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FRACTIONAL ANISOTROPY IN DEGENERATIVE CERVICAL STENOSIS SURGERY PROGNOSTIC: A SYSTEMATIC REVIEW

ANISOTROPIA FRACIONADA NO PROGNÓSTICO DE CIRURGIA DE ESTENOSE CERVICAL DEGENERATIVA: REVISÃO SISTEMÁTICA

ANISOTROPÍA FRACCIONAL EN EL PRONÓSTICO DE CIRUGÍA DE LA ESTENOSIS CERVICAL DEGENERATIVA: REVISIÓN SISTEMÁTICA

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ABSTRACT

Cervical spondylotic myelopathy (CSM) is a common disease with an increased anticipated burden to health systems worldwide. Methods to predict outcomes in these patients are needed so physicians can provide more effective care. Fractional anisotropy (FA) analysis is a promising technique used to quantify how preserved the diffusion is in neural pathways. A systematic review and meta-analysis were performed using the PRISMA guidelines. Full articles available online were searched for correlation coefficients between FA values and mJOA scores. Average FA values, preoperative mJOA, and postoperative mJOA scores were gathered to perform a correlation analysis. A total of 5 articles presented correlations between FA and mJOA change and were included in the correlation meta-analysis. Correlation coefficients varied from -0.42 and 0.55. The number of patients in each study varied from 15 to 95. The Random effects model resulted in a non-significant correlation coefficient of 0.1315 (95% CI: -0.2575 to 0.4839; p= 0.5124). Spearman's correlation analysis was significant for preoperative vs postoperative mJOA (r = 0.79, p = 0.02), while preoperative FA did not correlate significantly with preoperative or postoperative mJOA. At this point, the data available in the literature is insufficient to determine a real correlation between FA and mJOA scores. More studies are necessary for a better understanding of this matter. ***Level of Evidence III; Study Review.***

Keywords: Anisotropy; Physicians; Neural Pathways; Diffusion.

RESUMO

A mielopatia espondilótica cervical (CSM, pelas suas siglas em inglês) é uma doença comum com elevados gastos para os sistemas de saúde em todo o mundo. Métodos para prever resultados nesses pacientes são necessários para que a atenção médica seja mais eficaz. A análise de anisotropia fracionada (FA) é uma técnica promissora usada para quantificar a preservação da difusão nas vias neurais. Uma revisão sistemática e meta-análise foi realizada usando as diretrizes PRISMA. Artigos completos disponíveis online foram avaliados em busca de coeficientes de correlação entre valores de FA e escores de mJOA. Valores médios de FA, escores de mJOA pré-operatórios e pós-operatórios foram coletados para realizar uma análise de correlação. Um total de 5 artigos apresentaram correlações entre alteração de FA e mJOA e foram incluídos na meta-análise de correlação. Os coeficientes de correlação variaram entre -0,42 e 0,55. O número de pacientes em cada estudo variou de 15 a 95. O modelo de efeitos aleatórios resultou em um coeficiente de correlação não significativo de 0,1315 (95% CI: -0,2575 a 0,4839; p= 0,5124). A análise de correlação de Spearman foi significativa para mJOA pré-operatório vs. pós-operatório (r = 0,79, p = 0,02), enquanto a FA pré-operatório não apresentou correlação significativa com o mJOA pré-operatório ou pós-operatório. Os dados disponíveis na literatura neste momento são insuficientes para determinar uma correlação real entre os escores FA e mJOA. Mais estudos são necessários para uma melhor compreensão deste assunto. ***Nível de Evidência III; Revisão de Estudos.***

Descritores: *Anisotropia; Médicos; Vias Neurais; Difusão.*

RESUMEN

La mielopatía cervical espondilótica (CSM, por sus siglas en inglés) es una enfermedad común con una mayor carga anticipada para los sistemas de salud en todo el mundo. Se necesitan métodos para predecir los resultados en estos pacientes para que los médicos puedan brindar una atención más eficaz. El análisis de anisotropía fraccional (FA) es una técnica prometedora que se utiliza para cuantificar cuán preservada está la difusión en las vías neurales. Se realizó una revisión sistemática y un metanálisis utilizando las pautas PRISMA. Se buscaron artículos completos disponibles en línea para encontrar coeficientes de correlación entre los valores de FA y las puntuaciones de mJOA. Se recopilaron los valores promedio de FA, mJOA preoperatorios y mJOA postoperatorios para realizar un análisis de correlación. Un total de 5 artículos presentaron correlaciones entre el cambio de FA y mJOA y se incluyeron en el metanálisis de correlación. Los coeficientes de correlación variaron entre -0,42 y 0,55. El número de pacientes en cada estudio varió de 15 a 95. El modelo de efectos aleatorios resultó en un coeficiente de correlación no significativo de 0,1315 (IC 95%: -0,2575 a 0,4839; p= 0,5124). El análisis de correlación de Spearman

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fue significativo para la mJOA preoperatoria frente a la posoperatoria (r = 0,79, p = 0,02), mientras que la FA preoperatoria no presentó una correlación significativa con la mJOA preoperatoria o posoperatoria. Los datos disponibles en la literatura en este momento son insuficientes para determinar una correlación real entre las puntuaciones de FA y mJOA. Son necesarios más estudios para una mejor comprensión de este asunto. ***Nivel de Evidencia III; Revisión de Estudios.***

Descriptores: *Anisotropía; Médicos; Vías Nerviosas; Difusión.*

INTRODUCTION

Cervical spondylotic myelopathy (CSM) is a common disease affecting around two-thirds of people at one point in life.[1] The surgical burden of this disease is also relevant, with studies reporting surgical treatment incidence of 1.6 cases per 100,000 people for £681.6 million per year.[2,3]

Diffusion Tensor Imaging (DTI) is an MRI acquisition modality that measures the direction of water molecules' diffusion inside tissues.[4] The diffusivity is mostly limited by myelin sheets in neural tissues, which allows for evaluation of the integrity of these pathways. In functional tracts, there are high diffusion gradients parallel to the nervous fibers and low diffusion gradients perpendicular to those fibers.[5,6] One of the most used variables is Fractional Anisotropy (FA), which measures the degree of preferred diffusion in a specific direction.[7-9]

The relevance of DTI as a prognostic tool has been questioned in the literature.[9] Ellingson et al. applied a combination of DTI variables and MRI measurements to produce a model to predict mJOA scores in a sample of pre-surgical cervical spondylotic patients.[10] The authors identified that FA is correlated to mJOA scores. Dong et al. identified that higher preoperative FA scores are more likely to achieve better scores in motor function after decompression.[11]

Therefore, we aim to gather the available data to understand better the correlations between FA and mJOA scale in CSM patients.

MATERIALS AND METHODS

Literature review

We performed a systematic literature review on studies reporting the prognostic value of DTI measures for surgery in CSM patients. The guidelines for PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) were followed. MEDLINE, Embase, Google Scholar, and Web of Science databases were investigated for studies presenting data on FA and mJOA scores before and after surgery. The following search terms were applied on March 21st, 2023: (Cervical spondylotic myelopathy OR Cervical stenosis) AND (DTI OR Diffusion tensor imaging OR fractional anisotropy OR Mean diffusivity) AND (surgery).

Research Question

We applied the PICO strategy to develop a research question. The aim was to apply pre-surgical FA as a prognostic tool in patients with CSM. More favorable outcomes were hypothesized as more likely for patients with better FA scores.

Eligibility criteria and selection of studies

We included prospective and retrospective studies in English. Two authors evaluated the titles and abstracts of studies (L.C.P.P. and R.A.C.) to eliminate those irrelevant to the study's objectives. A third author (E.R.N.) was responsible for settling disagreements in data evaluation between the authors. Only studies with the most contemporary cohorts were considered in cases with duplicates. The studies included in the analysis were evaluated using the Newcastle-Ottawa scale for quality control.

Studies with at least three patients with CMS presented pre-operatory FA data with correlations with changes in mJOA scores. Studies presenting preoperative-postoperative mJOA difference or preoperative-postoperative mJOA ratio were included. A clinical follow-up of patients for a minimum period of 3 months was required. Studies that did not present mJOA change correlation to FA but presented absolute values were included for a correlation of averages.

Outcomes

The primary outcome was the correlation between pre-operatory FA scores and mJOA variation. The secondary outcomes were average values of pre-operatory FA, pre-operatory mJOA, and post-operatory mJOA scores. All studies were examined, and the variables were extracted to obtain the total number of patients in every category for each study.

Statistical analysis

A meta-analysis of correlations was performed as described in previous methodological studies.[12,13] The correlations were transformed using Fisher's z transformation of correlations.[14] A random effects model was applied to obtain better control for inter-study variability. A restricted maximum likelihood was used as an estimator for tau^2.[14,15] A funnel plot was obtained from the dispersion of Fisher's Z values and standard errors for better visualization of publication bias influence.

When available, average values of FA, pre-op mJOA, and post-op mJOA were used to produce a correlation curve of the averages.[16] The Spearman's rank correlation coefficient was applied. This method has known limitations and was implemented only for illustrative purposes.

The Software R Studio (Version 2023.03.0+386) and the meta package (version 5.2-0) were used for the analysis.

Ethical aspects

The project did not present any patient exposure or patient information to risks. It was carried out through a restricted analysis of the literature.

RESULTS

A total of 447 unique publications were found using the search term. The diagram for study inclusion is demonstrated in Figure 1.

A total of 5 articles presented correlations between FA and mJOA change and were included in the correlation meta-analysis. Correlation coefficients varied from -0.42 and 0.55. The number of patients in each study varied from 15 to 95. The summary of data is presented in Table 1.

The correlation meta-analysis produced a non-significant correlation coefficient of 0.1315 (95% CI: -0.2575 to 0.4839; p= 0.5124). The detailed data is exposed in Table 2 and Figure 2. The funnel plot, used to evaluate publication bias, is shown in Figure 3.

Studies presenting values for pre-operative FA, pre-operative mJOA and post-operative mJOA were analyzed for average correlations as performed in previous studies.[16] The data is presented in Table 3. Pre-operative FA averages varied from 0.44 to 0.59, while pre-operative mJOA averages varied from 8.55 to 13.7 and post-operative mJOA from 9.65 to 15.43. The correlation curves are exhibited in Figures 4-6. Pre-operative mJOA averages presented a statistically significant correlation with post-operative mJOA averages (R = 0.79, p = 0.02). The other correlations presented were not significant.

DISCUSSION

The increasing incidence of CSM in the aging population is expected to be responsible for a significant rise in healthcare costs.[3] Many of these patients demand complex surgeries and long in-hospital periods. Therefore, prognostic prediction is crucial to plan care strategies better. To our knowledge, this is the first quantitative

analysis of data on the correlation between FA and mJOA score change after surgery.

Several studies have tried to use MRI-derived variables, such as DTI, as prognostic tools.[17-19] Most studies present associations between FA and an outcome scale, such as the mJOA scale. FA is the most common DTI parameter used in CSM studies.[20] The mJOA scale presents scores from 0 to 18 points, with higher scores given to more functional patients.[21,22] Theoretically, a higher FA value should be associated with healthier neural tracts and could be associated with better outcomes.[17,18] Therefore, it should be expected that healthier tracts would correlate to higher mJOA scores and more functional patients. However, some studies propose that patients with worse FA and mJOA values are expected to be able to improve more when compared to their basal levels.[23] Our study found no common trend in literature at this point. Some studies present a negative correlation between preoperative FA and change in mJOA, suggesting that worse FA values could predict increased relative gains. In contrast, others correlate positively, suggesting that patients with higher FA values improve more. (Table 1, Figure 2)

Predicting outcomes is critical in treatment decisions and expectation management for patients, families, and physicians. This article adds to the literature that no definitive decision can be taken from preoperative FA values. Several other variables have better evidence support as potential predictors of outcomes in patients with CSM. Among them are age, cervical mobility, gender, weight/body mass index, smoking, diabetes, hypertension, MRI abnormalities, and preoperative mJOA scale.[24-26] A recent study found that age and pre-operative mJOA were independent predictors of outcome.[24] Those variables should be carefully controlled in future studies on the topic.

Recent advances in artificial intelligence have been used to produce a model that can help predict prognosis for CSM patients.[27] The association between FA and mJOA scores might be more complex, and therefore, a more sophisticated model could help determine the real association between these variables. However, it must be noted that the studies examined in this analysis were mostly small case series and presented significant heterogeneity due to different populations and study protocols.

It is known that patients with worse preoperative mJOA scores have worse recoveries.[28,29] Our correlation of averages helped to illustrate this already-known trend. Even after applying average study values, the correlation is still statistically significant. (Figure 6)

However, one of the challenges in dealing with these CSM patients is to detect those patients that will present a good recovery despite poor preoperative mJOA. Also, it is crucial to identify patients who will not have a satisfactory recovery despite presenting good mJOA scores. The answer to these questions is still unanswered in the literature.

The limitations of our study include those for review articles. Nakamura et al. have reported on the difficulty of obtaining FA values in cervical stenosis cases.[30] This difficulty can be accounted for by some of the heterogeneity in the results. A way around this problem might be the selection of regions of interest far from the compression levels. Some trauma studies have reported on the applicability of internal capsule DTI as an alternative.[20,31]

The small number of articles included is also a limitation and a statement of the heterogeneity in methodologies for the studies. The correlation analysis should be done with complete raw data instead of averages from studies. However, not having the original data, this method allows data organization to make new hypotheses for new studies. The objective of the correlations is not to draw conclusions but to raise questions.

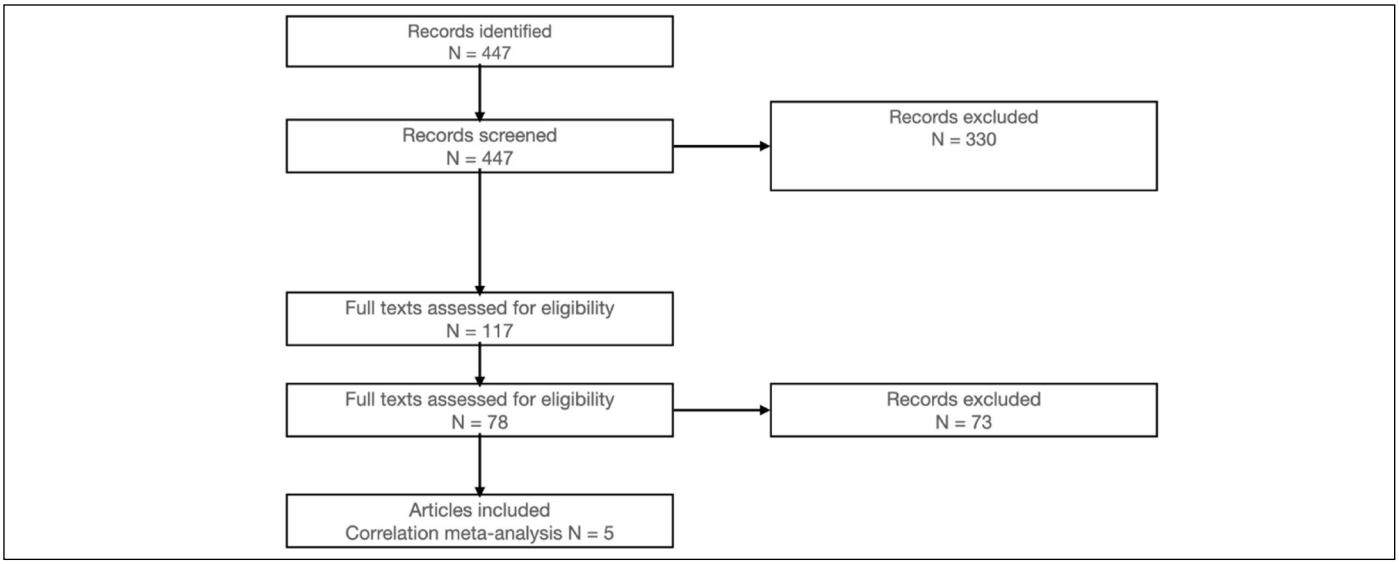

Figure 1. Search algorithm.

Table 1. General data on the articles presented a correlation between pre-op FA values and mJOA change.

Author-Year	Year	Title	N-patients	Correlation preop FA -mJOA change post-op	Type of correlation
Tian, 2021[32]	2021	Correlations between preoperative diffusion tensor imaging and surgical outcome in patients with cervical spondylotic myelopathy	95	0.353	mJOA recovery rate
Kitamura, 2020[18]	2020	Longitudinal diffusion tensor imaging of patients with degenerative cervical myelopathy following decompression surgery	15	0.55	mJOA difference
Rao, 2018[23]	2018	Diffusion Tensor Imaging in a Large Longitudinal Series of Patients With Cervical Spondylotic Myelopathy Correlated With Long-Term Functional Outcome	44	-0.2435	mJOA difference
Maki, 2017[17]	2017	Diffusion tensor imaging can predict surgical outcomes of patients with cervical compression myelopathy	26	0.42	mJOA difference
Vedantam, 2016[33]	2016	Diffusion Tensor Imaging Correlates with Short-Term Myelopathy Outcome in Patients with Cervical Spondylotic Myelopathy	27	-0.42	mJOA difference

Table 2. Correlation meta-analysis data.

	Correlation	95% Confidence interval	p-value	Tau^2	Tau^2 CI
Random effects model	0.1315	[-0.2575; 0.4839]	0.5124	0.1658	[0.0355; 1.7433]

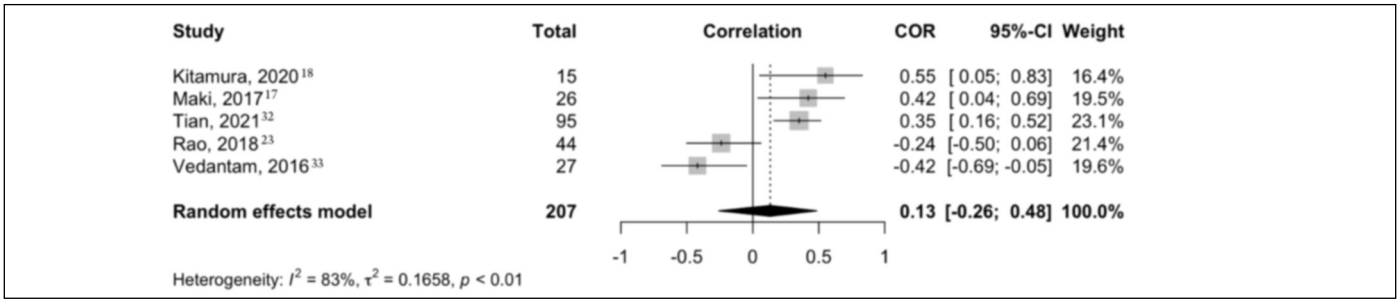

Figure 2. Forest plot for the correlation meta-analysis.

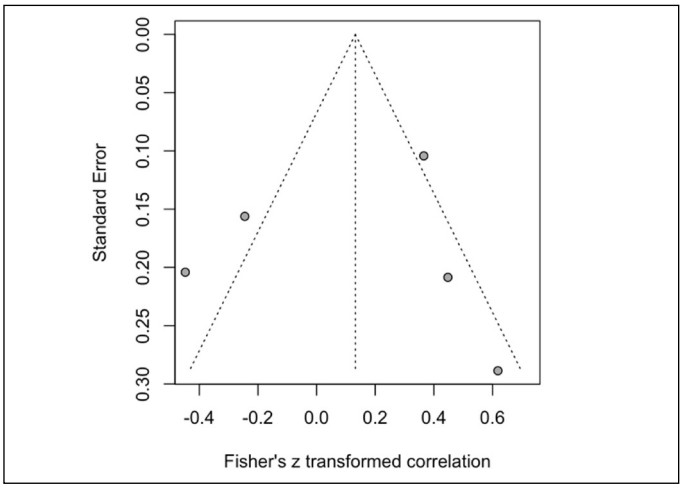

Figure 3. Funnel plot presenting a symmetrical distribution of studies.

Table 3. FA, pre-op mJOA, and post-op mJOA data.

Author	N	pre- op FA	pre-op mJOA	post-op mJOA
Tian, 2021 Group 1 [32]	47	0.57	10.52	14.37
Tian, 2021 Group 2 [32]	48	0.46	8.55	9.65
Zhang, 2020 [19]	36	0.44	11.98	15.43
Kitamura, 2020 [18]	15	0.56	8.87	12.30
Iwasaki, 2019 [34]	28	0.57	10.80	14.30
Maki, 2017 [17]	26	0.59	9.10	12.13
Vendatam, 2016 [33]	27	0.50	13.70	14.70
Dong, 2018 [11]	60	0.55	10.61	15.43

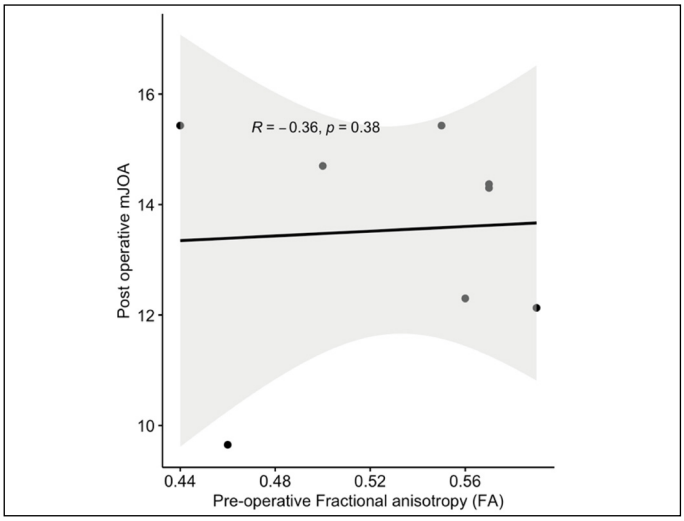

Figure 4. Pre-operative FA averages correlate to post-operative mJOA averages. R=-0.36, p=0.38.

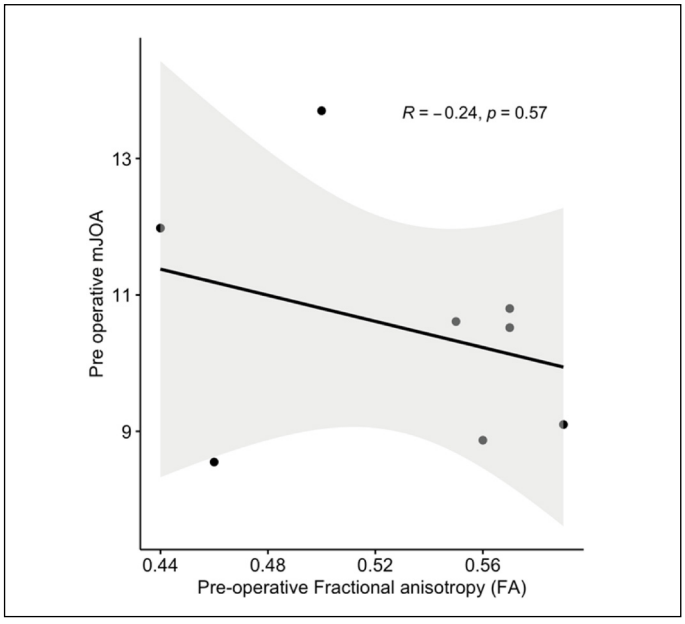

Figure 5. Pre operative FA averages correlation to pre-operative mJOA averages. R = -0.24, p = 0.57.

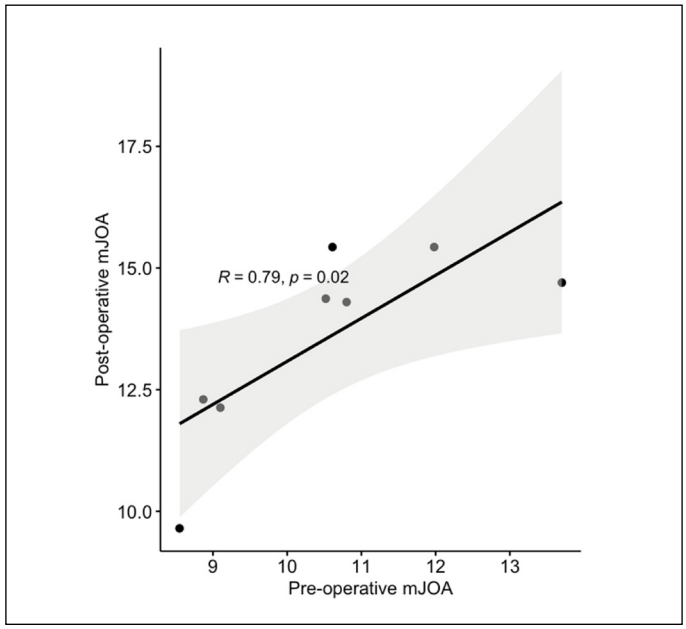

Figure 6. Pre-operative mJOA averages correlation to post-operative mJOA averages. R = 0.79, p = 0.02.

CONCLUSION

The associations between FA and post-operative prognosis are conflicting. Some studies present a statistically significant positive correlation, while others present a statistically significant negative correlation. At this point, no clear association can be drawn. More standardized studies and new methodologies are needed to understand this association better.

All authors declare no potential conflict of interest related to this article.

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