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Original Article

Correlation between oxidative stress level and clinical outcome in rotator cuff injury patients

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Abstract: Objective: To investigate the relationship between oxidative stress (OS) and clinical outcome in patients with rotator cuff injury (RCI). Methods: Eighty-two surgically treated RCI patients (May 2022-February 2025) were enrolled in this retrospective study. All participants underwent arthroscopic rotator cuff repair and were further grouped into a good prognosis group (n=39) or a poor prognosis group (n=43) based on the University of California, Los Angeles (UCLA) Shoulder Rating Scale (UCLA ≥29 vs. UCLA <29). Relevant clinical details like age, sex, tear area, disease duration, injury pattern, and UCLA scores, were collected. Serum samples were tested pre- and post-operatively for the quantification of OS biomarkers: reactive oxygen species (ROS), malondialdehyde (MDA), superoxide dismutase (SOD), and glutathione peroxidase (GPx). Pearson correlation analysis was used to evaluate the association between OS biomarkers and UCLA scores. Receiver operating characteristic (ROC) curve analysis was used to assess their predictive value for clinical outcomes. Prognostic determinants were identified using univariate and multivariate logistic regression analyses. Results: ROS and MDA concentrations were markedly elevated in poor-prognosis patients compared to favorable-prognosis individuals, whereas SOD and GPx activities were reduced. Surgical intervention significantly elevated the levels of SOD and GPx, and reduced the levels of ROS and MDA. Correlation analyses linked higher UCLA scores to elevated ROS/MDA levels and reduced SOD/GPx activity. ROC curve analysis showed that the predictive accuracy (area under the curve [AUC]) for individual OS biomarkers ranged from 0.750-0.810, which was markedly improved (AUC=0.939) when used in combination. Univariate and multivariate logistic regression analysis further identified ROS, MDA, SOD, and GPx as independent factors influencing clinical prognoses in RCI patients. Conclusion: OS levels can serve as a key determinant of clinical outcome in RCI patients.

Keywords: Rotator cuff injury, oxidative stress, clinical outcomes, correlation

Introduction

The rotator cuff is a key set of muscles and tendons that maintain the glenohumeral joint stability during extensive motion [1]. Rotator cuff injuries (RCIs), in the form of full- or partial-thickness tears, can result from a sudden incident or develop gradually over time, leading to shoulder pain, reduced function, and disability [1, 2]. Individuals aged ≥60 are particularly susceptible to RICs, with approximately 36% experiencing shoulder pain and around 17% suffering from asymptomatic shoulder tears [3]. Arthroscopic shoulder surgery is a preferred treatment. However, post-operative adverse events such as recurrent rotator cuff defects, persistent or intensified pain, and shoulder joint stiffness are common, posing a great burden on patients, communities, and healthcare systems [4, 5].

The pathophysiology of RCIs remains incompletely understood, though oxidative stress (OS) is implicated in this process [6]: OS may contribute to cellular shrinkage and degradation of collagen matrices, increasing the risk of such injuries. OS, characterized by an imbalance between reactive oxygen species (ROS) production and antioxidant capacity, has been implicated in the progression of rotator cuff disease [7]. Such insights suggest a relationship between OS and patient recovery following RCI.

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ROS, a hallmark of elevated OS, can partially reflect both acute and chronic tendon injuries [8]. Malondialdehyde (MDA), a byproduct of lipid peroxidation, may mediate tendon injury and repair processes [9]. Superoxide dismutase (SOD)-mediated oxidative imbalance is strongly associated with degenerative rotator cuff tears, and glutathione peroxidase (GPx), an effective antioxidant, is known to mitigate tendinopathy-related OS [10, 11]. This study aims to investigate the roles of these classical OS indices in the prognosis of patients with RCIs - an area where research remains limited.

Patients and methods

Case selection

This retrospective study comprised 82 RCI patients who presented to Beijing Jishuitan Hospital Guizhou Hospital between May 2022 and February 2025. The patients were categorized into a favorable prognosis group (n=39) and a poor prognosis group (n=43) according to the University of California, Los Angeles (UCLA) Shoulder Rating Scale (≥29 vs. <29) [5]. This study was approved by the Ethics Committee of Beijing Jishuitan Hospital Guizhou Hospital.

Inclusion criteria: Clinical presentation suggestive of rotator cuff disorders, (shoulder pain plus limited internal rotation and abduction); American Society of Anesthesiologists [ASA] Physical Status Classification I or II; A definitive RCI diagnosis based on clinical findings (history, imaging, physical assessments) [12]; Patients who underwent arthroscopy; Postoperative compliance with rehabilitation; Preserved cognitive and communication abilities; Complete clinical and image records available.

Exclusion criteria: Prior surgical or traumatic shoulder interventions; Aborted arthroscopic procedures requiring open techniques; Central/peripheral neurological impairments (e.g., epilepsy, cervical spondylosis); Upper limb motor dysfunction or fracture-dislocation predating the rotator cuff tear; Concurrent shoulder pathology; Developmental shoulder anomalies or hemiplegia; Massive RCIs (exceeding 3 cm); Systemic infections or moderate-to-severe osteoarthritis; Systemic autoimmune diseases; Neuropathies involving the upper extremities; Life-threatening comorbidities (e.g., cardiovascular, hepatorenal, coagulation, and oncological disorders); Previous psychiatric diagnosis.

Interventions

The surgical procedures were performed by the same attending surgeon. Patients underwent general anesthesia in the contralateral decubitus position [13]. Following strict disinfection and draping, the involved limb was held in 45° abduction and 30° forward flexion, with 5-6 kg of sustained traction applied. Via a standard posterior approach to the shoulder joint, the labrum (anterior, posterior, and superior) and the proximal biceps tendon were then sequentially inspected. Rotator cuff tears measuring ≤3 cm in size were repaired using arthroscopic single-row rotator cuff repair.

Postoperative rehabilitation

Shoulder joint range of motion exercises: On the surgical day, after returning to the ward, the family was instructed to gently massage the patient's shoulder and arm, with the pressure kept within the patient's comfort level. On postoperative day 1, the patient was instructed to perform upper limb elevation and lifting exercises, with the elbow supported by the other hand. On postoperative day 2, hair-combing exercises were initiated. On day 3, the patient started lifting one hand over the head to touch the opposite ear. On day 4, fan-like arm movements were initiated. Appropriate muscle electrical stimulation: According to the activity status of the muscles, electrical stimulation was applied. Electrodes from the PRW-Q8800 low-frequency therapy device (Shanghai Jumu Medical Equipment Co., Ltd.) were placed on the rotator cuff muscles. Intermittent waves were used, adjusted to induce rhythmic muscular twitching that was tolerable for the patient, with 30 minutes per session, once a day, five times a week.

Data collection

Pre- and post-operatively (8^{th} week), 2 mL of fasting venous blood was collected and centrifuged to assess the serum OS marker levels (ROS, MDA, SOD, and GPx) using enzyme-linked immunosorbent assay (ELISA). The experimental procedures strictly followed the instructions of corresponding ELISA kits (Shanghai Xuanke Biotechnology Co., Ltd., XK-E1707h, XK-E1395h, XK-E1425h, XK-E1633h).

The UCLA scale was used to evaluate patients' shoulder joint recovery 8 weeks after treat-

Table 1. Comparison of clinical data between the two groups

Variable	n	Favorable prognosis group (n=39)	Poor prognosis group (n=43)	χ^2/t	P
Age (years)	82	67.36±6.47	64.51±8.92	1.641	0.105
Sex				0.115	0.734
Male	51	25 (64.10)	26 (60.47)		
Female	31	14 (35.90)	17 (39.53)		
Rotator cuff tear area (cm^2)	82	3.04±0.29	3.07±0.26	0.494	0.623
Disease duration (d)	82	10.26±3.05	10.51±3.17	0.143	0.887
Injury pattern				0.388	0.533
Full-thickness tear	45	20 (51.28)	25 (58.14)		
Partial-thickness tear	37	19 (48.72)	18 (41.86)		
UCLA shoulder score (points)	82	32.26±1.83	22.14±4.98	11.973	<0.001

Note: UCLA, University of California, Los Angeles.

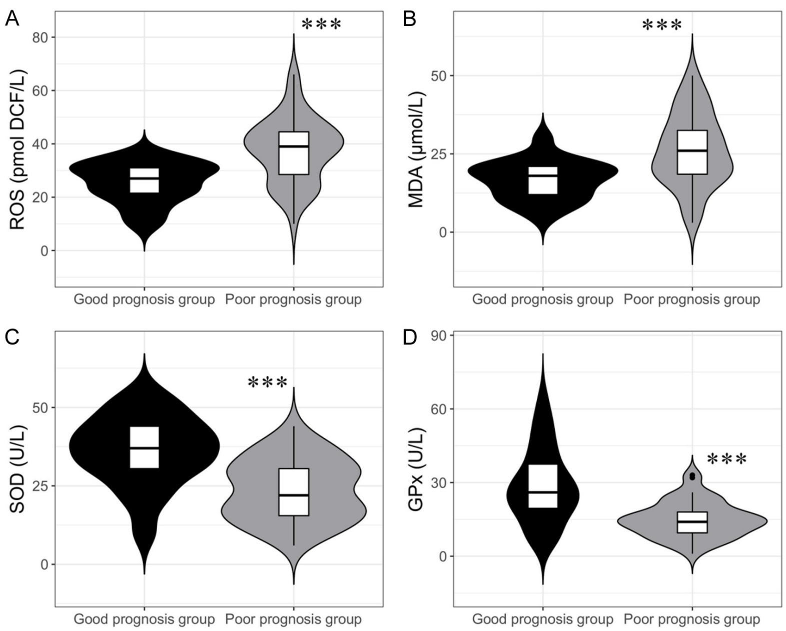

Figure 1. Comparison of oxidative stress markers between poor and favorable prognosis groups. A. ROS; B. MDA; C. SOD; D. GPx. Note: ROS, reactive oxygen species; MDA, malondialdehyde; SOD, superoxide dismutase; GPx, glutathione peroxidase. ***P<0.001 vs. good prognosis group.

ment. The scale covers five domains, categorizing rotator cuff function into three levels: excellent (34-35 points), good (29-33 points), and poor (below 29 points). Higher total scores indicate better joint function.

Both OS markers and shoulder joint function severed as the primary endpoints.

Statistical methods

The data collected were processed using SPSS 20.0. Categorical data were expressed as numbers and frequency (n/%), and between-group comparisons were conducted using χ^2 tests. Measured data were expressed as mean ± standard deviation (SD), and between-group differences were assessed using independent-samples t-tests, while within-group differences (e.g., before and after treatment) were compared using paired t-tests.

Pearson correlation analysis was performed to assess the relationship between OS markers and UCLA scores. Predictive performance of OS biomarkers for clinical prognosis in RCIs was evaluated using receiver operating characteristic (ROC) curve analysis. Independent predictors of clinical outcome were identified through univariate and multivariate logistic regression. A *P* value of <0.05 was considered significant.

Results

Comparison of baseline data between the two groups

No significant differences were observed between the favorable- and poor-prognosis groups in terms of baseline data, including age distribution, gender composition, rotator cuff tear area, disease duration, or injury patterns

(P>0.05). However, the UCLA score was significantly higher in the favorable-prognosis group compared to the poor prognosis group (P<0.05; **Table 1**).

Comparison of post-operative OS markers between the two groups

ELISA results showed that the poor-prognosis group exhibited higher serum ROS and MDA levels but lower SOD and GPx levels compared to the favorable-prognosis group (P<0.001; **Figure 1**).

Changes in OS markers before and after treatment

As shown in **Figure 2**, a marked decline was observed in ROS and MDA concentrations after treatment, whereas SOD and GPx levels showed a substantial rise (P<0.01).

Correlation between OS marker levels and UCLA score

As shown in **Figure 3** and **Table 2**, higher ROS/MDA levels were inversely correlated with UCLA score (r=-0.435, -0.499; P<0.001), while positive associations were observed between SOD/GPx activities and UCLA score (r=0.442 and 0.381, P<0.001).

Predictive value of OS markers for clinical outcomes in RCI patients

As shown in **Figure 4** and **Table 3**, the area under the curve (AUC) of ROS for predicting the prognosis of RCIs

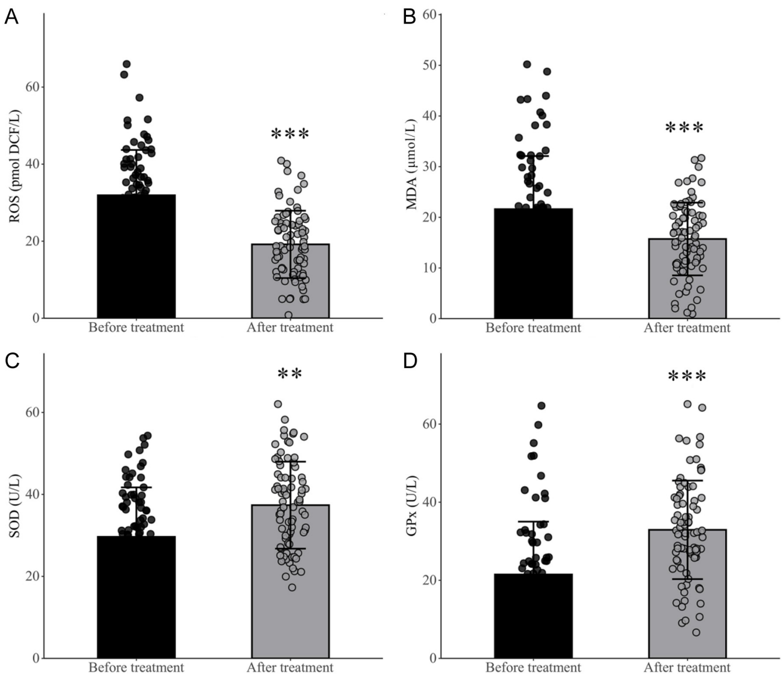

Figure 2. Alteration in oxidative stress markers before and after treatment. A. ROS; B. MDA; C. SOD; D. GPx. Note: ROS, reactive oxygen species; MDA, malondialdehyde; SOD, superoxide dismutase; GPx, glutathione peroxidase. **P<0.01, ***P<0.001 vs. pre-treatment measurement.

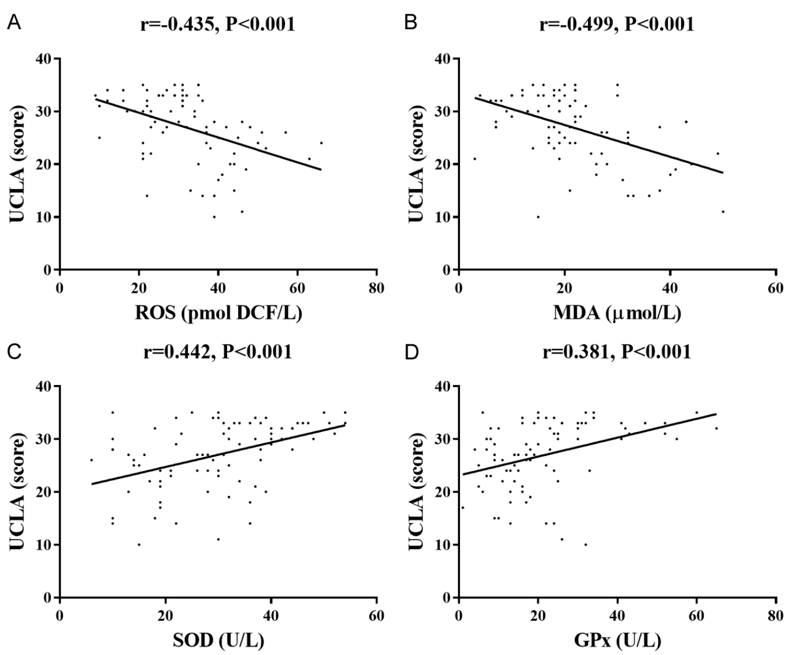

Figure 3. Correlations between oxidative stress markers and UCLA score. A. Correlation between ROS level and UCLA score; B. Correlation between MDA level and UCLA score; C. Correlation between SOD level and UCLA score; D. Correlation between GPx level and UCLA score. Note: UCLA, University of California, Los Angeles; ROS, reactive oxygen species; MDA, malondialdehyde; SOD, superoxide dismutase; GPx, glutathione peroxidase.

Table 2. Pearson correlation analysis between OS markers and UCLA score

Correlation	UCLA (points)	
	r	P
ROS (pmol DCF/L)	-0.435	<0.001
MDA (μoml/L)	-0.499	<0.001
SOD (U/L)	0.442	<0.001
GPx (U/L)	0.381	<0.001

Note: UCLA, University of California, Los Angeles; ROS, reactive oxygen species; MDA, malondialdehyde; SOD, superoxide dismutase; GPx, glutathione peroxidase; OS, oxidative stress.

was 0.804 (0.706-0.903), with a cutoff value of 36.5 pmol DCF/L, corresponding to a sensitivity of 62.79% and a specificity of 100.00%; MDA demonstrated an AUC of 0.754 (0.648-0.859), with a cutoff value of 24.5 μmol/L, corresponding to 53.49% sensitivity and 94.87% specificity. SOD showed an AUC of 0.808 (0.713-0.903), and the corresponding sensitivity and specificity were 74.42% and 74.36% at the cutoff value of 30.5 U/L. Finsally, the AUC for GPx was 0.795 (0.693-0.897), and the cutoff value was 18.5 U/L, with corresponding sensitivity and specificity of 76.74%, and 76.92%, respectively. Notably, their combination led to an AUC of 0.939 (0.884-0.994), with a cutoff of 0.339, and the corresponding sensitivity and specificity were 84.62% and 89.02%, respectively.

Univariate and multivariate approaches

Further exploration into the factors affecting RCI patients' clinical prognoses was carried out by univariate and multivariate analyses (**Tables 4**, **5**). Univariate screening identified ROS, MDA, SOD and GPx as significant predictors (P<0.05). Multivariate analysis, performed using binary Logistic regression, identified elevated ROS levels (≥30 pmol DCF/L), increased MDA concentrations (≥22 μmol/L), and reduced antioxidant enzyme activities (SOD <32 U/L, GPx <23 U/L) as independent risk factors for poor prognosis for RCIs (P<0.05).

Discussion

As the primary stabilizer of shoulder motion, the rotator cuff utilizes crescent/coronal transverse orientation to evenly distribute loads during most movements. Glenohumeral joint instability arises when a tear is present, which in turn hinders the performance of normal activities [14]. Hypoxia-driven rotator cuff tendon degradation and fibroblast apoptosis were identified in a murine model of RCI, implicating OS as a critical modulator and suggesting the potential of antioxidation as a therapeutic approach for such injuries [15]. This study focused on assessing OS' influence on RCI patients' clinical prognoses.

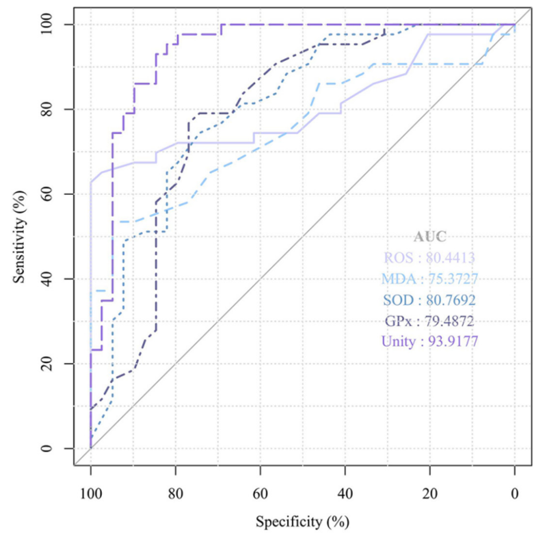

Figure 4. ROC curve analysis of OS markers for predicting prognosis of patients with rotator cuff injury. Note: ROC, receiver operating characteristic; AUC, area under the curve; ROS, reactive oxygen species; MDA, malondialdehyde; SOD, superoxide dismutase; GPx, glutathione peroxidase.

Our initial findings revealed significant correlation between OS markers and patient prognosis and therapeutic efficacy. Xiang et al. [16] suggested that tumor necrosis factor-α (TNF-α) and nerve growth factor (NGF) pathway interactions may regulate ROS/SOD/GPx responses in rodent RCI models, possibly explaining OS alterations in RCI patients. In addition, Wani et al. [17] demonstrated that platelet-rich plasma (PRP) and methotrexate (MTX) co-administration markedly decreased MDA concentrations in a rat nephrotoxicity model, mirroring the outcomes of this investigation. Subsequently, OS was found to be implicated in both RCI pathogenesis and post-surgical shoulder functional recovery. This relationship may be attributed to the pathologic overexpression of specific biomarkers observed in the surgical specimens of patients undergoing rotator cuff repair surgery, including S-100 Calcium Binding Protein A11 (S100A11), Perilipin 4 (PLIN4), Hypoxia

Table 3. ROC parameters for OS markers in predicting postoperative outcome

Marker	AUC	95% CI	Best cut-off	Sensitivity	Specificity	Accuracy
ROS (pmol DCF/L)	0.804	0.706-0.903	36.5	62.79%	100.00%	80.49%
MDA (μoml/L)	0.754	0.648-0.859	24.5	53.49%	94.87%	73.17%
SOD (U/L)	0.808	0.713-0.903	30.5	74.42%	74.36%	74.39%
GPx (U/L)	0.795	0.693-0.897	18.5	76.74%	76.92%	76.83%
Unity	0.939	0.884-0.994	0.339	93.02%	84.62%	89.02%

Note: ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval; ROS, reactive oxygen species; MDA, malondialdehyde; SOD, superoxide dismutase; GPx, glutathione peroxidase; OS, oxidative stress.

Table 4. Univariate analysis of OS markers for clinical outcome in rotator cuff injury patients

Variable	n	Good prognosis group (n=39)	Poor prognosis group (n=43)	χ^2	P
ROS (pmol DCF/L)				10.808	0.001
<30	35	24 (61.54)	11 (25.58)		
≥30	47	15 (38.46)	32 (74.42)		
MDA (μoml/L)				5.386	0.020
<22	48	28 (71.79)	20 (46.51)		
≥22	34	11 (28.21)	23 (53.49)		
SOD (U/L)				8.094	0.004
<32	45	15 (38.46)	30 (69.77)		
≥32	37	24 (61.54)	13 (30.23)		
GPx (U/L)				9.447	0.002
<23	50	17 (43.59)	33 (76.74)		
≥23	32	22 (56.41)	10 (23.26)		

Note: ROS, reactive oxygen species; MDA, malondialdehyde; SOD, superoxide dismutase; GPx, glutathione peroxidase.

Table 5. Multivariate analysis of OS markers for clinical outcome in rotator cuff injury patients

Category	B	SE	WALD	P	OR	95% CI
ROS (pmol DCF/L)	1.660	0.569	8.525	0.004	5.259	1.726-16.027
MDA (μoml/L)	1.301	0.588	4.901	0.027	3.672	1.161-11.613
SOD (U/L)	-1.670	0.577	8.376	0.004	0.188	0.061-0.583
GPx (U/L)	-1.178	0.572	4.234	0.040	0.308	0.100-0.946

Note: ROS, reactive oxygen species; MDA, malondialdehyde; SOD, superoxide dismutase; GPx, glutathione peroxidase.

Upregulated 1 (HYOU1), and Chloride Intracellular Channel 1 (CLIC1) [18].

Next, ROC curve analysis revealed an AUC range of 0.750-0.810 for ROS, MDA, SOD, and GPx in predicting RCI patients' clinical outcomes, and their combination reached a markedly improved AUC. Further univariate and multivariate analyses identified ROS and MDA as independent risk factors for adverse prognosis, whereas SOD and GPx were protective factors. Hence, OS markers (ROS, MDA, SOD, GPx) correlate significantly with shoulder function recovery in RCI patients, highlighting their use as potential intervention targets. Earlier work by Itoigawa et al. [19] demonstrated that recurrent post-surgical rotator cuff tears were independently influenced by patient age, lesion size, and SOD levels, findings that align with and complement the present study's conclusions. Gong et al. [20] demonstrated that adhesive capsulitis, massive rotator cuff tears, increased intraoperative anchor use, diabetes, and trauma-related tears all elevate the risk of adverse outcome after arthroscopic rotator cuff repair. This corroborates the observations in this study. Besides, prognostic indicators for improved clinical results in arthroscopic rotator cuff repair, as reported by Malavoltaet al. [21], included male sex, absence of rheumatic conditions, older age, minimal supraspinatus fatty infiltration, and superior baseline ASES scores, reinforcing the current findings.

This study has some limitations. First, the sample size was relatively small, with only 82 surgically treated RCI patients included, possibly introducing a certain information collection bias. Second, there was no in-depth analysis of the causal relationship between OS indicators and clinical prognosis. Third, the underlying mechanism linking OS to patient outcomes needed further clarification. To further enhance the rigor of this study, future work should expand samples through multi-center recruitment and incorporate additional causal inference analyses and mechanistic investigations.

Conclusion

Significant oxidative stress is observed in RCIs, manifested by upregulated ROS and MDA coupled with downregulated SOD and GPx. These OS markers were independent factors showing a significant correlation with patients' shoulder functional recovery, possibly serving as clinical outcome predictors.

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Disclosure of conflict of interest

None.

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