Logistic Regression and Elastic Net Regularization for the Diagnosis of Fibromyalgia: A Quantitative approach using B-mode Ultrasound

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Abstract

Background: Fibromyalgia (FM) is a chronic widespread pain disorder characterized by widespread tenderness, psychological distress, fatigue, and sleep disturbance. The cause of FM continues to be unknown. Current methods of fibromyalgia (FM) diagnosis remains a challenge for clinicians due to a lack of objective diagnostic tools. One proposed solution is the use of quantitative ultrasound (US) techniques, such as image texture analysis, which has demonstrated discriminatory capabilities with other chronic pain conditions like Myofascial Pain Syndrome (MPS). We propose the use of US image texture variables to construct an elastic net regularized, logistic regression model, for differentiating between the trapezius muscle in the healthy and FM patients.

Methods: Ethical approval has been obtained from the University Health Network (UHN) Research Ethics Board. This proposed study is a diagnostic case-control study with one major independent binary outcome measure (FM present or Healthy), to create 2 patient cohort groups. Ultrasound imaging data will be collected from both cohorts and the image texture variables will be used to construct predictive logistic regression models.

Discussion**:** This will be the first study that assesses the discriminative capabilities of B-mode ultrasound image texture of healthy muscles and muscles with FM present. Findings from this study will allow further research into diagnostic modelling for FM.

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Keywords: Ultrasound, Imaging, Logistic, Regression, Fibromyalgia, Regularization

List of Abbreviations:

US: Ultrasound

FM: Fibromyalgia

MPS: Myofascial pain syndrome

MTrP: Myofascial trigger points

LASSO: Least absolute shrinkage and selection operator

Background

Fibromyalgia (FM) is a chronic widespread pain disorder characterized by widespread tenderness, psychological distress, fatigue, and sleep disturbance[1]. It has an estimated prevalence of 1.1-6.4% of the general population[2]. In the United States, greater disease burden has been reported in FM patients which involve poorer health status, function, sleep, lower productivity, pain-related medications, increased comorbidities and higher costs[3]. The cause of FM continues to be unknown. The current clinical method of diagnosis of FM is by applying the 2016 FM criteria[4,5]. These are subjective and do not require a physical examination. Therefore, subjectivity is present when diagnosing FM.

Another method to diagnose FM could be to create a diagnostic biomarker that is objective, reliable and based on the underlying pathophysiology. A biomarker is a characteristic that can be measured objectively to indicate the underlying pathophysiological process[6]. The FDA has identified that qualified biomarkers are one of the following: diagnostic, prognostic, predictive, and pharmacodynamic. "A diagnostic biomarker is a disease characteristic that categorizes a person by the presence or absence of a specific physiological or pathophysiological state or disease". Our study was designed to create a diagnostic biomarker that could be feasible for clinical utilization and assist in reducing subjectivity and heterogeneity when combined with the current clinical criteria[4].

From an imaging perspective, there is very little literature available. Magnetic resonance imaging of the muscles in FM patients have been studied in the past which did not show any significant abnormality[7]. Ultrasonography (US) has also been used to study the trigger points found on the outer aspect of the greater trochanter in FM patients[8]. Similarly, this study did not show any significant abnormalities in FM patients. However, the study was limited due to a

small sample size and the absence of a healthy control group. Currently, no study exists to compare FM patients and healthy controls using clinical findings and quantitative US.

Rationale for Utilization of Quantitative Ultrasound

There is evidence in the literature for altered nociception in patients with FM[9]. FM is also characterized by heightened pain sensitivity to sensory stimuli, possibly as a result of the changes in the central processing in the brain, referred to as central sensitization[1]. From a mechanistic perspective, the abnormal efferent activity could be reflected in the affected skeletal muscle. Our study objective is to explore this possibility using image texture feature analysis in B-mode US imaging. We believe that this may be possible since we have previously shown that texture features can not only discriminate between healthy controls and patients with neck pain but also between the two clinical phenotypes of Myofascial Pain Syndrome (MPS), namely groups that contain latent and active myofascial trigger points (MTrPs)[10]. Towards this, we propose to use the image texture features to construct a regularized logistic regression model in order to predict and discriminate between healthy controls and fibromyalgia affected muscle.

To summarize, our specific research questions are as follows:

a. Can a regularized logistic regression model, built on texture variables extracted from B-mode ultrasound images of the upper trapezius discriminate between healthy, and FM subjects? Our hypothesis is that the model should effectively differentiate the two cohorts due to our previous work/success with other chronic pain disorders (MPS).
b. How does regularization impact the overall performance of the trained model? Our hypothesis is that it should improve its generalizability.
c. Does the holdout, test data validate the predicted performance of the logistic regression model? Our hypothesis is that it will be within 1 standard error of the prediction mean.

Methods & Design

Study Design:

The study conforms to the Consolidated Standards of Reporting Trials recommendations. Ethical approval is approved by the University Health Network (UHN) Research Ethics Board. This study is registered under the National Institutes of Health ClinicalTrials.gov. This proposed study is a diagnostic case-control study with one major independent binary outcome measure (FM present or Healthy), to create 2 patient cohort groups.

Participants:

Recruitment

Study participants will be recruited from the MSK/pain specialty outpatient clinic at the Toronto Rehabilitation Institute. Toronto Rehabilitation institute is the largest rehabilitation hospital in Canada, owned and operated by the University Health Network (UHN). The recruitment procedures will run in line with the approved guidelines from the UHN research ethics boards. Informed consent was obtained from each participant. Participants will not be coerced into participating and will be informed that they have the right to withdraw at any time during the experimental procedures. They will also be informed they have the right to withdraw their data prior to publication. Participants will be briefed and consented on recruitment prior to commencing the study procedures.

Eligibility Criteria

A specialist in physical medicine and rehabilitation with 25 years of experience (Dinesh Kumbhare) will perform the standardized physical assessment on consecutive patients referred to the clinic. Female or male participants who meet the following inclusion criteria will be included in the study as FM participants: (1) chronic widespread pain, (2) fitting the 2016 FM criteria, (3)

absence of myofascial pain syndrome trigger points, (4) participants agree to sign a consent to volunteer for the research, and (5) between the ages of 20 and 65 years (44.3 ± 13.9 years). Age matched healthy controls with no past medical history were also collected.

Exclusion Criteria

Participants were excluded if they demonstrated clinical evidence of another cause for widespread pain, such as: (1) polymyositis, (2) dermatomyositis, (3) endocrine disorders, etc. Additionally, no participants will be recruited that have performed any physical exercise up to three days prior to entry into the study.

Experimental Protocol

Data Acquisition

The experimental protocol will be carried out in the MSK/pain specialty outpatient clinic at Toronto Rehabilitation Institute. Following the completion of the preliminary intake forms and participant debriefing, informed consent will be obtained. Each participant will be seated upright with their hands comfortably on their thighs in a chair that has a high supportive back. They will be asked to relax their neck and shoulder muscles. Dr. Kumbhare will then apply the inclusion and exclusion criteria to the patient and assess entry into the study. A research associate, blinded to the clinical status of the study participant, will collect the ultrasound images using a Sonosite X-porte ultrasound system (SonoSite Canada Inc. c/o Visualsonics, 3080 Yonge Street, Suite 6100, Toronto, Ontario M4N 3N1, Canada) at a depth of 3.0 cm or less and with a linear ultrasonic transducer of 6-15 MHz. The image settings such as depth, sector size, and time gain compensation (TGC), will be kept constant for all participants. The transducer will then be placed perpendicular on the upper trapezius muscle on each side, and its angle was adjusted to acquire the highest quality image. Ultrasound Gel will be used to coat the entire surface of the

transducer before it touched the skin surface. The location on the muscle will be standardized across study participants by being at the midpoint of the muscle belly between the C7 spinous process and the acromioclavicular joint. From that position, the transducer will be moved at a speed of approximately 1 cm/sec toward the acromioclavicular joint to obtain a 10-sec video. One video will be acquired from each side of the muscle group per participant.

Image Pre-processing

All images pre- and post-processing will be performed with MATLAB and the image processing toolbox[11]. Images will be visually and statistically inspected for quality based on image intensity, contrast, and ability to discriminate muscle fibers. This is necessary to maintain a high standard of imaging data quality, and suspect no more than 15% of the data should be removed due to constraints. Next, since we are analyzing ROI's in the muscle we must extract only a certain number of frames from each video series. We will achieve this using an image filtering method that has been previously used by our group called the CW-SSIM[12] filtering method[13]. It will be used to objectively calculate and extract image frames from each video series in order to obtain the maximal number of images, while still maintaining uniqueness (minimal image overlap). After this procedure is finished we will extract a rectangular ROI estimation of the upper trapezius muscle excluding the upper and lower fascial borders. Lastly, the images will be labelled and organized for further processing.

Feature Extraction

Texture variables will then be extracted from the image ROI's using MATLAB and the image processing toolbox. The features to be extracted are as follows:

1. First order histogram parameters associated with image grayscale. These include mean, standard deviation, skewness, and kurtosis.

2. Gray level co-occurrence matrices (GLCM)[14] will be calculated utilizing 4 directions (0,45,90,135 degrees). 76 variables are then created.
3. Lastly run-length parameters[15] will be determined by gray level run-length matrices based upon the four given directions. Averaging the directions together gives seven features.

In total 88 feature variables will be extracted from each ROI, providing a feature descriptor dataset.

Elastic Net Regularized Logistic Regression

We will then construct and train an elastic net regularized logistic regression model on the dataset using the binary class labels constructed earlier[16]. This will be done using MATLAB and the Statistics and Machine Learning Toolbox[17] and performed on a train/test split (80/20) of the original training data. The model will be regularized using the elastic net, which will improve the generalizability of the classification model on unseen data (avoid overfitting problems). The elastic net penalization method also provides a form of variable selection helping to minimize the effect of rank deficiency.

Model Validation

The model will be validated using 10-fold nested cross validation on the training data due to the fact the model needs hyper-parameter tuning alongside the validation process. This requires a nested procedure where the hyper-parameter tuning is done in an inner loop and the validation of the model is in an outer loop. This will allow for an optimized, trained model that should generalize well to unseen data. This generalization will be tested using the final holdout set and will either confirm or deny whether the constructed model is a good classifier for this task.

Results

After the methodology is applied to all training data, performance metrics can be extracted from the results to demonstrate the model efficacy. Performance metrics like sensitivity, specificity, area under the curve (AUC) and accuracy will be extracted in order to characterize the model performance. These metrics will be averaged across the 10-folds (mean + stdev), and these values will be compared to the final metrics extracted from the holdout test set. If the test set values fall within 1 stdev, it will confirm the accuracy of the performance estimation during the training.

Primary Outcome

The primary outcome measures:

1. Binary classifier discriminates effectively (>70 % accuracy) between the healthy and muscle with FM.
2. Impact of regularization on the model performance.
3. Holdout test validation of the predicted performance.

Discussion

The overarching goal of our research utilizing image texture features is to eventually provide diagnostic aid to clinicians through the usage of clinically feasible, objective and reliable quantitative ultrasound techniques. While computer aided diagnosis research in ultrasound has been heavily explored in areas such as cancer and liver diseases[18-20], there has been little to no work in chronic pain[13]. This is the basis for this project proposal utilizing logistic regression modeling with elastic net regularization; the objective is to develop a statistical model with good predictive and diagnostic capabilities.

We are using logistic regression as our classification model due to its efficiency, computational resource requirement, interpretability, input feature scaling invariance, and ease of regularization[21]. The fact that logistic regression intrinsically calculates the predictive probability is a major strength of the model, as other classification techniques require further computationally intensive cross-validation to achieve this.

Regularization is a specific technique that is often used as a remedy to solve overfitting in classification models for machine learning[22]. In a general sense, regularization techniques are used to reduce a model's predictive error on unseen data by minimizing model variance with a given training set by smoothing the predictions. This is done by constraining (regularizing) the regression coefficients towards zero which discourage overly complex (flexible) models. What must be noted is that regularization does not improve the performance of the model on the data it was trained on. More intuitively, regularization acts as a penalty against complexity and steers the model away from memorizing (overfitting) the dataset. For this protocol we are utilizing elastic net regularization (a well-known technique) to improve the performance against the unseen data.

Until now, the literature shows that the diagnosis of FM remains challenging, in part due to its non-specific symptoms, which overlap with many other disorders such as myofascial pain syndrome. Even though patients who present symptoms such as chronic widespread pain, emotional distress, cognitive and sleep disturbances may be formally diagnosed with FM, it is possible that their primary disorder is not FM and has an entirely different pathophysiological mechanism. This protocol should demonstrate the effectiveness of texture analysis techniques when differentiating between FM patients and healthy individuals. Post-image acquisition texture analyses may provide some insight into the pathophysiology underlying FM.

Limitations and Conclusions

Our study has limitations and one of them concerns the generalizability of our findings, since we are evaluating images of the upper trapezius for patients and healthy participants. The upper trapezius muscles may not be representative of the whole patient or the differences between patients who have varying symptomatology and areas of pain. Further research is needed to replicate our findings using muscle groups other than the upper trapezius. We plan to conduct these studies and to correlate our findings with the extent of central sensitization. Another potential limitation is the amount of healthy control recruits available. It is difficult to find participants that do not possess stiffness and myofascial trigger points in their upper trapezius muscle, even among seemingly healthy populations. We suspect this may limit our numbers for this group and fully expect to deal with an unbalanced dataset. There are many methods of compensating for this discrepancy during model construction, training and statistical analysis and will employ them as needed.

In conclusion this study should provide an effective, discriminatory classifier trained on B-mode ultrasound images that can differentiate between healthy muscle and muscle with FM in the upper trapezius. This is one more step in our overarching goal of providing increasingly objective diagnostic tools for clinicians when diagnosing chronic pain disorders.

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Declarations

Ethics approval and consent to participate:

Informed consent will be obtained from all subjects participating in this study. Ethical approval was approved by the University Health Network (UHN) Research Ethics Board (Approval

Number: 15-9488.8). The approval form is included in the supplementary files of this submission. This study is registered under the National Institutes of Health ClinicalTrials.gov.

Consent for publication:

Not applicable.

Availability of data and material:

The datasets used and/or analyzed during the study will be available from the corresponding author upon reasonable request.

Data Monitoring Committee

A DMC is not applicable for this study since it is not a multi-location study.

Trial Status:

Protocol version and date: Version 1, Sept. 10, 2019

Recruitment: Completed Sept. 6, 2019

Competing interests:

The authors declare that they have no competing interests.

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Authours' Contribution:

All authors (MB, SS,VE, DK) contributed to the study design; drafted, reviewed and finalized the study protocol; critically revised the manuscript and approved the final manuscript.

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