The combination of T2-mapping value of lacrimal gland and clinical indicators can improve the stage prediction of Graves' ophthalmopathy compared to clinical activity scores

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Research Article

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Abstract

Purpose

To explore radiological changes of the lacrimal gland (LG) in Graves' ophthalmopathy (GO) and whether a combination of MRI parameters and clinical indicators can better predict individual clinical manifestation of GO compared to clinical activity scores (CAS) assessment.

Methods

A total of 28 patients with GO (56 eyes) were enrolled between July 2020 and July 2021. Patients were classified into either the active GO group (CAS ≥ 3) and the inactive GO group (CAS < 3). MRI data and clinical data of LG were collected. The diagnostic performance of MRI parameters and models was assessed by receiver operating characteristic curve analysis. Logistic regression predictive models for staging GO were compared.

Results

There were statistically significant differences in T2-mapping values ($p < 0.001$), the proportion of mild or no obvious redness of conjunctival ($p < 0.001$), and the proportion of swelling of caruncle or plica ($p < 0.001$) between inactive and active groups. In MRI based logistic regression model, the T2-mapping value was an independent risk factor (AUC = 0.832). When combining MRI and clinical indicators, T2-mapping value and age resulted as independent risk factors (AUC = 0.928). Swelling of eyelids, redness of conjunctiva, swelling of conjunctiva, swelling of caruncle or plica, and spontaneous retrobulbar pain can be replaced by other objective indicators (AUC = 0.937, 0.852, 0.876, 0.896, and 0.891, respectively).

Conclusion

The combination of the T2-mapping value of LG and clinical indicators can improve the stage prediction of Graves' ophthalmopathy compared to CAS and provide a new idea for improving the objectification level of GO data collection.

Introduction

Graves' ophthalmopathy (GO) is the most common extrathyroidal manifestation of Graves' disease (GD), which can involve the retro-ocular tissue [1] and significantly affect the quality of life [2, 3]. GO has a biphasic process; it first presents as an active phase characterized by orbital inflammation and then as an inactive phase characterized by fibrosis [4]. Clinical management of GO is a challenging process. The exact GO staging is critical for deciding the best treatment option [5].

The clinical activity score (CAS) is widely used to evaluate the activity of GO (assessing inflammatory signs and symptoms) and to predict the response to treatment [5]. CAS assessment is based on 7 indicators,

including spontaneous retrobulbar pain, pain on attempted upward or downward gaze, redness of eyelids, redness of conjunctiva, swelling of caruncle or plica, swelling of eyelids, and swelling of the conjunctiva. If three or more indicators result positive, the disease is regarded to be in an active stage. CAS is a clear standard that is convenient to use, and has strong clinical applicability as a two-category result corresponding to completely different clinical interventions. However, as the evaluation criterion for the active stage requires that any three or more conditions are met, there is often no direct comparison of clinical manifestations between patients in the same active stage, which also leads to the unreliable direct head-to-head comparison between different studies. This reduces the heavy reliance on specific evaluators within the research team and increases the difficulty of data audit, which objectively weakens the credibility of the research. In addition, information fragmentation greatly reduces the value of the content pooling research, thus reducing the feasibility of researchers to make further calculations and draw conclusions based on the conclusions of others.

Another problem with CAS for clinical staging of GO patients is that each indicator is derived from the subjective judgment of evaluators rather than standardized, unified standards or scale-consistent measurements. This adds significant training costs to multi-center clinical studies, as qualified, standardized CAS evaluators require a certain amount of evaluation experience. In general clinical studies, independent evaluation committees are often set up for subjects requiring subjective judgment, and only large centers may have sufficient evaluators other than investigators with the above CAS evaluation capabilities. This undoubtedly reduces the possibility for more centers to participate in clinical research and thus limits the ability of relevant research results to be generalized. In addition, although the appearance of many items of CAS can be recorded by photos on the spot, the re-evaluation based on photo results often fails to reach satisfactory results (e.g., factors such as light, angle, and fixation of subjects' non-relaxed eye position caused by taking photos).

Recent studies suggested that clinical scores should be integrated by imaging modalities. Previous studies suggested that expanded extraocular muscles and orbital fat tissues observed on the MRI may accurately detect GO staging. However, some CT and MRI studies also suggested that a direct lacrimal gland (LG) involvement leading to a decrease in tear secretion with an LG volume is higher in patients with GO than in healthy controls [6–8]. Thus, whether the morphology and MRI parameters of LG can improve the staging assessment in GO remains debatable [9, 10]. Moreover, most of the MRI parameters are either semi-quantitative or based on signal intensity, which is not directly proportional to specific tissue properties.

T2-mapping, also known as the T2 relaxation time map, is a quantitative analysis technique that can measure the T2 value of tissues and reflect changes in extracellular fluid and collagen content [11]. T2-mapping can improve reproducibility, repeatability, and performances of radiomics compared to conventional T2-weighted imaging (T2WI) and has been widely used in the study of articular cartilage and myocardium [12]. Moreover, T2-mapping technology has high orbital tissue resolution and signal-to-noise ratio (SNR) and is not easy to produce sensitive magnetic artifacts, laying a foundation for the accurate evaluation of GO ocular tissue changes [12].

In this study, we combined clinical data and MRI quantitative measurements (ADC value, T2 value, and dynamic contrast-enhanced [DCE] MRI parameters) of LG to predict GO staging. We also investigate whether

the above MRI parameters and clinical indicators can predict individual clinical manifestation in CAS.

Materials And Methods

Patients

We enrolled consecutive 28 patients (10 men, 18 women; mean age 48.32 ± 12.19) with GO (56 eyes) from July 2020 to July 2021. GO was diagnosed according to Bartley's diagnostic criteria [13]. Clinical data, which were collected on the first visit, included sex, age, history of treatment, interorbital distance, proptosis, MRD-1, MRD-2, CAS indicators (spontaneous retrobulbar pain, pain on attempted upward or downward gaze, redness of eyelids, redness of conjunctiva, swelling of caruncle or plica, swelling of eyelids, swelling of conjunctiva), corneal injury, diplopia, restricted eye movement and smoking index. Clinical data and imaging parameters ae recorded in Table 1. The GO activity was measured by CAS [14], with a CAS ≥ 3/7 representing active GO. The patients were classified into either the active GO group (CAS ≥ 3) and the inactive GO group (CAS < 3). All ocular changes were graded in accordance with CAS. Patients with other orbit diseases, such as trauma, optic neuropathy, other inflammatory diseases of unknown origin, and with contraindications for MRI were excluded from the study.

Table 1
Clinical and MRI data of lacrimal gland between active and inactive groups

Variables	Inactive Group (n = 24)	Active Group (n = 32)	P-value
1.Sex (F/M)	17/7	19/13	0.376
2.Age	44.04 ± 11.90	51.53 ± 11.35	0.02*
3.K^{trans} (10^{-3}/min)	169.91 ± 89.50	163.53 ± 73.21	0.77
4.Kep (10^{-3}/min)	177.30 ± 137.16	159.08 ± 117.36	0.595
5.Ve (10^{-3})	980.16[480.73, 1313.54]	919.25[666.34,1651.18]	0.492
6.Vp (10^{-3})	0.07[0.00, 5.68]	0.67[0.00, 4.99]	0.986
7.IAUC (mM*s)	133.94[96.29, 196.34]	143.90[104.54, 200.00]	0.908
8.ADC Value (mm^2/s)	1.06 ± 0.12	1.10 ± 0.18	0.416
9.T2 Value (ms)	66.38 ± 6.16	78.10 ± 12.11	< 0.001*
10.History of treatment(%)	9[37.5, untreated]	19[59.4, untreated]	0.21
	3[12.5, I^{131}]	3[9.4, I^{131}]	
	10[41.7, hormone]	10[31.2, hormone]	
	2[8.3, radiotherapy]	0[0.0, radiotherapy]	
11.Interorbital distance	99.83 ± 3.95	100.81 ± 4.66	0.411
12.Proptosis	17.71 ± 2.77	19.56 ± 3.11	0.025
13.MRD-1	4.46 ± 1.18	4.09 ± 1.17	0.256
14.MRD-2	4.71 ± 1.30	5.12 ± 1.22	0.224
15. Diplopia (%)	14[58.3, N]	12[37.5, N]	0.009*
	10[41.7, Y]	20[62.5, Y]	
16.Restricted eye movement(%)	12[50.0, N]	17[53.1, N]	0.166
	12[50.0, Y]	15[46.9, Y]	
17. Smoking index(%)	20[83.3, N]	22[68.8, N]	0.35
	4[16.7, Y]	20[31.2, Y]	

Abbreviations: K^{trans} the rate constant for transfer of contrast agent from plasma to extravascular, extracellular space (EES); *Kep* the rate constant for transfer of contrast agent from EES to plasma; *Ve* contrast agent distribution volume, EES volume fraction; *IAUC* initial Area Under the Curve; *ADC* apparent diffusion coefficient; *MRD* margin reflex distance; *Y* yes; *N* no.

This study was approved by the Ethics Committee of Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine. (number: SH9H-2021-T246-1).

MRI examination

Examinations were performed on a 3.0-T MRI system (Ingenia CX, Philips Medical Systems) with a 32-channel brain coil. DCE-MRI was conducted with T1 high-resolution insotropic volume examination after intravenous administration of gadopentetate dimeglumine (Gd-DTPA)(Magnevist, Bayer Schering Pharma AG, dosage of 0.1 mmol/kg at the injection rate of 4 mL/s). The DCE-MRI scan was repeated sixty times (4.8 s for each scanning time) on the coronal plane, with a total scanning time of 290 s. During diffusion weight imaging (DWI), Turbo Spin-Echo (TSE)-DWI sequence was used to collect images with *b* values of 0 s/mm^2 and 1000 s/mm^2. T2-mapping data were obtained using a multi-spin-echo sequence. The acquisition parameters of the sequences are shown in Table 2.

Table 2
Parameters of MRI sequences

Sequence	Plane	TR	TE	Thickness/gap	Matrix	Fov	NSA	FA
DCE MRI	Coronal	10	1.97	3/0	168×118	220×179	1	8
DWI	Coronal	3000	54	3/1	124×89	124×89	1	90
T2-mapping	Coronal	1236	20,40,60,80,100	3.5/0.35	136×140	120×160	1	90

Abbreviations: TR repetition time; *TE* echo time; *FOV* field of view; *NSA* number of signal averages; *FA* flip angle; *DCE-MRI* dynamic contrast-enhanced MRI; *DWI* diffusion-weighted imaging

MRI data were separately evaluated by two experienced head and neck radiologists (more than 10 years of experience in radiology) who were blinded to the clinical information. Image post-processing and data measurement were carried out at Philips Workstation IntelliSpacePortal (Version 9.0). The freehand region of interest (ROI) was drawn on the largest coronal section of the LG, and the ROI covered the largest possible area of LG (Fig. 1). The detailed apparent diffusion coefficient (ADC) value, T2 value, and DCE parameters (K^{trans}, Kep, Ve, Vp, IAUC) were also recorded.

Statistical analysis

The statistical tools used in this study were Graphpad Prism 7.0 and R software package. Multivariate Logistic regression was used to construct a multivariate regression model, in which each judgment factor of subject staging and CAS were taken as a dependent variable, and possible influencing factors (including MRI parameters, ophthalmic clinical records indexes, and demographic indexes) were taken as independent variables. A multi-factor regression model was constructed to find the possibility and method of substituting the CAS judgment factors for objectification, as well as the main factors affecting disease staging. The

diagnostic performance of the model was evaluated by the area under the curve (AUC) of the subject operating characteristic curve. A P value < 0.05 was considered to be statistically significant.

Results

There were statistically significant differences in T2-mapping values ($p < 0.001$), the proportion of mild or no obvious redness of conjunctival ($p < 0.001$), and the proportion of swelling of caruncle or plica ($p < 0.001$) between inactive and active groups. Patient clinical data and MRI quantitative measurements of LG (Model I, variables in Table 1, 1–9 items) were useful in predicting the phases of GO (AUC = 0.832); the valuable variables were sex and T2 values (Table 3). Compared with Model I, objective eye manifestations (Model II, variables in Table 1, 1–17 items) were added to establish Model II (AUC = 0.928); age, ADC value, T2 value, history of treatment, interorbital distance, MRD-1, and MRD-2 showed ideal practical utility for staging GO (Fig. 2).

Table 3
Logistic regression analysis of Clinical and MRI data of lacrimal gland for predicting active GO

Term	estimate	std. error	statistic	p. value
(Intercept)	-12.196	3.618	-3.371	0.001*
Sex (male)	1.280	0.718	1.783	0.075
T2 Value	0.170	0.051	3.337	0.001*

Clinical data and MRI quantitative measurements of LG were established (Model III, variables in Table 1, 1–17 items) for predicting each CAS index with the aim to find a method to evaluate each CAS index by objective items. We found that swelling of eyelids (AUC = 0.937), redness of conjunctiva (AUC = 0.852), swelling of the conjunctiva (AUC = 0.876), Swelling of caruncle or plica (AUC = 0.895), and Spontaneous retrobulbar pain (AUC = 0.89) could be predicted and replaced by MRI parameters and clinical indicators (Fig. 3 and Table 4).

Table 4
The regression model of eyelid swelling judgment was replaced by objective indicators (e.g., eyelid swelling)

Term	estimate	std. error	statistic	p-value
(Intercept)	-13.157	7.892	-1.667	0.096
Age	0.081	0.046	1.766	0.077
T2 Value	0.171	0.115	1.480	0.139
Relevel (History of treatment, "untreated")I^{131}	-1.513	1.306	-1.159	0.247
Relevel (History of treatment, " untreated ") hormone	19.330	3367.035	0.006	0.995
Relevel (History of treatment, " untreated ") radiotherapy	17.299	12005.625	0.001	0.999

Discussion

GO is an autoimmune inflammatory disease of the orbit. Early diagnosis of the orbital tissues (active or inactive phase) is critical in deciding the best treatment option [15].

Previous radiological studies of GO were mainly concentrated on extraocular muscles. However, the LG is one of the most prevalently involved peripheral organs in GO [16, 17]. Go patients usually present with ocular discomforts, such as abnormal tear secretion [18]. Some studies have indicated that oxidative stress markers, cytokines, and growth factors are elevated in GO patients' tear fluid and positively correlated with CAS [19–21]. Although a few imaging studies in recent years have shown that LG herniation and MRI quantitative parameters were related to GO activity, the accuracy of predicting GO activity may be further improved. The aim of this study was to establish and validate a new prediction model based on MRI quantitative parameters and objective clinical manifestations for predicting the GO stage.

T2-mapping is a kind of multi-echo spin-echo pulse sequence. By drawing ROI, the T2 value could be acquired by quantifying water content and collagen tissue [22]. Some studies have shown that the T2 value is valuable in the early evaluation of cartilage degeneration and myocardial disease [23, 24]. Moreover, the T2 value of LG is a good indicator for GO staging [10]. In our study, the T2 value of LG (especially in model I and II) resulted as the best predictor for GO staging. Furthermore, the T2 value of LG in the GO active phase was significantly higher than that in the inactive phase, reflecting inflammatory edema of LG.

DWI is a functional MRI technique that is increasingly applied in GO staging, therapeutic evaluation, and prognostic estimation [10, 25]. The DWI signal reflects the degree of diffusivity of water molecules. Also, ADC value provides quantified information on physiologic tissue characteristics. Compared to traditional Echo-Planar Imaging (EPI) DWI, Turbo Spin-Echo (TSE) DWI could provide distortion-free images with a similar signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR) [26]. Therefore, in this study, the coronal TSE DWI sequence was adopted to enable the bilateral LG to be clearly displayed, and the ROI can be accurately delineated on the ADC map. No significant statistical difference was found in ADC values of LG between the active and inactive groups, which was inconsistent with some previous studies [10]. Further research is needed to determine whether the result is related to sample size, machine model, or B values.

DCE-MRI quantitative parameters were calculated based on the extended Tofts model, which reflects the microcirculation and hemodynamics of the tissue [27]. K^{trans}, Kep, Ve, Vp, and IAUC did not show statistical differences between the active and inactive groups, nor did they result as valuable variables in Model I and II. In a previous report on DCE-MRI of LG, only K^{trans} and Kep were significantly different between the two groups [10]. Although LG size and herniation have been reported to be useful for staging GO, regrettably, no significant differences between the inactive and active phases were found in our study regarding the internal microcirculation of LG.

In this study, we combined sex, age, and objective clinical data with imaging parameters. We found that in Model I (that included patient age, sex, and imaging parameters), sex was a good independent predictor. A previous study suggested that an active GO phase is often seen in male patients compared to females [15]. It is speculated that this may be due to the high proportion of smoking among male subjects [15]. It has been

documented that GO tends to be more severe in men, and smoking is the most important modifiable risk factor for GO [4]. Yet, the mechanism by which smoking adversely affects GO is unclear. Oxygen-free radical generation, enhanced production of cytokines, hypoxia in orbit, and stimulation of adipogenesis have all been associated with smoking [4].

In Model II, age, history of treatment, interorbital distance, MRD-1, and MRD-2 all showed all good value in predicting the GO stage. A previous study found that the mean age of patients with moderate to severe GO was significantly higher than that of patients with mild GO, thus suggesting that age is a relevant factor affecting the severity of GO [28]. In our case, the average age of the GO active group was significantly higher than that of the inactive group, which was consistent with previous studies. It is not difficult to understand that moderate to severe GO is usually in the active stage, and CAS is higher than that of the inactive stage, active stage is more common in the elderly. Moreover, most of patients who received the treatment of I^{123}, corticosteroids, or radiotherapy were sensitive to treatment and in the inactive phase at the time of visit, while most of the untreated patients were still in the active phase at the time of visit. Additionally, the accurate measurement and evaluation of interorbital distance, MRD1, and MRD-2, were conducive to staging GO. The AUC of Model II was 0.928, and that of Model I was 0.832. Thus, it was concluded that patient demographics and MRI parameters were not sufficient for GO staging prediction, and ophthalmic clinical indicators measured by ophthalmologists could be used to better establish the model.

Although CAS itself is an exact value, the 7 CAS indicators are obtained using the subjective judgment of evaluators. In this study, we investigated new methods to evaluate the objective items (clinical and imaging data) of each CAS indicator. Among the newly added variables in Model II compared to Model I, we found that swelling of eyelids, redness of the conjunctiva, swelling of the conjunctiva, swelling of caruncle or plica, and spontaneous retrobulbar pain in CAS could be predicted by demographics, objective ocular manifestations, and quantitative MRI measurements of the lacrimal gland. Based on this, considering these 5 CAS indicators, we tried to use objective indicators and MRI parameters to replace the subjective clinical judgment of CAS. The result section partially presented the substitution formula of the 5 indicators that could be verified and optimized in the subsequent related research. Future studies should also explore the other two transformation methods that failed to achieve objective substitution indicators in this study.

This study has a few limitations. This is a cross-sectional study with small sample size. In addition, indicators of patients were collected before treatment and did not involve the analysis and prediction of intervention methods and efficacy.

In this study, various MRI parameters of LG, patient demographics, and clinical indicators of GO patients were creatively combined to establish a prediction model for GO staging, acihieving satisfactory results. The value of introducing clinical indicators was also proved by the improvement of model AUC. On this basis, this study achieved the substitution of objectification of 5 CAS evaluation indexes, providing a new idea for improving the objectification level of GO data collection.

To sum up, our preliminary data suggest that sex and the T2-mapping value of LG could be useful indicators for predicting the phase of GO. Finally, the objective replacement of the CAS index provides a new idea for multi-center GO diagnosis and treatment and quantitative research.

Declarations

Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Acknowledgements

Not applicable.

Authors' contributions

YL, JS, and XT designed the study, MJ, XS, HZ, and YL collected the data, GY, XS, and YW analyzed the data, GY provided statistical analysis, MJ, XS, And HZ wrote the manuscript, HZ, JS, and YL revised the manuscript. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest

The authors declare that they have no competing interests.

Ethics approval

This study was approved by the Ethics Committee of Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, with a waiver of the requirement to obtain patient informed consent.

Consent for publication

Informed consent was obtained from all individual participants included in the study.

Consent to participate

Patients signed informed consent regarding publishing their data and photographs.

Publisher's note

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Figures

Figure 1

MRI scans of lacrimal gland. (A-C) Patient I. A 36-year-old woman with CAS = 0. **(D-F)** Patient II. A 42-year-old man with CAS = 4. (A, D) T2-mapping; (B, E) ADC maps; (C, E) DCE MRI

Figure 2

Model II: nomogram of demographics, objective eye manifestations, and MRI quantitative measurements of Lacrimal gland (variables table 1, 1-17 items) for predicting active GO.

Figure 3

Model III: substitution model of CAS evaluation index objectification (variables table 1, 1-17 items).