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DOI:
10.1016/j.msksp.2022.102634

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (Harvard):
Asquini, G, Devecchi, V, Borromeo, G, Viscuso, D, Morato, F, Locatelli, M & Falla, D 2022, 'Predictors of pain reduction following a program of manual therapies for patients with temporomandibular disorders: A prospective observational study', *Musculoskeletal Science and Practice*, vol. 62, 102634.
https://doi.org/10.1016/j.msksp.2022.102634

Musculoskeletal Science and Practice 62 (2022) 102634

Contents lists available at ScienceDirect

Musculoskeletal Science and Practice

journal homepage: www.elsevier.com/locate/msksp

Original article

Predictors of pain reduction following a program of manual therapies for patients with temporomandibular disorders: A prospective observational study

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ARTICLE INFO

Keywords:
Temporomandibular disorders
Physiotherapy
Pain
Prediction
Manual therapy

ABSTRACT

Background: Clinical guidelines recommend conservative treatment for the management of temporomandibular disorders (TMD), and manual therapy (MT) is commonly applied to reduce pain and improve function.
Objectives: To identify predictors of pain reduction and functional improvement following a program of manual therapies (MTP) in patients with TMD and develop a first screening tool that could be used in clinical practice to facilitate decision-making.
Design: A cohort of 102 adults with a diagnosis of TMD were treated with four weekly sessions within a MTP applied to craniomandibular structures. Candidate predictors were demographic variables, general health variables, psychosocial features, TMD characteristics and related clinical tests. A reduction of pain intensity by at least 30% after the MTP was considered a good outcome. Logistic regression was adopted to develop the predictive model and its performance was assessed considering the explained variance, calibration, and discrimination. Internal validation of the prediction models was further evaluated in 500 bootstrapped samples.
Results: Patients experiencing pain intensity greater than 2/10 during mouth opening, positive expectations of outcome following a MTP, pain localized in the craniocervical region, and a low Central Sensitization Inventory score obtained a good outcome following the MTP. Predictive performance of the identified physical and psychological variables was characterized by high explained variance (R2 = 58%) and discrimination (AUC = 89%) after internal validation. A preliminary screening clinical tool was developed and presented as a nomogram.
Conclusions: The high discrimination of the prediction model revealed promising findings, although these need to be externally validated in future research.
Trial registration number: NCT03990662.

1. Introduction

Temporomandibular disorders (TMD) are a health challenge given their prevalence and related socio-economic impact (Lipton et al., 1993; NIDCR and National Institute of Health, 2014). In Spain, the incidence of TMD increased from 8% in 1993 to 14% in 2015, notwithstanding a general improvement in oral health over the same period (Montero et al., 2018a). Epidemiological data from the USA showed that patients with TMD not only complain of jaw pain and restricted jaw mobility but often suffer from neck and back pain or pain at other sites (De Leeuw and Klasser, 2013; Plesh et al., 2011). In the USA alone, the estimated cost of TMD management is US$4 billion per year (NIDCR and National Institute of Health, 2014).

People with TMD are often referred to physical therapists for the management of TMD related pain and loss of function (Greene and Bertagna, 2019). Manual therapy (MT) directed to the craniomandibular

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https://doi.org/10.1016/j.msksp.2022.102634
Received 23 May 2022; Received in revised form 4 July 2022; Accepted 22 July 2022
Available online 31 July 2022

structures significantly reduces TMD pain (Armijo-Olivo et al., 2016; Asquini et al., 2022), although the superiority of MT versus other treatments (e.g., education and exercise) remains unclear (Asquini et al., 2022; Kalamir et al., 2013; Brochado et al., 2018). When managing patients with TMD, the clinician's decision on what specific treatment is the best for a patient is influenced by different factors such as the clinician's expertise and knowledge of the available evidence, professional attitude and habits and clinical reasoning skills (Su et al., 2019). However, specific features of the individual's presentation should also be considered when choosing the best treatment for each patient. For example, in people with neck or low back pain, MT is superior at decreasing pain in comparison to other treatments if targeted towards patients with specific clinical features (e.g., the onset of symptoms within 30 days) (Childs et al., 2004; Flynn et al., 2002). However, to date there has been no attempt to examine whether features of the patient's presentation can predict pain reduction and functional improvement following a program of manual therapies (MTP) for people with TMD. Such knowledge could support a more personalized management approach by positively affecting clinical decision-making.

In a prospective cohort study (Forssell et al., 2017), patients with TMD who had numerous previous healthcare visits, complained of high-intensity pain at other body sites and with a greater number of disability days, had a higher risk of presenting future clinically significant pain one year after the first evaluation (Forssell et al., 2017). In addition, another study (Kapos et al., 2018) found that baseline health-related quality of life of patients with TMD is inversely proportional with pain intensity at an 8-year follow-up (Kapos et al., 2018). These previous studies can facilitate clinicians to recognize more challenging patients to treat because of clinical features associated with persistent pain. However, they did not investigate predictors of pain reduction related to a specific therapeutic intervention such as MT.

This study aims to identify predictors of pain reduction and functional improvement following a MTP in patients with TMD and to develop a first screening tool that can be considered in clinical practice to facilitate decision making. The knowledge gained from this study is expected to facilitate clinical decision-making by providing clinicians with key factors to consider in order to determine whether or not a patient with TMD is likely to have a clinically relevant reduction of pain following a MTP.

2. Methods

2.1. Study design

A prospective observational cohort study design was conducted as described in the published study protocol (Asquini et al., 2019). The study protocol was submitted for publication before participant recruitment. All collected data (e.g., outcome measures and predictors) were prospectively reported in the study protocol (Asquini et al., 2019). Ethical approval was obtained from the Ethics Committee of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico and the University of Birmingham Ethics Committee. The study was conducted in accordance with the Declaration of Helsinki and followed the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) statement in which recommendations on prediction model development and validation are provided (Collins et al., 2015). The study was registered prospectively (NCT03990662).

2.2. Setting and participants

Participants were recruited from the TMJ Unit of the Italian Stomatologic Institute (Dental Hospital) in Milan, Italy between June 2019 and May 2021. Participants were assessed at baseline before starting the treatment period and one month later at the end of the fourth MTP session. Previous studies have demonstrated the effectiveness of MT for pain relief in people with TMD over the same duration which supported the choice of the intervention duration for this study (Bishop et al., 2015; Vigotsky and Bruhns, 2017; Calixtre et al., 2015).

2.3. Eligibility criteria

Inclusion criteria were: adults aged ≥18 years; TMD diagnosis according to the Diagnostic Criteria for TMDs (DC/TMD) (Schiffman et al., 2014); no therapeutic interventions received (for their TMD) in the previous 6 months (Wahlund et al., 2015); capacity to use and understand written and verbal Italian language; mental capacity to provide written informed consent.

Participants were excluded if, during the study, they started other interventions to treat the TMD (e.g. pharmacology, oral appliance, others). Other exclusion criteria were TMD pain related to rheumatoid/inflammatory arthritis; any physical or mental impairments impacting study outcomes.

2.4. Recruitment

To facilitate the interpretation of findings and their use in clinical practice, the number of potential predictors was not reduced with an exploratory factor analysis as anticipated in the study protocol (Asquini et al., 2019). Instead, selection of predictors was conducted by means of penalised logistic regression after removal of the redundant factors (see statistical analysis). Penalised regression is an effective shrinkage method recommended when the number of events per candidate predictor is low (<10) (Pavlou et al., 2015). Therefore, we aimed to collect data from 90 participants to reach at least 5 cases per candidate predictor to power the analysis (Peduzzi et al., 1996). Given that 75% of eligible participants typically consent to participation (Childs et al., 2004; Flynn et al., 2002) we aimed to assess 130 people with TMD. Feasibility data from the previous 5 years of activity at the TMJ Unit of the Italian Stomatologic Institute showed that at least 130 eligible participants would have been available for recruitment in 13 months. Due to the COVID-19 pandemic, almost 23 months were necessary to recruit the desired number of participants. All patients who attended the TMJ Unit during the study period were screened for the presence of a TMD. According to the DC/TMD, TMD diagnosis was confirmed using the Italian translation of the protocol by a dentist with over ten years of experience in managing TMD patients (Ohrbach et al., 2017). Participants provided their written informed consent before being included in the study. Participants were subsequently referred to a physiotherapist (an independent assessor with more than five years of experience in managing patients with TMD) for baseline assessments (outcome measures and candidate predictors). All outcome measures were assessed by the same physiotherapist after the last treatment at one month from baseline. Participant flow through the study is outlined in Fig. 1.

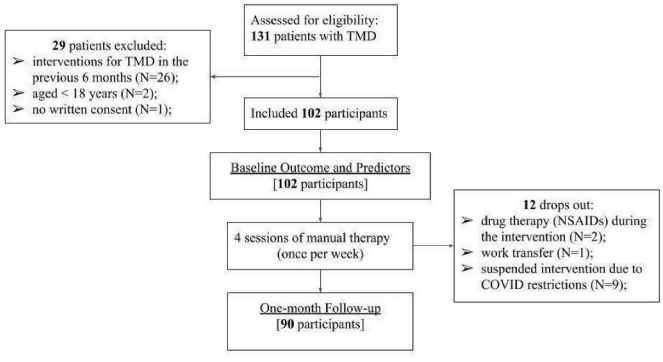

Fig. 1. Participant flow through the study.

2.5. Intervention

Over four weeks, each patient received a MTP consisting of four sessions (once per week) of MT applied to craniomandibular structures (Crockett et al., 1986; Guarda-Nardini et al., 2012; Nascimento et al., 2013). The treating physiotherapists targeted the MT techniques to the temporomandibular joints, temporal muscles, masseter muscles, pterygoid muscles and suprahyoid muscles. MT techniques were not targeted to other areas (i.e. on the neck) to allow a more localised MTP. Treatments were performed by two physiotherapists with more than 5 years of experience in the use of MT applied to craniomandibular structures and specific training on TMD assessment and management. They were not involved in participant recruitment, assessment or collection of outcome measures. According to their examination of each patient, combined with knowledge existing evidence and their clinical reasoning the treating physiotherapists determined the most suitable MT techniques to apply. Clinical reasoning decisions were principally based on the patient's pain severity and irritability, main pain mechanisms, pain sources and contributing factors identified during the examination. Several techniques were performed including temporomandibular joint mobilization with glides in different directions (i.e. caudal, ventral, anterior, transversal lateral/medial) (von Piekartz and Hall, 2013) and/or trigger point therapy of the masticatory muscles (Miernik et al., 2012) and/or myofascial induction therapy (Fernandez-de-las-Pena and Mesa-Jimenez, 2018). The overall goals of MTP were to reduce pain, reduce muscle tightness, enhance temporomandibular joint movement and improve function. The same physiotherapists delivering the MTP also provided explanations about the patient's clinical condition and answered any questions. In accordance with Kalamir et al. and Nascimento et al., each treatment session lasted from 20 to 30 min (Kalamir et al., 2013; Nascimento et al., 2013). No other treatments (e.g., oral appliance) were administered. During the study period, any patient requiring treatment for an acute episode of pain at another anatomical site (e.g., neck pain, low back pain, shoulder pain) had to withdraw from the study.

2.6. Outcome measures

All outcome measures adhered to those reported in the study protocol (Asquini et al., 2019). Considering that TMD patients usually report pain as their main problem, the primary outcome measure was pain intensity (Montero et al., 2018b). Current pain intensity, average pain intensity over the previous week, and worst pain intensity over the previous week were rated on a Visual Analogue Scale (VAS) and the average score was considered as the outcome measure (Haefeli and Elfering, 2006; Dworkin et al., 2005). A 10 cm horizontal line without marks, with "no pain" written at the left extremity and "worst pain imaginable" at the right extremity was used (Haefeli and Elfering, 2006). The VAS is a reliable and valid scale to evaluate pain intensity in intervention studies (Dworkin et al., 2005) A reduction in the total VAS score equal or greater than 30% was defined as a good outcome in this study (Haythornthwaite, 2010); a reduction in the total VAS score less than 30% was defined as poor outcome.

The Patient Specific Functional Scale (PSFS) was used to detect potential changes in function (Pet et al., 1995; Horn et al., 2012; Abbott and Schmitt, 2014; Maughan and Lewis, 2010). The PSFS is considered a valid, reliable, and responsive outcome measure and has a high test-retest reliability (Chatman et al., 1997; Hefford et al., 2012; Westaway et al., 1998). Outcome measures were assessed, pre-treatment and post-treatment, by the same independent evaluator to minimize any detection bias (Higgins et al., 2011).

2.7. Predictor variables

The selection of candidate predictors was based on previous studies related to prognostic factors for TMD and altered pain modulation in musculoskeletal disorders (Bair et al., 2016; Clark et al., 2017) (Table 1; for full description see (Asquini et al., 2019)). In particular, demographic variables were collected since age and gender are considered risk factors for TMD onset (Fillingim et al., 2011). Education levels were investigated because previous work showed that people with lower levels of education have the tendency to catastrophize about their pain (Roth and Geisser, 2002). Regarding general health variables, it is known that health-related quality of life can impact treatment outcomes for TMD (Kapos et al., 2018), and poor sleep is related to chronic pain,

Table 1
Summary of predictors.

Domain/predictor	Measure/data item
Demographical variables	
Age	Years
Gender	Female/male
Education	Basic education, intermediate education and university-level education
General health variables	
Health-related quality of life	EuroQol EQ-5D-5L (Brooks, 1996)
Sleep quality	11-point [0–10] Numerical Rating Scales, relating to current pain, from 'best possible sleep' to 'worst possible sleep' (Cappelleri et al., 2009)
Psychosocial features	
Coping strategies applied during a painful experience	Coping Strategies Questionnaire 27 (CSQ-27) (Monticone et al., 2014) (Domain: Distraction, Catastrophizing, Ignoring pain sensations, Distancing from pain, Coping self-statements, and Praying)
Anxiety and depression	Hospital Anxiety and Depression Scales (HADS) (Zigmond and Snaith, 1983)
Treatment expectation	Positive/negative expectation (Puentedura et al., 2012)
TMD characteristics	
Pain duration	Years
Pain intensity	VAS: averaging ratings of current pain, average pain, and worst pain in the past week (Davis et al., 2014)
Pain location	Pain drawing as described in the protocol of Diagnostic Criteria for TMD (Schiffman et al., 2014)
Central sensitization	Central Sensitization Inventory (CSI) (Mayer et al., 2012)
Classification of TMD	In according to DC/TMD Taxonomy (Peck et al., 2014): (1) TMJ Disorders, (2) Masticatory Muscle Disorders, (3) Headache, (4) Associated Disorders, (5) Mixed TMD (simultaneous presence of TMJ Disorders and Masticatory Muscle Disorders)
Oral behaviours	Oral Behaviours Checklist (OBC) (Ohrbach et al., 2008)
Characteristic pain intensity and disability	Graded Chronic Pain Scale (GCPS) version 2.0 (Italian version - www.rdctmdinternational.org)
Temporomandibular joint (TMJ) and masticatory muscles clinical test	
TMJ range of motion	Maximal Mouth Opening (MMO) without pain measured in mm through a ruler as described in the DC/TMD protocol (Schiffman et al., 2014)
TMJ palpation pain	Dynamic TMJ lateral pole palpation [1 kg of palpation pressure] in according to DC/TMD protocol (Schiffman et al., 2014) Score range: 0–1 [no pain = 0; pain = 1]
Muscle palpation pain	Palpation in the following 6 bilateral points: lateral pterygoid area [0.5 kg intraoral palpation], temporalis tendon [0.5 kg intraoral palpation], masseter muscle [1 kg extraoral palpation] as described in the DC/TMD protocol (Schiffman et al., 2014). Score range: 0–1 [< 3 sites with familiar pain = 0; ≥3 sites with familiar pain = 1]
JAW-test (Asquini et al., 2019)	Immediate effects of brief intraoral MT techniques on rest pain, mouth clenching pain and opening pain (Numeric Rating Scale (NRS)), and TMJ range of motion (MMO). Score range 0–2: [0 = no change; 1 = pain improvement or MMO improvement; 2 = improvement of both]

even if it is not possible to draw a causal relation (Janssen et al., 2008). In addition, different psychosocial factors and coping strategies (e.g. anxiety, depression, catastrophising, distancing from pain, distraction) were assessed since they can influence TMD onset and maintenance (Kight, Gatchel, Wesley). High severity and persistence of TMD pain are associated with psychological distress (Dworkin et al., 1990). People with chronic TMD commonly showed depression and high levels of stress (Keefe et al., 2004; Gatchel et al., 2007; Asquini et al., 2021). Additionally, there is agreement on the predictive strength of psychosocial factorsfor different musculoskeletal pain disorders (Mallen et al., 2007; Artus et al., 2017a). According to results from past studies examining predictors of outcome in TMDs, pain features were investigated as potential predictors (e.g. pain duration, pain intensity and extent) (Forssell et al., 2017; Kapos et al., 2018; Grossman et al., 2018). Moreover, in different pain conditions, characteristics of pain held predictive value for pain modulation (Mallen et al., 2007; Clay et al., 2010, 2012; Kamaleri et al., 2009). Finally, pain was assessed during temporomandibular movements and during palpation of temporomandibular joint/muscles (Schiffman et al., 2014). Notably, some predictors included more than one measure or score. For example, the JAw test contained the Jaw score, the mouth opening pain and the pain during mouth clenching.

2.8. Data handling

The independent physiotherapist evaluator collected the candidate predictors. All data were confidentially protected by archiving on a password-protected computer accessible only by the principal investigator (GA).

2.9. Statistical analysis methods

Descriptive statistics were used to present baseline values for each candidate predictor in patients showing poor or good outcome. Mean and standard deviation were used for continuous predictors and frequencies for categorical data. Sparse levels within categorical predictors were collapsed in order to result in a relatively balanced number of patients (Cowley et al., 2019). The non-data-driven dichotomization of continuous predictors was conducted by selecting cut off points with clinical meaning (Moons et al., 2015). Multicollinearity was evaluated by identifying correlation greater than 0.8 across predictors and a variance inflation criterion (VIF) greater than 10 [17]. In the presence of collinearity between predictors, the more reliable and simpler to use in clinical practice was included in the analysis (Collins et al., 2015; Moons et al., 2015).

2.10. Primary analysis

Penalised logistic regression was developed with treatment outcome (good versus poor) as the dependent variable. Before being entered into the model, continuous predictors were scaled to z-scores with a mean of 0 and standard deviation of 1. Coefficients of predictors were regularized by means of Least Absolute Shrinkage and Selection Operator (LASSO) (Tibshirani, 1111). Due to the penalty used by the LASSO, the coefficients of predictors can be shrunk to be zero and it leads to predictor selection. Several values of λ are tested with leave-one-out cross-validation (LOOCV) to identify the optimum penalty, which iteratively fit the model with different amounts of shrinkage. A conservative lambda value was selected as one standard error larger than the best fit to reduce the risk of overfitting and increase parsimony in the model (Steyerberg, 2019). Then, selected predictors were used to develop the logistic model. Overall performance of the identified model was evaluated using the R^2 Nagelkerke's, which compares the observed outcome with the predicted probability (Steyerberg, 2019). Discrimination of the model was measured by the area under the curve (AUC). Calibration of the model was assessed with the Hosmer-Lemeshow test and a p-value greater than 0.05 was considered as a good calibration. Since measures of model performance risk being too optimistic because they are computed from the original sample (apparent validity) (Steyerberg, 2019), optimism-adjusted performance was obtained after bootstrap validation ($n = 500$) and using the value of λ previously identified. Bootstrap validation resamples n times from the original sample and computes the amount of optimism affecting the measures of interest. Also, bootstrap estimation of optimism was conducted including variable selection in every bootstrap sample since the measure of optimism is underestimated when variable selection is not included (Steyerberg et al., 2003).

2.11. Secondary analysis

A linear regression model was fitted with the percentage of pain intensity change as the dependent variable. Again, the measure of performance (R^2 and root mean squared error, RMSE) were reported for apparent and internal validity (optimism-adjusted) after bootstrap validation. Finally, a penalised regression model with LASSO was developed to identify predictors of functional improvement (dependent variable) evaluated as change on the PSFS. Selected predictors and model performance were reported. All analyses were conducted in R with packages "glmnet" and "rms" (Steyerberg et al., 2003).

3. Results

Of the 131 patients that were screened, 102 were recruited and assessed at baseline from June 2019 to May 2021. Ninety participants completed the four-week program and the follow-up assessment. Twelve participants dropped out: 2 participants commenced drug therapy (NSAIDs) during the intervention, 1 was transferred for work, and 9 suspended the intervention due to COVID travel restrictions. Therefore, 90 patients were included in the analysis and complete datasets were obtained for all. There were no adverse events.

Levels within categorical variables with relatively few participants were collapsed. Specifically, basic and intermediate education were collated as were the III and IV categories of the Graded Chronic Pain Scale (GCPS). Both pain during mouth opening and pain during clenching were dichotomized in ≤ 2 or >2 (out of 10) to define people who experience no or minimal pain versus pain. Similarly, the number of pain locations was dichotomized in ≤ 2 (specifically, TMJ and neck) or > 2 to define patients who experienced localized or widespread pain in other body regions. Ultimately, the score resulting from the JAw test was not included in the analysis for two reasons. First, it depends on the skills of the examiner which may reduce the accuracy of assessment by people with limited experience in MT. Secondly, the immediate assessment of a technique on pain risks to overestimate and bias the final prediction model. Descriptive statistics for all of the included predictors are reported in Table 2.

3.1. Primary analysis

Potential predictors were assessed for multicollinearity, and none were excluded. After LASSO regularization with different levels of shrinkage and cross-validation, four predictors were retained for the logistic regression model. Specifically, the included predictors were pain during mouth opening, central sensitization measured with the Central Sensitization Inventory (CSI), treatment expectations, and pain locations. Their coefficients are presented in Table 3. Performance measures of the developed model are also reported in Table 3, and they revealed high explained variance ($R^2 = 64\%$) and discrimination (AUC = 0.9, Fig. 2). Furthermore, performance remained high after internal validation assessed with bootstrapping ($R^2 = 58\%$ and AUC = 0.9). Adequate calibration was ensured in the developed model since the Hosmer-Lemeshow test was non-significant ($p > 0.05$).

Table 2
Descriptive statistics of candidate predictors. Mean (SD) or percentage.

Predictors	Good outcome (*n = 63*)	Poor outcome (*n = 27*)	Total (*n = 90*)
Age	35.9 (13.9)	39.3 (15.8)	36.9 (14.5)
Gender			
Female	51 (81%)	23 (85%)	74 (82%)
Male	12 (19%)	4 (15%)	16 (18%)
Education,			
Basic-intermediate	27 (43%)	16 (59%)	43 (48%)
University	36 (57%)	11 (41%)	47 (52%)
EQ-5D (0–1)	0.9 (0.1)	0.7 (0.2)	0.8 (0.2)
Sleep quality (0–10)	5.9 (2.5)	4.4 (2.2)	5.4 (2.5)
History of TMD pain, (*years*)	0.5 (1.0)	1.7 (2.1)	0.8 (1.5)
Pain intensity, baseline (*VAS, 0–100*)	52.9 (19.5)	56.4 (17.4)	53.9 (18.8)
Pain location,			
n ≤ 2,	50 (79%)	7 (26%)	57 (63%)
n > 2	13 (21%)	20 (74%)	33 (37%)
GCPS			
Low dis/low int	20 (32%)	5 (19%)	25 (28%)
Low dis/high int	28 (44%)	13 (48%)	41 (45%)
High dis/high int	15 (24%)	9 (33%)	24 (27%)
Coping strategies (*CSQ-27*)	58.4 (20.6)	62.1 (21.4)	59.5 (20.8)
Anxiety (*HADS*)	6.5 (3.4)	10.4 (4.0)	7.6 (4.0)
Depression (*HADS*)	3.3 (2.7)	8.0 (4.6)	4.7 (4.0)
Central sensitization (*CSI*)	29.8 (10.7)	46.0 (12.8)	34.7 (13.6)
Treatment expectation,			
Negative	3 (5%)	14 (52%)	17 (18%)
Positive	60 (95%)	13 (48%)	73 (81%)
TMD classification			
Mixed	41 (65%)	15 (55%)	56 (62%)
Muscular	12 (19%)	7 (26%)	19 (21%)
Articular	10 (16%)	5 (19%)	15 (17%)
0-10 Pain mouth opening,			
≤ 2	8 (13%)	20 (74%)	28 (31%)
> 2	55 (87%)	7 (26%)	62 (69%)
0-10 Pain mouth clenching,			
≤ 2	25 (40%)	23 (85%)	48 (53%)
> 2	38 (60%)	4 (15%)	42 (47%)
Pain TMJ palpation,			
No pain	12 (19%)	7 (26%)	19 (21%)
Pain	51 (81%)	20 (74%)	71 (79%)
Pain muscle palpation,			
No pain	10 (16%)	5 (19%)	15 (17%)
Pain	53 (84%)	22 (81%)	75 (83%)
TMJ range of motion, (*mm*)	29.2 (9.4)	37.5 (6.7)	31.7 (9.4)
Oral behaviours, (*OBC*)	28.7 (9.6)	34.2 (11.3)	30.3 (10.4)

Table 3
Multivariable logistic regression model with pain group (good or poor) as outcome.

Predictors	Coefficient	R^2	Optimism-adjusted R^2	AUC	Optimism-adjusted AUC
Constant	1.40	0.64	0.58	0.91	0.89
CSI	−0.08				
N pain location (>2)	−0.31				
Treatment expectation (positive)	1.63				
Pain mouth opening (>2)	2.34				

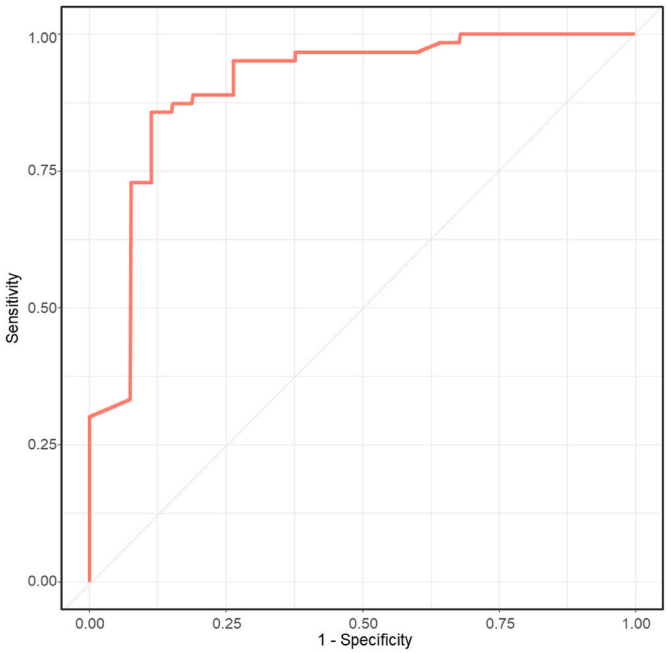

Fig. 2. Receiver operating characteristics (ROC) curve for the prediction model. The area under the curve (AUC) is 0.91.

3.2. Secondary analyses

Predictors selected in the primary analysis were further considered to evaluate their ability to predict the percentage change of pain after the four-week intervention. A linear regression model was developed, and coefficients of predictors and performance measures are reported in Table 4. Explained variance remained moderate also after internal validation (R^2 = 40%), and the RMSE showed an increase from 22.9 to 24.4.

Based on the activities reported by participants in the PSFS, the most disabling patient-specific functional activities were opening the mouth and chewing.

Linear regression with LASSO regularization was conducted to predict functional improvement. Two predictors only were retained in the model after regularization, namely maximal mouth opening (MMO) and pain duration. Coefficients of included predictors and performance for both apparent and optimism-adjusted measures are reported in Table 4.

Table 4
Multivariable prediction models of pain and functional improvement.

Predictors	Coefficient	R^2	Optimism-adjusted R^2	RMSE	Optimism-adjusted RMSE
Outcome: pain improvement (% VAS change) – Linear regression model					
Constant	45.5	0.46	0.40	22.9	24.4
CSI	−0.59				
N pain location (>2)	−5.00				
Treatment expectation (positive)	18.96				
Pain mouth opening (>2)	20.43				
Outcome: functional improvement – Linear regression model					
Constant	4.11	0.30	0.26	1.42	1.46
MMO	−0.06				
History of TMD pain[a]	−0.39				

[a] Log transformed.

3.3. Development of a clinical screening tool

The logistic regression model obtained from the primary analysis was used to develop a clinical screening tool presented as a nomogram (Fig. 3). The nomogram reveals the outcome probability of the patient following the MTP. For instance, if a patient reports a positive treatment expectation about MT they would receive 33 points for this predictor. This score is calculated by selecting the corresponding baseline value for the predictor (in this case: "Yes") and determining the corresponding points on the "Points" line at the top of the plot. The "Total predictor points" value can be obtained if the same process is replicated for each predictor and each score is summed. Then, a vertical line is drawn from the "Total predictor points" line to the "Good outcome probability" line at the bottom of the plot to estimate the probability of good outcome.

4. Discussion

Our findings revealed that patients experiencing pain intensity greater than 2/10 during mouth opening, positive expectations of outcome following MT, pain localized in the craniocervical region and a low CSI score had a good outcome following a MTP applied to the craniomandibular structures. Predictive performance of the identified physical and psychological variables was characterized by high explained variance (R^2 = 58%) and accuracy (AUC = 89%) also after internal validation. Of relevance, the predictors identified in our study are included in the cluster of features adopted to classify patients with nociplastic or nociceptive pain (Shraim et al., 2021). Moreover, we found that a shorter pain duration and limitations in MMO were predictors for functional improvement.

The majority (87.3%) of the participants that had a good outcome, reported pain during mouth opening greater than 2 out of 10. Alone, the experience of pain during mouth opening predicted a change in pain intensity of 20% after the four sessions of the MTP (Table 4). MT is a movement-based therapy which provides effects on tissue by enhancing tissue extensibility, reducing muscle spasm and enhancing mobility (Bialosky et al., 2009, 2018). The experience of pain during a specific movement is thought to be a clear sign of a mechanical pain presentation (Shraim et al., 2021) thus, it is reasonable that patients experiencing pain during mouth opening reported a significant pain reduction following a treatment which can address mechanical factors (Shraim et al., 2021; von Piekartz et al., 2020).

Treatment expectations also played an important role on pain reduction following the intervention (Nicholas et al., 2011). A positive treatment expectation predicts a good outcome because the expectation of benefit has a robust effect on pain (Vase et al., 2009). The current data showed that a positive expectation predicts a change in pain intensity by approximately 19% after treatment (approximately 10 points on the VAS scale based on the average pain intensity at baseline). If we consider the role of treatment expectations as a mechanism of placebo-related hypoalgesia (Bialosky et al., 2011), our results align with studies on patients with low back pain reporting the magnitude of the effectiveness of placebo interventions as approximately 8 points on a 0–100 pain scale (Strijkers et al., 2021).

Approximately 75% of those with poor outcome, reported pain in more than two body sites. Likewise, 80% with good outcome reported that their pain was localized to the craniocervical region. This finding aligns with previous research investigating predictors of outcomes in people with TMD, which showed poorer prognosis and treatment response in patients experiencing widespread pain (Su et al., 2019; Forssell et al., 2017; Wahlund and Larsson, 2017; Nijs et al., 2011). Moreover, widespread pain is considered a generic prognostic factor associated with poor outcomes for musculoskeletal conditions, regardless of the pain site (Artus et al., 2017b). In line with our findings, widespread pain is also recognized as a factor likely representing the presence of central sensitization (Jo et al., 2021; Neblett et al., 2013, 2017), and, in the current study, central sensitization measured with the CSI was also a predictor to discriminate between good versus poor outcome. The mean CSI score for those with good outcome was 29.8 on average, which is considered a subclinical form of central sensitization (Neblett et al., 2017; Neblett, 2018). On the other hand, those with poor outcome had an average CSI score of 46, which indicates mild to moderate central sensitization (Neblett et al., 2017; Neblett, 2018). A CSI score greater than 40 indicates the presence of a central sensitivity syndrome (sensitivity 81%, specificity 75%) (Neblett et al., 2013); in our sample, participants with a CSI higher than 40 were 11 in the good outcome group (14%) and 20 in the poor outcome group (74%).

In addition to the mentioned variables predicting a good pain outcome, we also found that the duration of TMD pain and TMJ range of motion predicted functional improvement. Previous studies have shown that the response to different therapeutic interventions for patients with TMD is better for those with less duration of symptoms (Grossman et al., 2018; Wahlund and Larsson, 2017). As with other musculoskeletal disorders, people with a chronic condition may benefit more from a multimodal management approach including psychosocial-based treatment approaches (Nijs et al., 2011). Consistent with our findings, a shorter duration of pain predicts good outcomes following MT in other musculoskeletal pain conditions such as low back pain (Childs et al., 2004; Flynn et al., 2002).

Interestingly, an MMO of less than ~30 mm predicted a significant functional improvement following the MTP, but this feature was less relevant in the prediction of the extent of pain reduction. This finding is in contrast with previous research, which observed that a reduction in

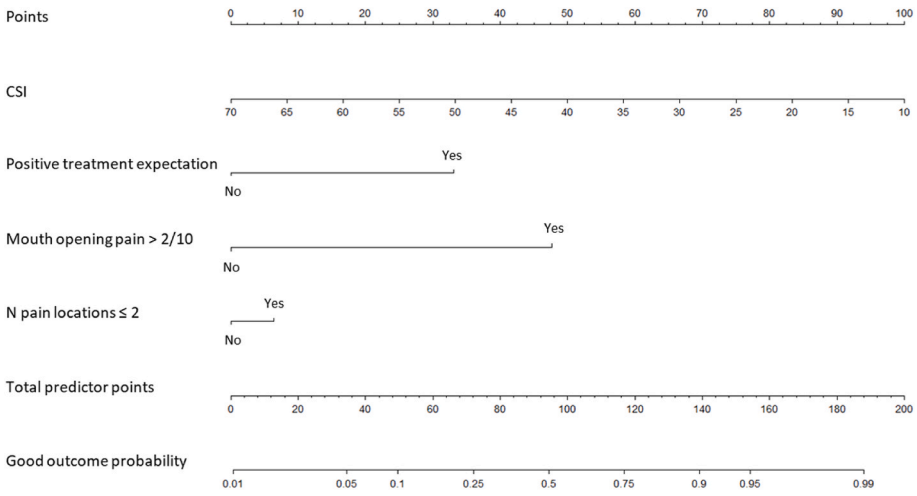

Fig. 3. The predictive nomogram for good probability of outcome in patients with temporomandibular pain after manual therapy developed from the logistic model. For example, a patient with 4/10 mouth opening pain would obtain 48 points for this predictor. This score is obtained by selecting the corresponding baseline value for the predictor and determining the corresponding points on the "Points" line at the top of the plot. The same procedure should be repeated for each predictor value by obtaining the related predictor points. To calculate the probability of good outcome, a vertical line is drawn from the "Total predictor points" line (at the value resulting from the sum of predictors' points) to the probability line at the bottom of the plot ("Good outcome probability").

mandibular vertical mobility negatively influences treatment outcome and predicts potential TMD pain persistence (Grossman et al., 2018; Meloto et al., 2019). However, those patients with TMD and limited mouth opening probably presented with a mechanical limitation (Shraim et al., 2021; von Piekartz et al., 2020), which benefits from MT given that manual therapy can improve range of motion (Bialosky et al., 2009).

Overall, the high performance of selected predictors to identify responders to the MTP could be explained by the mechanisms underpinning the experience of pain across the two groups, namely nociceptive versus nociplastic pain (Nijs et al., 2021). Those with poor outcome showed signs of nociplastic pain (e.g., duration of TMD pain >1 year, no signs of mechanical pain of the TMJ, widespread pain, and CSI score >40) (Nijs et al., 2021). In contrast those with a good outcome largely displayed signs of nociceptive pain (e.g., mechanical pain) (Shraim et al., 2021; Nijs et al., 2021). In accordance with current models of care (Hodges, 2019), our findings support the importance of recognising pain mechanisms to guide clinicians in the selection of the appropriate treatment. Specifically, MT appears as an appropriate treatment when the patient presents with the features identified as predictors of good outcomes which appear to define the presence of mechanical-based pain. Although it must be noted that we did not specifically screen for different pain mechanisms and did not assess the craniocervical or other regions and so this remains speculative.

Age and gender did not play any role in influencing treatment outcome even though they are significant factors in TMD incidence and prevalence (Lipton et al., 1993). Likewise, the level of education did not predict any treatment response. This aligns with findings from Artus et al. investigating prognostic factors for musculoskeletal pain, although there is some evidence that patients with lower levels of education could catastrophize about their pain (Roth and Geisser, 2002; Artus et al., 2017b). Although quality of life was not retained as a predictor of good pain outcome in the final model, the VAS score from the Health-related quality of life questionnaire was selected in the model with the best fit (not used because more prone to overfitting and lower calibration). This finding partially aligns with Kapos et al. (2018), who showed that a higher health-related quality of life predicted lower TMD pain intensity at an 8-year follow-up. Sleep quality was better in those with a good outcome, but the variable was not predictive even if it is known that chronic pain patients may suffer from poor sleep quality (Sayar et al., 2002). About 60% of the participants showed a mixed form of TMD (i.e. simultaneous presence of TMJ disorders and masticatory muscle disorders), approximately 20% showed TMJ disorders, and 20% showed masticatory muscle disorders. The TMD classification according to DC/TMD Taxonomy (Peck et al., 2014) did not predict good versus poor outcome. It should be noted that the MTP was performed based on clinical reasoning to select appropriate techniques. Consequently, participants with muscle and/or joint disorders were addressed with MT techniques targeting the impaired tissue.

In contrast with our expectations, the coping strategies measured with the CSQ-27 did not play any role in predicting outcome. This finding is not aligned with Forssell et al. (2017) who found that low capacity to manage pain raises the risk for TMD pain at one year regardless of the type of treatment. In other musculoskeletal pain conditions, coping strategies are weakly associated with poor prognosis (Artus et al., 2017b). Another variable that contrasted our expectation in terms of prediction ability was oral behavior measured with the OBC. Indeed there is moderate evidence supporting that parafunctional habits play a significant role in the development and persistence of TMD pain (Glaros et al., 2016; Ohrbach and Michelotti, 2018).

4.1. Methodological considerations

This was a single site study, which reduces the external validity and generalizability of the results. Although we performed an internal validation of the model by means of bootstrapping, the decrease in the overall performance might indicate the risk of overfitting and support the need to test the identified predictors in a new sample. Moreover, the design of the study (i.e., single-arm) cannot prove with certainty if the good outcome at the end of the four weeks of the MTP was the result of the applied intervention or the natural history of the condition. However, the selected predictors can help to rule out patients who will not benefit from manual therapy interventions. Secondly, the choice to exclude participants starting other treatments before (6 months) and during the study could have produced a selection bias resulting in a non-representative sample. For instance, we may have excluded participants with higher levels of pain who perhaps are more likely to have received other treatments. However, this choice was taken to ensure an adequate internal validity and to reduce possible confounding bias. Furthermore, even though predictors were selected based on existing studies examining prognostic factors for TMD and altered pain modulation in musculoskeletal disorders (Bair et al., 2016; Clark et al., 2017), other outcome measures may have been relevant. For instance, the presence of neck pain and headache was not considered. Another potential limitation is the lack of a pause between the last treatment and the reassessment of outcomes. It is possible that acute treatment effects influenced the follow-up measures. Nevertheless, this issue was mitigated by averaging three pain measures, with two measures related to pain experienced during the last week. The absence of a longer follow-up does not allow us to draw conclusions about pain and function in the longer term. The planned future study to validate this model will include a longer follow-up.

Notwithstanding, there are many strengths of this study. This is the first study to examine and identify predictors of pain reductoin and functional improvement in people with TMD following a MTP. The results will have important clinical implications once externally validated as they will provide guidance to clinicians managing people with TMD to ensure that the right treatment is chosen for the right patient. Importantly, the predictors identified are relatively simple to measure in a clinical setting. The developed nomogram is easy to complete and can be integrated easily into the initial clinical assessment. Following validation, a digital online version of the nomogram will be developed which will be made accessible so that it is easy to implement.

4.2. Covid-19 pandemic impact on study process and development

According to the study protocol (Asquini et al., 2019), 13 months were planned to complete participant recruitment but 23 months were required because of the COVID-19 pandemic. Secondly, about 12% of participants dropped out (9 out of the 12 participants due to COVID restrictions). The loss to follow-up rate would have been approximately 3% when not considering COVID-19 related dropouts and this is in line with previous comparable studies (Kalamir et al., 2013; Brochado et al., 2018). In order to detect the impact of COVID-19 on study participants, in June 2020, participants were asked to complete the COVID Stress Scales (CSS) (Taylor et al., 2020). Previous studies have examined the association between TMD and stress, showing that psychological distress is correlated with elevated TMD related pain and pain-related disability (Manfredini et al., 2010; Fillingim et al., 2013). However, from October 2020, we discontinued with the collection of the CSS for the following reasons: (1) The CSS is not validated in Italian, (2) the rotation of periods of complete restrictions to periods of no restriction could have influenced the results for different participants, (3) participants that started before the COVID-19 pandemic couldn't complete the CSS, (4) CSS does not sufficiently examine isolation distress; (5) the CSS was not included in the study protocol (Asquini et al., 2019).

5. Conclusion

This study identified four predictors of pain reduction and two predictors of functional improvement in patients with TMD following a MTP directed to craniomandibular structures. The results showed that

participants with a pain intensity greater than 2/10 during mouth opening, positive expectations of outcome following MT, pain localized in the craniocervical region and a low CSI score had significant pain reduction following the MTP. Participants with a shorter pain duration and limitations in MMO showed greater functional improvements. A preliminary screening clinical tool was developed and is presented as a nomogram. The high discrimination of the prediction model revealed promising findings although these need to be externally validated by future research.

Funding statement

Not supported by external funding.

Data sharing statement

Data are available on request.

Declaration of competing interest

There are no competing interests.

Acknowledgements

The authors acknowledge Nicola Heneghan and Alison Rushton for their earlier contribution to development of the study protocol.

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