METHODS

Study design

Patient and public involvement

Patients or the public were not involved in the design, recruitment, conduct, reporting or dissemination plans of our research. Dissemination of the results to participants was done by sending an email with all general results.

Participants

Patients with FS were recruited at the orthopaedic departments of the University Hospitals of Valencia and Malaga (Spain) and AZ Monica campus Deurne (Belgium), and through general practitioner practices in Antwerp (Belgium). The eligibility criteria are presented in table 1.

Procedure

First, patients completed a general demographic survey and four questionnaires: Shoulder Pain and Disability Index (SPADI), Visual Analogue Scale, 36-item Short Form Health Survey (SF-36) and Composite Autonomic Symptom Score-31. These questionnaires have shown to be valid and reliable.54–57

Second, quantitative sensory testing (QST) including pressure pain threshold (PPT), temporal summation (TS) and conditioned pain modulation (CPM) was performed as a proxy for central pain processing. Finally, ROM of both shoulders was determined. Patients were examined by six physical therapists, all previously trained by two physical therapists with more than 10 years of experience in the examination of shoulder disorders and QST measurements.

All these measurements were repeated at 3, 6 and 9 months follow-up after baseline measurement. For the current research question only the follow-up scores from the SPADI and SF-36 were used in the analysis. The
Frozen shoulder at stage 1 or 2 according to Hannafin and Chiaia\(^\text{78}\); duration of symptoms <9 months, pain with active and passive shoulder ROM and significant limitation of flexion, abduction, internal rotation and external rotation. ▶ Understanding of Spanish or Dutch language in speaking and writing. ▶ Passive ROM restriction of at least 25% in at least two movement planes and 50% in glenohumeral external rotation compared with the unaffected shoulder (in total a restriction in three movement planes).\(^2\) ▶ Pain and movement restriction present for at least 1 month that reached a plateau or was deteriorating.\(^2\) ▶ Written informed consent provided.

ROM, range of motion.

remaining data will be used to provide information about the natural history of FS in another paper.

### Quantitative sensory testing

#### Pressure pain thresholds

Mechanical hyperalgesia was assessed by determining PPTs. The PPTs were measured on the affected side at the centre of the belly of the anterior deltoid (2 cm below the acromion) and quadriceps muscle (middle point between the anterior superior iliac spine and superior edge patella as described previously\(^\text{54}\) while the patient was seated on a bench without arm rests. The quadriceps site was chosen to explore hyperalgesia at a remote area (widespread hyperalgesia), which might indicate altered central pain processing.\(^51\) Mechanical pressure pain was measured on the above-mentioned sites in an Excel-generated random order using a digital algometer with a rubber tip of 1 cm\(^2\) (Wagner Force Dial FDX 50, Wagner Instruments, Greenwich, USA). To determine the PPT, the assessor applied a gradually increasing pressure at a speed of 1 kg/s until the patient experienced the stimulus as annoying and uncomfortable. Thirty seconds after the application of the inflatable cuff, the patient was requested to rate the intensity of perceived pain of the conditioning stimulus on an NPRS. Next, the cuff pressure was adapted (ie, increased or decreased) until the patient experienced a pain intensity of three on the NPRS. Then the PPT was repeated at the deltoid muscle as described above. The cuff was deflated immediately after the second test stimulus. The CPM effect was calculated following the formula: \(\frac{\text{PPT at baseline} - \text{PPT during CPM}}{\text{PPT at baseline}}\) , with negative values implying an anti-nociceptive effect and positive values a pronociceptive effect. This method was found to be reliable and effective in evaluating descending pain modulation pathways.\(^64\)\(^65\)

#### Temporal summation

TS was measured following the procedure described by Cathcart et al.\(^64\) A train of 10 repeated pressure stimuli was applied at the quadriceps muscle belly using a digital algometer. The pressure used for TS was the mean PPT previously determined for the quadriceps. Patients rated the pain intensity on a Numeric Pain Rating Scale (NPRS), ranging from 0 (no pain) to 10 (worst imaginable pain) perceived during the 1st, 5th and 10th repetition of the train stimuli. TS was calculated as the difference between the tenth and the first pulse as previously reported.\(^64\)

#### CPM at the unaffected upper arm

CPM provides information about the efficacy of descending pain modulation pathways and was evaluated in this study by examining the effect of a conditioning stimulus on a test stimulus. The test stimulus consisted of mechanical pressure stimuli elicited as described above in the PPTs section. The conditioning stimulus was provided by means of an ischaemic occlusion applied to the unaffected arm with an inflatable air cuff (Boso Profitest). The cuff was positioned just above the cubital fossa and inflated until the patient experienced the stimulus as annoying and uncomfortable. Thirty seconds after the application of the inflatable cuff, the patient was requested to rate the intensity of perceived pain of the conditioning stimulus on an NPRS. Next, the cuff pressure was adapted (ie, increased or decreased) until the patient experienced a pain intensity of three on the NPRS. Then the PPT was repeated at the deltoid muscle as described above. The cuff was deflated immediately after the second test stimulus. The CPM effect was calculated following the formula: \(\frac{\text{PPT at baseline} - \text{PPT during CPM}}{\text{PPT at baseline}}\) , with negative values implying an anti-nociceptive effect and positive values a pronociceptive effect. This method was found to be reliable and effective in evaluating descending pain modulation pathways.\(^64\)\(^65\)

#### Shoulder active ROM

Shoulder ROM was measured with a gravity referenced analogue plurimeter (Dr. Jules Rippstein) into the directions of external rotation (in 0° abduction), flexion and abduction. Both the affected and unaffected sides were measured. The side measured first was allocated based on an Excel-generated random sequence. For measuring shoulder external rotation, the inclinometer was attached to the dorsal side of the forearm and patients, while lying supine, were asked to perform shoulder external rotation while keeping the shoulder at 0° of abduction.

During the assessment of shoulder flexion and abduction, patients were sitting on the bench with the hips and knees flexed 90° and the feet flat on the floor. The plurimeter was attached to the upper arm just below the insertion of the deltoid muscle. Shoulder flexion and abduction were performed in the sagittal and frontal plane, respectively, with the thumb pointing upwards.

### Statistics

The group with at least one follow-up measurement was compared with the complete sample at baseline by
Mixed models were fitted using add-on packages lme4 and lmerTest.

RESULTS

Subjects

Figure 1 shows the flow diagram of this study. Initially 149 patients were included, 121 patients completed at least one follow-up measurement and 88 completed all follow-up measurements. Patient characteristics of the full sample at baseline and patients completing at least one follow-up measurement are presented in Table 2.

None of the characteristics shows a strong difference between the total sample and the sample analysed, making it quite unlikely that the results presented here have been biased due to attrition bias.

Development over time

Figure 2 shows the mean scores and 95% CIs for the SPADI for all follow-up measurements and the mean scores for the eight domains of the SF-36 for all follow-up measurements.

Table 3 shows the strength and direction of the analysis over time and indicates a significant improvement for the SPADI (F=32.274, p<0.001) and for the physical functioning (F=3.187, p=0.044), physical problem (F=3.176, p=0.045), emotional problem (F=5.768, p=0.004) and vitality (F=11.126, p<0.001) domains of the SF-36. Post hoc comparison reveals a difference from 3 months follow-up to 6 and 9 months follow-up (p<0.01) for the SPADI and vitality domain and from 6 to 9 months follow-up for the SPADI and emotional problem domain (p<0.03). No post hoc differences were found for the physical functioning and physical problem domains of the SF-36 (p>0.05).

Time explained 1.5%–5.9% of the outcome over 9 months follow-up.

Prognostic factors

Table 4 shows the strength and direction of the candidate prognostic factor analysis. Active external rotation was found to be a prognostic factor for the physical functioning (F=11.203, p=0.001) and pain (F=4.082, p=0.048) domains of the SF-36 and explained 2.6%–6.3% of the outcome over 9 months follow-up. DM was found to be a prognostic factor for SPADI (F=4.936, p=0.030) and the physical functioning (F=4.156, p=0.046) domain of the SF-36 and explained 2.5%–2.6% of the outcome over 9 months follow-up. Thyroid disorder was found to be a prognostic factor for the emotional problem (F=4.650, p=0.035) domain and explained 2.9% of the outcome over 9 months follow-up. Finally, autonomic symptoms were found to be a prognostic factor for the emotional problem (F=8.228, p=0.006), mental health (F=9.488, p=0.003), vitality (F=6.675, p=0.012), pain (F=4.007, p=0.049) and general health (F=5.378, p=0.024) domains of the SF-36 and explained 2.5%–5.0% of the outcome over 9 months follow-up.
Table 2  Patient characteristics at baseline and for the sample with at least one follow-up measurement

<table>
<thead>
<tr>
<th></th>
<th>Total sample (n=149)</th>
<th>Sample with at least one follow-up (n=121)</th>
<th>Mean difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>52.68±9.35 (51.11 to 54.24)</td>
<td>52.76±8.13 (51.35 to 54.17)</td>
<td>−0.08 (−2.26 to 2.09)</td>
</tr>
<tr>
<td>Female gender</td>
<td>98 (65.77%)</td>
<td>77 (63.64%)</td>
<td>NA</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>168.13±8.68 (166.77 to 169.49)</td>
<td>168.64±8.16 (167.21 to 170.07)</td>
<td>−0.51 (−2.60 to 1.57)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>70.60±14.44 (68.27 to 72.93)</td>
<td>70.58±13.94 (68.09 to 73.08)</td>
<td>0.02 (−3.41 to 3.44)</td>
</tr>
<tr>
<td>BMI (kg/cm²)</td>
<td>24.73±3.97 (24.11 to 25.35)</td>
<td>24.54±3.94 (23.85 to 25.22)</td>
<td>0.20 (−0.79 to 1.18)</td>
</tr>
<tr>
<td>Hand dominance (right)</td>
<td>121 (82.88%)</td>
<td>97 (82.20%)</td>
<td>NA</td>
</tr>
<tr>
<td>Affected side (right)</td>
<td>70 (47.95%)</td>
<td>52 (44.07%)</td>
<td>NA</td>
</tr>
<tr>
<td>Affected side (dominant)</td>
<td>75 (52.08%)</td>
<td>55 (47.41%)</td>
<td>NA</td>
</tr>
<tr>
<td>Cause (idiopathic FS)</td>
<td>95 (63.7%)</td>
<td>80 (66.12%)</td>
<td>NA</td>
</tr>
<tr>
<td>Diabetes mellitus (yes)</td>
<td>20 (13.51%)</td>
<td>15 (12.50%)</td>
<td>NA</td>
</tr>
<tr>
<td>Thyroid disorder (yes)</td>
<td>13 (8.84%)</td>
<td>12 (10.00%)</td>
<td>NA</td>
</tr>
<tr>
<td>Work</td>
<td>NA</td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td>No</td>
<td>70 (47.62%)</td>
<td>54 (45.38%)</td>
<td></td>
</tr>
<tr>
<td>Part time</td>
<td>28 (19.05%)</td>
<td>22 (18.49%)</td>
<td></td>
</tr>
<tr>
<td>Full time</td>
<td>49 (33.33%)</td>
<td>43 (36.13%)</td>
<td></td>
</tr>
<tr>
<td>Sport (yes)</td>
<td>61 (42.07%)</td>
<td>48 (41.03%)</td>
<td>NA</td>
</tr>
<tr>
<td>Shoulder pain and disability (SPADI, 0–100)</td>
<td>60.75±21.16 (57.46 to 64.05)</td>
<td>60.20±25.10 (56.54 to 63.87)</td>
<td>0.55 (−4.65 to 5.75)</td>
</tr>
<tr>
<td>Pain intensity during last 24 hours (VAS, 0–100)</td>
<td>48.68±27.77 (44.17 to 53.19)</td>
<td>46.81±27.85 (41.82 to 51.81)</td>
<td>2.07 (−5.20 to 9.33)</td>
</tr>
<tr>
<td>Quality of life (SF-36, 0–100)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical functioning</td>
<td>67.88±19.16 (65.41 to 70.35)</td>
<td>68.44±18.98 (65.65 to 71.23)</td>
<td>−0.56 (−6.25 to 5.13)</td>
</tr>
<tr>
<td>Social</td>
<td>64.08±22.57 (61.17 to 67.00)</td>
<td>63.43±21.81 (60.22 to 66.63)</td>
<td>0.65 (−5.96 to 7.27)</td>
</tr>
<tr>
<td>Physical problems</td>
<td>22.63±32.22 (18.47 to 26.79)</td>
<td>23.77±32.33 (19.01 to 28.52)</td>
<td>−1.13 (−10.77 to 8.50)</td>
</tr>
<tr>
<td>Emotional problems</td>
<td>70.18±41.96 (64.76 to 75.59)</td>
<td>72.02±41.32 (65.94 to 78.09)</td>
<td>−1.84 (−14.26 to 10.58)</td>
</tr>
<tr>
<td>Mental health</td>
<td>64.97±17.16 (62.75 to 67.18)</td>
<td>65.14±17.24 (62.60 to 67.67)</td>
<td>−0.17 (−5.30 to 4.97)</td>
</tr>
<tr>
<td>Vitality</td>
<td>50.32±20.56 (47.66 to 52.97)</td>
<td>50.99±20.45 (47.98 to 53.99)</td>
<td>−0.67 (−6.79 to 5.45)</td>
</tr>
<tr>
<td>Pain</td>
<td>42.17±23.93 (39.09 to 45.26)</td>
<td>41.43±23.16 (38.03 to 44.84)</td>
<td>0.74 (−6.28 to 7.76)</td>
</tr>
<tr>
<td>General health</td>
<td>58.54±22.04 (55.69 to 61.38)</td>
<td>58.53±21.68 (55.34 to 61.72)</td>
<td>0.01 (−6.52 to 6.53)</td>
</tr>
<tr>
<td>Autonomic symptoms (COMPASS 31, 0–100)</td>
<td>17.40±12.46 (15.45 to 19.36)</td>
<td>17.36±12.37 (15.18 to 19.54)</td>
<td>0.05 (−3.02 to 3.12)</td>
</tr>
<tr>
<td>Shoulder active ROM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>External rotation (0° abduction)</td>
<td>12.29±15.79 (9.75 to 14.83)</td>
<td>12.36±15.22 (9.63 to 15.08)</td>
<td>−0.07 (−3.82 to 3.68)</td>
</tr>
<tr>
<td>Flexion</td>
<td>106.50±30.00 (101.68 to 111.32)</td>
<td>105.99±28.56 (100.87 to 111.11)</td>
<td>0.51 (−6.57 to 7.59)</td>
</tr>
<tr>
<td>Abduction</td>
<td>77.80±30.21 (72.95 to 82.64)</td>
<td>77.29±29.09 (72.10 to 82.49)</td>
<td>0.50 (−6.70 to 7.70)</td>
</tr>
<tr>
<td>PPT shoulder</td>
<td>3.97±2.72 (3.53 to 4.41)</td>
<td>3.90±2.64 (3.43 to 4.38)</td>
<td>0.06 (−0.58 to 0.71)</td>
</tr>
<tr>
<td>PPT quadriceps</td>
<td>7.09±5.81 (6.15 to 8.03)</td>
<td>7.00±5.16 (6.05 to 7.91)</td>
<td>0.11 (−1.21 to 1.42)</td>
</tr>
<tr>
<td>Temporal summation</td>
<td>1.50±1.94 (1.19 to 1.82)</td>
<td>1.59±1.95 (1.24 to 1.94)</td>
<td>−0.08 (−0.55 to 0.39)</td>
</tr>
<tr>
<td>CPM</td>
<td>−0.14±0.33 (−0.20 to −0.09)</td>
<td>−0.15±0.30 (−0.21 to −0.10)</td>
<td>0.002 (−0.07 to 0.08)</td>
</tr>
<tr>
<td>Treatment received</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>7 (6.36%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive treatment (including CSI)</td>
<td>11 (10.00%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical therapy</td>
<td>46 (41.82%)</td>
<td></td>
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</tbody>
</table>

Continued
DISCUSSION

Our results showed that shoulder pain and disability decreased, and quality of life (reflected by emotional problem and vitality domains) improved over 9 months follow-up in patients with FS. There were different factors that influenced clinical outcomes over 9 months follow-up adjusted for baseline scores, age, gender, treatment received and geographical region. Only DM was found to be a prognostic factor for shoulder pain and disability, while for the physical functioning domain of the SF-36, external rotation ROM and presence of DM were found to be prognostic factors. Furthermore, for the emotional problem domain presence of thyroid disorder and self-reported autonomic symptoms were found to be prognostic factors and for mental health and vitality domains of the SF-36, self-reported autonomic symptoms were found to be a prognostic factor. For the pain domain, active external rotation and self-reported autonomic symptoms were found to be prognostic factors and for the general health domain, self-reported autonomic symptoms were found to be a prognostic factor.

In this study, a significant improvement in shoulder pain and disability and quality of life (vitality domain) was found from 3 months to 6 and 9 months. Shoulder pain and disability and quality of life (emotional problem domain) improved from 6 months to 9 months follow-up. There seems to be rather an early increase (from 3 months follow-up to 6 and 9 months follow-up) observed in the vitality domain of quality of life that slowed with time, while the emotional problem domain improved.
only from 6 to 9 months. This delayed improvement might be a consequence of improved shoulder pain and disability and vitality.

**Prognostic factors**

In this study, no factors were found to be prognostic for all outcomes.

Higher levels of external rotation ROM at baseline resulted in a worse score on the physical functioning and pain domain of the SF-36. This is an unexpected finding, as we hypothesised that less ROM would result in worse scores. It might be possible that patients with more movement restriction receive more treatment focused on this restriction, however, our data do not contain this detailed information to confirm this hypothesis. Contrary to our results, Yang et al. found a prognostic value of shoulder external rotation ROM on shoulder function. This difference might be explained by the fact that Yang et al. provided standardised treatment including mobilisation and stretching techniques and this study was an observational study without standardised treatment.

Presence of DM was found to be a prognostic factor for worse improvement of shoulder pain and disability and the physical functioning domain of the SF-36. A recent systematic review reported conflicting evidence regarding DM as a possible prognostic factor for influencing clinical outcomes in patients with FS. This is confirmed by our results, as it was found to be a prognostic factor in only one domain of quality of life.

Presence of thyroid disorder was found to be a prognostic factor for improvement in the emotional problem domain. This unexpected finding might be explained because patients with thyroid disorder could have already gone through a period with emotional problems and be able to put the complaints of FS into perspective more easily.

The presence of more self-reported autonomic symptoms at baseline resulted in a worse prognosis over 9 months follow-up in terms of quality of life (physical functioning, emotional problem and mental health domain). These autonomic symptoms might be the result of the interaction between the nervous, endocrine and immune system. It is suggested that a disturbance in one of these systems will lead to a disturbance in another system. Since the pathogenesis of FS is thought to be one of chronic inflammation, the immune system may be disturbed, resulting in a disturbance of the autonomic nervous system. Whether these autonomic symptoms were already present before the development of FS or developed simultaneously with the FS complaints is unknown. However, autonomic symptoms appear to be present before other disorders such as DM or rheumatoid arthritis develop.

If this is the case in patients with FS as well, autonomic symptoms may be considered a risk factor for the development of FS.

**Variance explained**

All the prognostic factors investigated in this study explained between 2.5% and 6.3% of clinical outcomes over 9 months follow-up, which would indicate there are more variables that contribute to shoulder pain and disability and to the different domains of quality of life in patients with FS. Other studies have suggested that muscle strength, number of comorbidities and scapular movement could contribute to the prognosis in this population. In addition, there is conflicting evidence regarding

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**Table 3** Results of time analysis

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>Regression coefficient (SE)</th>
<th>m/c R²</th>
<th>Tukey post hoc</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPADI</td>
<td>6 months: -10.72 (2.11)</td>
<td>0.058</td>
<td>3 months to 6 and 9 months (p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td>9 months: -17.00 (2.15)</td>
<td>0.085</td>
<td>6 months to 9 months (p=0.011)</td>
</tr>
<tr>
<td>SF-36</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical functioning</td>
<td>6 months: -0.08 (3.10)</td>
<td>0.019</td>
<td>No pairwise differences</td>
</tr>
<tr>
<td></td>
<td>9 months: 6.88 (3.14)</td>
<td>0.015</td>
<td></td>
</tr>
<tr>
<td>Social</td>
<td>6 months: 2.46 (2.93)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>9 months: 5.47 (2.97)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Physical problem</td>
<td>6 months: 0.33 (5.11)</td>
<td>0.015</td>
<td>No pairwise differences</td>
</tr>
<tr>
<td></td>
<td>9 months: 11.51 (5.17)</td>
<td>0.012</td>
<td></td>
</tr>
<tr>
<td>Emotional problem</td>
<td>6 months: -7.41 (4.64)</td>
<td>0.026</td>
<td>6 months to 9 months (p=0.003)</td>
</tr>
<tr>
<td></td>
<td>9 months: 8.55 (4.69)</td>
<td>0.033</td>
<td></td>
</tr>
<tr>
<td>Mental health</td>
<td>6 months: -5.02 (2.50)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>9 months: -2.05 (2.54)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Vitality</td>
<td>6 months: -13.39 (2.87)</td>
<td>0.059</td>
<td>3 months to 6 and 9 months (p&lt;0.01)</td>
</tr>
<tr>
<td></td>
<td>9 months: -8.61 (2.91)</td>
<td>0.077</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>6 months: -2.63 (3.30)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>9 months: 1.85 (3.35)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>General health</td>
<td>6 months: -4.23 (2.91)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>9 months: -2.38 (2.95)</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>

Significant differences over time in bold (p<0.05).
c, conditional; m, marginal; SF-36, 36-item short form health survey; SPADI, shoulder pain and disability index.
Table 4  Results of the prognostic factor analysis for SPADI and the eight domains of quality of life (SF-36)

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>SPADI</th>
<th>Physical functioning</th>
<th>Social</th>
<th>Physical problem</th>
<th>Emotional problem</th>
<th>Mental health</th>
<th>Vitality</th>
<th>Pain</th>
<th>General health</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RC (SE)</td>
<td>m/c R²</td>
<td>RC (SE)</td>
<td>m/c R²</td>
<td>RC (SE)</td>
<td>RC (SE)</td>
<td>m/c R²</td>
<td>RC (SE)</td>
<td>m/c R²</td>
</tr>
<tr>
<td>Active ROM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>External rotation</td>
<td>0.12 (0.18)</td>
<td>–</td>
<td>–0.47 (0.14)</td>
<td>0.063</td>
<td>–0.08 (0.11)</td>
<td>–0.36 (0.28)</td>
<td>–</td>
<td>–0.33 (0.26)</td>
<td>–</td>
</tr>
<tr>
<td>Flexion</td>
<td>–0.10 (0.09)</td>
<td>–</td>
<td>–0.10 (0.08)</td>
<td>–0.01 (0.06)</td>
<td>–0.05 (0.15)</td>
<td>0.22 (0.14)</td>
<td>0.00 (0.06)</td>
<td>0.00 (0.08)</td>
<td>–</td>
</tr>
<tr>
<td>Abduction</td>
<td>0.02 (0.08)</td>
<td>–</td>
<td>–0.12 (0.07)</td>
<td>–0.02 (0.05)</td>
<td>–0.07 (0.13)</td>
<td>0.16 (0.12)</td>
<td>0.03 (0.05)</td>
<td>–0.02 (0.07)</td>
<td>–</td>
</tr>
<tr>
<td>Central pain processing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPT affected shoulder</td>
<td>–0.64 (1.38)</td>
<td>1.08 (1.18)</td>
<td>–0.13 (0.88)</td>
<td>3.66 (2.11)</td>
<td>3.25 (2.01)</td>
<td>–0.12 (0.87)</td>
<td>0.79 (1.10)</td>
<td>1.00 (1.37)</td>
<td>0.69 (1.07)</td>
</tr>
<tr>
<td>PPT quadriceps</td>
<td>–1.05 (0.99)</td>
<td>1.23 (1.05)</td>
<td>–0.10 (0.79)</td>
<td>3.44 (1.89)</td>
<td>1.52 (1.86)</td>
<td>–0.30 (0.79)</td>
<td>1.07 (0.98)</td>
<td>1.00 (0.95)</td>
<td>1.46 (1.10)</td>
</tr>
<tr>
<td>TS</td>
<td>2.37 (1.51)</td>
<td>–1.35 (1.29)</td>
<td>–0.79 (0.77)</td>
<td>–0.20 (2.43)</td>
<td>0.83 (2.26)</td>
<td>–0.13 (0.96)</td>
<td>–0.17 (1.26)</td>
<td>0.68 (1.51)</td>
<td>–1.29 (1.17)</td>
</tr>
<tr>
<td>CPM</td>
<td>–11.43 (7.90)</td>
<td>3.09 (6.88)</td>
<td>5.13 (5.12)</td>
<td>–9.32 (12.62)</td>
<td>–1.62 (11.94)</td>
<td>–4.10 (5.07)</td>
<td>0.10 (6.46)</td>
<td>–7.99 (7.95)</td>
<td>–1.83 (6.27)</td>
</tr>
<tr>
<td>Metabolic factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus (yes)</td>
<td>17.78 (8.00)</td>
<td>0.026</td>
<td>0.001</td>
<td>–14.33 (7.02)</td>
<td>0.025</td>
<td>0.006</td>
<td>1.37 (5.43)</td>
<td>–8.73 (13.13)</td>
<td>–6.00 (12.70)</td>
</tr>
<tr>
<td>Thyroid disorder (yes)</td>
<td>–1.49 (7.67)</td>
<td>6.43 (6.44)</td>
<td>4.62 (4.62)</td>
<td>14.51 (11.82)</td>
<td>22.97 (10.65)</td>
<td>0.029</td>
<td>0.002</td>
<td>6.31 (4.58)</td>
<td>5.65 (5.92)</td>
</tr>
<tr>
<td>Autonomic symptoms</td>
<td>–0.15 (0.25)</td>
<td>–0.41 (0.22)</td>
<td>–0.29 (0.16)</td>
<td>–0.46 (0.38)</td>
<td>–0.99 (0.35)</td>
<td>0.048</td>
<td>0.004</td>
<td>–0.46 (0.15)</td>
<td>0.05 (0.20)</td>
</tr>
</tbody>
</table>

Significant prognostic factors in bold (p<0.05).
c, conditional; CPM, conditioned pain modulation; m, marginal; PPT, pressure pain threshold; RC, regression coefficient; ROM, range of motion; SF-36, 36-item Short Form Health Survey; SPADI, Shoulder Pain and Disability Index; TS, temporal summation.
the role of gender, age and duration of symptoms and preliminary evidence for onset pain intensity to be prognostic factors for disability in patients with FS. Interestingly, the latter factor was also found in a longitudinal study about the long-term outcomes of FS. Future studies should include these variables to determine whether all of them in isolation or in combination could provide even better prognostic models for patients with FS than those provided so far.

Clinical implications and suggestions for further research

Our results indicate that increased external rotation ROM and presence of DM and autonomic symptoms at baseline may result in a worse prognosis of patients with FS. This information may be useful to tailor treatment in this population. For instance, if more autonomic symptoms are present, it could be beneficial in patients with FS to target the autonomic nervous system (ie, vagal nerve stimulation or yoga). Vagal nerve stimulation and yoga have been found to be effective for improving disease activity and sympathovagal balance in patients with rheumatoid arthritis and vagal nerve stimulation improved pain and disability in patients with osteoarthritis. However, the presence of autonomic symptoms in this study was assessed with a self-reported questionnaire and although this questionnaire is valid and reliable, more objective tools to assess the autonomic nervous system, such as heart rate and blood pressure variability, should be investigated in patients with FS before implementing specific interventions to treat these symptoms.

Based on our findings, we suggest considering a more holistic assessment than focusing solely on the shoulder in patients with FS. It seems that DM, the autonomic nervous system and possibly some elements of central pain processing might play a role in the prognosis of patients with FS. This might be important to tailor treatment strategies. However, more evidence of the presence of these prognostic factors is needed and the results of this study need to be replicated in future studies. When these results are confirmed the assessment of these factors becomes more important.

Strengths

The greatest strength of this study is the multicentre design with different geographical locations. This provides multiple benefits when compared with a single centre design. One of those strengths is the large sample, even after dropouts, which has been used to determine prognostic factors for FS. Other benefits of this approach are decreased personal bias, stronger statistical data analysis and larger generalisability of the results. Furthermore, the assessment done in this study is convenient to apply in clinical settings and so it is easy to examine the relevant prognostic factors. Some assessment elements are common practice (eg, ROM, pain, disabilities), while others are not routinely performed (eg, self-reported autonomic symptoms). The assessment in this study was about more than simply joints and muscles. With the inclusion of elements of the autonomic and CNS and metabolic factors, we investigated a more holistic assessment approach. Finally, the stage of the FS condition was standardised to patients only in stage 1 or 2 as reflected by our inclusion criteria, minimising the influence of disease duration.

Limitations

Besides the strengths, some limitations need to be acknowledged as well. First, the diagnosis FS was based on recommended diagnostic criteria, but the presence of potential other disorders (ie, osteoarthritis) was not ruled out with imaging. Second, the diagnosis of DM was made by an endocrinologist and was used as the dichotomy present/absent. There was no verification of blood glucose levels with objective tools (ie, blood glucose measurement tool), so patients with prediabetic levels might have been given the level ‘absent’ and this might have influenced the results. The analysis of glucose levels in patients with FS is therefore recommended for future studies. Lastly, there were relatively high numbers of patients lost to follow-up. There were 121 patients with at least one follow-up measurement, however, only 88 patients (59%) completed all follow-up measurements. Therefore, results need to be interpreted with caution. Nevertheless, with the current sample, we are able to detect a correlation of 0.22 between candidate prognostic factors and final outcome with a power of 0.80 and a significance level of 0.05.

Conclusion

External rotation ROM, and presence of DM, thyroid disorder and autonomic symptoms at baseline emerged to be prognostic factors for shoulder pain, disability and quality of life over 9 months follow-up in patients with FS. These factors explained 2.5%–6.3% of the variance of those outcomes with adjustment for several covariates (ie, baseline score shoulder pain and disability and quality of life respectively, age, gender, treatment category and geographical region). There might be additional prognostic factors, such as muscle strength or number of comorbidities that might be important as suggested by previous studies. All these factors together should be investigated in future research to determine whether these factors in isolation or in combination have prognostic value for clinical outcomes in patients with FS. Finally, further research could investigate whether specific treatments targeting DM and autonomic nervous system symptoms at baseline result in better prognosis. Meanwhile, treatment of patients with FS should be performed according to clinical practice guidelines and assessment should focus on a more holistic approach to signal possible additional treatment goals.

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Acknowledgements

We would like to thank all participants who volunteered to take part in our study.

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MicM: data acquisition (including recruitment), data curation, formal statistical analysis, interpretation, writing—original draft and editing, responsible for overall content; Mertens: conceptualisation, methodology, interpretation, writing—review and editing, supervision; SN: conceptualisation, data acquisition (including recruitment), writing—review and editing; AL: data acquisition (including recruitment), writing—review and editing; OV: data acquisition (including recruitment), writing—review and editing; MR: data acquisition (including recruitment), writing—review and editing; MAR: data acquisition (including recruitment), writing—review and editing; YH: data acquisition (including recruitment), writing—review and editing; LF: data acquisition (including recruitment), writing—review and editing; ELG: conceptualisation, methodology, data acquisition (including recruitment), writing—review and editing; EJ: formal statistical analysis, writing—review and editing; EG: data acquisition (including recruitment), writing—review and editing; SN-L: data acquisition (including recruitment), data curation, writing—review and editing; MF-S: data acquisition (including recruitment), writing—review and editing; AL-S: data acquisition including recruitment, writing—review and editing; LD: data acquisition (including recruitment), conceptualisation, methodology, data curation, writing—review and editing. All authors approved the final version and agreed to be accountable for the work published.

Funding

The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests

None declared.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication

Not applicable.

Ethics approval

This multicenter prospective longitudinal study was performed in the research laboratories of the University of Valencia (Spain), University of Malaga (Spain), and the University of Antwerp (Belgium). The study was approved by the Human/Clinical Research Ethics Committees of the University of Valencia (H1432625002427), Hospital Costa del Sol (001_abr17_P2) and University Hospital Antwerp (B300201422072). Data were collected between November 2014 and October 2020. This study adhered to the Declaration of Helsinki.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

Data are available on reasonable request. Data are available on reasonable request at the corresponding author: filip.struyf@uantwerpen.be.

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motional review of definitions, operationalizations and measurement 

52 Gracyl RH, Schweinhardt P. Programmed symptoms: disparate effects 

53 Harte SE, Harris RS, Cathcart S, Rolan P et al. The neurobiology of central 

54 Roy J-S, MacDermid JC, Woodhouse LJ. Measuring shoulder 
function: a systematic review of four questionnaires. Arthritis Rheumat 


qualities of the Rand 36-item health survey 1.0: a multidimensional 

autonomic symptom scale 31 (COMPASS-31) in patients with and 

hypogalgesia in musicians with and without shoulder pain: 
a randomized controlled crossover study. Pain Physician 

59 Lewis GN, Heales L, Rice DA, et al. Reliability of the conditioned pain 
mobilization procedure to assess endogenous inhibitory pain 

error, and minimum detectable change of clinical pressure pain 
threshold testing in people with and without acute neck pain. 

threshold testing in neck pain: comparing protocols, responsiveness, 
and association with psychological variables. Phys Ther 

62 Vandenboom L, Oostendorp RAB, Vaes P, et al. Pressure algometry 

63 Farasyn A, Meeusen R. Pressure pain thresholds in healthy subjects: 
infuence of physical activity, history of lower back pain factors and 
the use of endomorphy as a placebo-like treatment. J Bodyw Mov 

summation and diffuse noxious inhibitory control. Pain Res Manag 

conditioned pain modulation paradigms and influencing personal 

66 Steyerberg EW, Moons KGM, van der Windt DA, et al. Prognosis 
research strategy (progress) 3: prognostic model research. PLoS 

67 Fitzmaurice GM, Laird NM, Ware JH. Applied longitudinal analysis. 

68 Nakagawa S, Schielzeth H. A general and simple method for 
inferring R2 from generalized linear mixed-effects models. Methods 

69 Wickham H. ggplot2: elegant graphics for data analysis. Springer 

70 Bates D, Mächler M, Bolker B, et al. Fitting linear mixed-effects 

71 Kuznetsova A, Brockhoff PB, Christensen RHB, lmerTest package: 

72 Yang J-Ian, Chang C-wei, Chen S-yee, et al. Shoulder kinematic 
features using arm elevation and rotation tests for classifying patients 
with frozen shoulder syndrome who respond to physical therapy. 

73 Hand GGR, Athanasou NA, Matthews T, et al. The pathology of 

the autonomic nervous system to reduce inflammation in rheumatoid 

75 Courties A, Berenbaum F, Sellam J. Vagus nerve stimulation in 

76 Ganesan S, Gaur GS, Negi VS, et al. Effect of yoga therapy on 
disease activity, inflammatory markers, and heart rate variability 

77 Sletten DM, Suarez GA, Low PA, et al. COMPASS 31: a refined and 
abbreviated composite autonomic symptom score. Mayo Clin Proc 
2012;87:1196–201.
