BMJ Open

Autoimmune Connective Tissue Diseases are Associated with a Risk of Rotator Cuff Repair Surgery

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-023848
Article Type:	Research
Date Submitted by the Author:	27-Apr-2018
Complete List of Authors:	Huang, ShihWei; Shuang Ho Hospital, Physical Medicine and Rehabilitation Lin, CheLi; Taipei Medical University Shuang Ho Hospital, Orthopedics Lin, LiFong; Shuang Ho Hospital, Physical Medicine and Rehabilitation Huang, ChiChang; Graduate Institute of Sports Science, National Taiwan Sport University Liou, Tsan-Hon; Shuang Ho Hospital, Physical Medicine and Rehabilitation Lin, Hui-Wen; Department of Mathematics, Soochow University
Keywords:	Rheumatology < INTERNAL MEDICINE, Orthopaedic sports trauma < ORTHOPAEDIC & TRAUMA SURGERY, Shoulder < ORTHOPAEDIC & TRAUMA SURGERY

Original Article

Autoimmune Connective Tissue Diseases are Associated with a Risk of Rotator Cuff Repair Surgery

Shih-Wei Huang[1,2,3] MD, Che-Li Lin[3,4] MD, Li-Fong Lin[1,5] PhD, Chi-Chang Huang[3] PhD, Tsan-Hon Liou[1,2] MD, PhD, Hui-Wen Lin[6,7]* PhD

Running title: ATCD increase the risk of rotator cuff surgery

[1]Department of Physical Medicine and Rehabilitation, Shuang Ho Hospital, Taipei Medical University, Taipei, Taiwan

[2]Department of Physical Medicine and Rehabilitation, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan

[3]Graduate Institute of Sports Science, National Taiwan Sport University, Taoyuan, Taiwan

[4]Department of Orthopedic Surgery, Shuang Ho Hospital, Taipei Medical University, New Taipei City, Taiwan

[5]Institute of Gerontology and Health Management, Taipei Medical University, Taipei, Taiwan

[6]Department of Mathematics, Soochow University, Taipei, Taiwan

[7]Evidence-Based Medicine Center, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan

*Address for reprints:

Hui-Wen Lin, PhD

Department of Mathematics, Soochow University, 70 Linhsi Road, Shihlin, Taipei, Taiwan

Tel: 886-2-2881-9471 ext. 6701

Fax: 886-2-8861-1230

E-mail:linhw@tmu.edu.tw

Abstract

Objectives

Autoimmune connective tissue diseases (ACTDs) commonly involve joint and muscle–related soft tissues, but clinical epidemiological studies investigating ACTDs involving tendons are scant. We investigated rotator cuff (RC) repair surgery risk in ACTD patients.

Design

Nationwide population-based case-control study.

Setting

All healthcare facilities in Taiwan.

Participants

A total of 30,114 patients were enrolled.

Methods

We conducted a retrospective cohort study with a 7-year longitudinal follow-up in Taiwan. Patients who had received systemic lupus erythematous, systemic sclerosis, sicca syndrome, dermatomyositis, and polymyositis diagnoses between 2004 and 2008 were enrolled. The control cohort comprised age- and sex-matched controls. The hazard ratio (HR) and adjusted HR (aHR) were estimated between the ACTD and control cohorts after adjustment for confounders. Effects of steroid and nonsteroidal anti-inflammatory drug (NSAID) use on RC surgery risk were analysed.

Results

We enrolled 5,019 ACTD patients and 25,095 controls in the ACTD and control cohorts, respectively. RC surgery incidence was 49 and 24 per 100,000 person-years in the ACTD and control cohorts, respectively. In the ACTD cohort, the crude HR for RC surgery was 2.08 (95% confidence interval [CI], 1.08–4.02, $P < 0.05$), and the aHR was 1.97 (95% CI, 1.01–3.82, $P < 0.05$). The ACTD patients who used NSAIDs had an aHR of 3.13 (95% CI, 1.21–8.07, $P < 0.05$) compared with controls, but the ACTD patients who used steroids did not have a significantly higher than controls.

Conclusions

ACTD patients have risk of RC repair surgery. ACTD patients with steroids are at a low risk of surgery, and aggressive inflammation control may be a strategy for managing subsequent lesions of the RC.

Keywords: Autoimmune connective tissue diseases; rotator cuff surgery; risk factor; population-

based study

Strengths and limitations of this study

- First large-scale, population-based study for risk of rotator cuff lesion among autoimmune connective tissue diseases (ACTD) patients.
- Compared with control cohort, patients with ACTD had higher risk of receiving rotator cuff repair surgery
- Steroid use can lower the risk of receiving rotator cuff repair surgery among ACTD patients.
- In additional to joint and muscle lesions, we should also pay attention to tendon lesion and controlling the inflammation process could be a potentially effective prevention strategy for the requirement of receiving rotator cuff repair surgery.
- The detailed information of ACTD severity cannot be presented in this population based study.

Introduction

Autoimmune connective tissue diseases (ACTDs), such as systemic lupus erythematosus (SLE), systemic sclerosis, sicca syndrome, dermatomyositis, and polymyositis, are systemic autoimmune disorders that affect multiple organ systems and exhibit intermittent relapse and remission. Owing to the various organs involved the chronic inflammatory process caused by autoantibody deposition and related inflammatory reactions, ACTD patients, particularly SLE patients, usually present heterogeneous clinical manifestations.[1] The musculoskeletal system is one of the organ systems that is often affected, and initial musculoskeletal symptoms are often similar to those of autoimmune diseases.[2] The severity of clinical musculoskeletal symptoms varies among individuals. SLE patients can present mild arthralgia, without deformity or erosion, nonerosive deforming arthritis, or erosive symmetric polyarthritis. In addition to arthritis and arthralgia, the musculoskeletal symptoms of SLE patients include osteonecrosis, tendonitis, myositis, and tendon rupture.[3] However, few studies have investigated and emphasised the lesions of the enthesis in SLE patients in connection with other ACTDs.[4 5]

Rotator cuff (RC) tear or rupture is one of the most common causes of shoulder dysfunction. RC tears may be asymptomatic, or their clinical presentations can be pain accompanied by a limited range of movement. RC disorders are observed in 30%–70% of patients presenting with shoulder

pain, and the incidence of RC tears is 5%–40%.[6] Because RC tears can be asymptomatic, different studies have reported diverse prevalence rates of RC tears. An ultrasound screening study revealed that the prevalence of RC tears was 20.47% among 1366 shoulders with or without clinical symptoms, and the prevalence increased with age.[7] Initially, RC tears can be treated using conventional methods such as exercise or injections.[8] Patients with extensive RC tears experience limited shoulder function while performing daily activities or working, and surgical repair is recommended to relieve symptoms and restore function. RC repair surgery and subsequent possible complications can increase patients' medical expenditure and the economic burden on the health care system.[9]

A recent cross-sectional study investigating hand tendon findings revealed the predominance of tenosynovitis or tendonitis.[10] Case reports have described rupture of patellar and hand tendons in SLE patients. [11 12] Thus, we hypothesise that SLE patients have a relatively high risk of RC repair surgery due to tendon lesions. In addition, case reports of tendon rupture have mentioned other ACTDs, such as dermatomyositis. [13] However, sufficient epidemiological research is not available to prove that SLE and other ACTDs are risk factors for RC tears that require repair surgery. Therefore, we conducted this longitudinal retrospective case–control cohort study to identify the temporal association between ACTD and the risk of RC repair surgery.

Methods

Study design

Using a health care database, this longitudinal retrospective case–control cohort study analysed the risk of RC repair surgery. In the study cohort, we included patients who had been diagnosed with ACTD between 1 January 2004 and 31 December 2008. Their data were obtained from the National Health Insurance Research Database (NHIRD) of Taiwan. A control cohort consisting of five age- and sex-matched non-ATCD controls per ATCD patient was obtained using the same database. The follow-up period was 7 years, till the end of 2010. The follow-up period ended when the patients or controls received RC repair surgery. To ensure patient privacy, the names and identity numbers were replaced by numbers and letters from the English alphabet codes, which are used for identifying patient data in the NHIRD. Because the linked identity data were removed, the patient data from the NHIRD could not be identified; hence, the requirement of informed consent was waived in this study. This study was approved by institutional review board of a university in Taipei.

A brief background on Taiwan's National Health Insurance, NHIRD, and Longitudinal Health Insurance Database 2005

The National Health Insurance (NHI) system of Taiwan, a form of social insurance, covers more than 96% of the population of Taiwan.[14 15] The NHI programme covers almost all medical services such as outpatient visits, admission service, and emergency hospitalisation. Diagnoses made using International Classification of Diseases Ninth Revision, Clinical Modification (ICD-9-CM) codes, medical prescriptions, procedures, and surgery are recorded in the NHIRD. The data used in this study were obtained from the Taiwan Longitudinal Health Insurance Database 2005 (LHID2005). The LHID2005 contains the data of 1,000,000 beneficiaries randomly sampled from the Registry for Beneficiaries of the NHIRD. For research purposes, the National Health Research Institutes of Taiwan collect and maintain registration files and original claims data from the NHI administration and then release them publicly through the NHIRD.

Inclusion and exclusion criteria

The study cohort included ACTD patients diagnosed with SLE (ICD-9-CM code 710.0), systemic sclerosis (ICD-9-CM code 710.1), sicca syndrome (ICD-9-CM code 710.2), dermatomyositis (ICD-9-CM code 710.3), and polymyositis (ICD-9-CM code 710.4) by using the American College of Rheumatology criteria between 1 January 2004 and 31 December 2008. To ensure the high accuracy of ACTD diagnosis, this study selected only patients who were diagnosed with ACTDs at least twice consistently, according to ICD-9-CM codes, in outpatient clinics or those

who had a primary diagnosis of ACTDs during hospitalisation within 1 year and were older than 20 years. ACTD patients who had undergone RC repair surgery before 2004, who had missing data, and who died during the follow-up period were excluded from this study. Finally, 5,019 SLE patients were enrolled in the study cohort (Figure 1).

Confounders and propensity score adjustment

In addition to the demographic variables of age and sex, economic status and comorbidities, such as diabetes mellitus (ICD-9-CM codes 250 and 251), hypertension (ICD-9-CM codes 401–405), hyperlipidaemia (ICD-9-CM codes 272.0–272.4), coronary heart disease, gout, steroid use, thyroid disorders, and fractures, were analysed in this study. To minimise the bias of data selection from the study database, we used propensity scores adjusted for comorbidities and income, as shown in Table 1.

Outcome identification

We used the first RC repair surgery with the relevant application codes (64121B and 64122B) as the study endpoint. All participants were followed up from the index date to the endpoint or until 31 December 2010, whichever was earlier, and the final-date observations were censored observations.

Statistical Analysis

Demographic characteristics and comorbidities were analysed using Pearson's chi-square test. We calculated the incidence of ACTDs and compared the risk of RC repair surgery between the two cohorts by using the Cox model after propensity score adjustment. Furthermore, we compared the risk of repair surgery in the ACTDs patients who did or did not receive medication (nonsteroidal anti-inflammatory drugs [NSAIDs] and steroids) with non-ACTD controls. To clarify the association between medication and RC tears, Kaplan–Meier hazard curves were plotted for RC tears in ACTDs patients who did or did not receive NSAIDs and controls as well as in ACTDs patients who did or did not receive steroids and controls for a 7-year follow-up period. All data analyses were performed using the Stata package (Version 11) and SAS statistical package (Version 9.1.3; SAS Institute, Cary, NC, USA). A value of $P < 0.05$ was considered statistically significant.

Patient involvement

No patients were involved in developing the hypothesis, the specific aims or the research questions, nor were they involved in developing plans for design or implementation of the study. No patients were involved in the interpretation of study results or write up of the manuscript. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

Results

Women constituted 77.5% in both cohorts, and the prevalence of the comorbidities of hyperlipidaemia, coronary heart disease, gout, and thyroid disorders were higher in the ACTD cohort than in the control cohort (Table 1). The incidence of RC repair surgery was 49.0 and 24.0 per 100,000 person-years in the ACTD and control cohorts, respectively. In the ACTD cohort, the crude hazard ratio (HR) of RC repair surgery was 2.08 (95% CI, 1.08−4.02, $P < 0.05$), and the adjusted HR (aHR) was 1.97 (95% CI, 1.01−3.82, $P < 0.05$) (Table 2). Figure 2A shows the Kaplan–Meier hazard curves for the risk of RC repair surgery in the ACTD and control cohorts during the 7-year follow-up period. A comparison of the ACTD patients who did and did not use NSAIDs (separately) with controls revealed that the ACTD patients with records of NASID use had a higher risk of RC repair surgery (aHR = 3.13, 95% CI, 1.21–8.07, $P < 0.05$) than did the ACTD patients without records of NSAID use (Table 3). Figure 2B shows the Kaplan–Meier hazard curves for the risk of RC repair surgery in the ACTD patients who used NSAIDs, the ACTD patients who did not use NSAIDs, and controls during the 7-year follow-up period. Further analysis of the association between steroid use and the risk of RC repair surgery showed that the crude HR was 2.32 (95% CI, 1.21–8.07, $P < 0.05$) among ACTD patients who used steroids. However, the aHR of the risk of surgery was not significantly higher in the ACTD patients than in controls (Table 4). Figure 2C represents the trend of the risk of RC repair surgery; the risk increased among the ACTD patients who used steroids but

was not significant during the 7 year follow-up period.

Discussion

Although case reports have described spontaneous ruptures in the supraspinatus tendon and the patellar tendon and hand flexor tendon,[11-13 16] no relevant epidemiological study has investigated the risk of RC lesions among ACTD patients until now. Our population-based cohort study revealed that the ACTD patients had a higher risk of RC repair surgery than controls. This finding indicates that in addition to the joints, the periarticular soft tissue is affected in ACTDs. During the 7-year longitudinal follow-up period, the number of events of RC repair surgery increased with ACTD progression. To improve the quality of life and prevent the negative effects of RC injuries among ACTD patients, identifying the possible mechanism of ACTD pathogenesis is crucial for developing an effective prevention strategy.

The factors involved in RC injury pathogenesis can typically be classified into extrinsic and intrinsic factors. [17] For ACTD patients, we suppose that intrinsic pathogenic aetiologies play a crucial role in increasing the risk of RC injuries and the subsequent requirement of repair surgery. ACTD patients exhibit the characteristics of systemic inflammatory processes, and inflammation

reactions subsequently affect the RC tendon. Subclinical inflammation persists in ACTD patients even after clinical symptoms are under control. Subclinical chronic inflammation can disrupt the tendon healing and remodelling process. It can lead to weakening of the tendon, thus increasing the risk of subsequent tendon rupture. Previous case reports have also found perivascular mononuclear cell infiltration in the ruptured tendon, which was caused by the ACTD inflammatory process. [18 19] The inflammatory phenomenon can also be detected using ultrasound techniques. A study reported that 49.4% of ultrasound abnormalities were tenosynovitis. [20] In addition to tenosynovitis, ultrasound detected chronic tendinopathy, which led to degeneration of the tendon. The weakened structure was highly vulnerable to injuries. These intrinsic aetiologies of tendon inflammation and subsequent tendon degeneration can lead a high risk of RC injuries and the subsequent requirement of repair surgery among ACTD patients.

ACTDs represent complicated chronic inflammatory autoimmune diseases that do not have curative treatment. To arrest the progression of autoimmune diseases, systemic steroids are often used and combined with nonsteroidal medication to control flare-up episodes. [21] Corticosteroids can accelerate weakness progression by inhibiting collagen synthesis and impairing blood supply. [22] Corticosteroids inhibit collagen synthesis and may also impair blood supply, thus weakening the tendons. [5] A critical zone near the insertion of the supraspinatus has been described using

microangiographic evidence of an area of hypovascularity in the tendon close to its humeral insertion. Relative ischaemia in this zone is reported to mimic tendon degeneration. [6] Previous studies have also mentioned that chronic synovitis, tenosynovitis, and long-term steroid use can lead to degeneration and thus increase the vulnerability of the flexor tendon in ACTD patients. [23 24] However, our study revealed that steroid use in all the patients and controls did not significantly increase the risk of RC repair surgery. Studies have shown that inflammatory changes occur at the site of tendon rupture; these changes have been observed in patients with ACTDs. [18 25] Although steroids can lead to tendon degeneration, inflammatory processes can be arrested by steroid administration. We hypothesised that the net effect of steroid use can increase the risk of RC repair surgery, but this effect was not significant in ACTD patients. Furthermore, ACTD-induced chronic inflammatory process and related degeneration can accelerate the weakening of the RC with ageing. When the fracture statuses of both cohorts were compared, both fracture and nonfracture statuses increased the risk of RC repair surgery in the ACTD cohort. The intrinsic pathogenesis factor may be the major cause of RC lesions among ACTD patients.

Our study revealed that ACTD is a risk factor for RC repair surgery. We hypothesised the possible mechanism underlying this association was chronic inflammation and tendon degeneration, which damage and weaken the RC structure. The strength of this study was its large sample size and

data analysis. Moreover, it is the first epidemiological study to investigate the association between ACTDs and the risk of RC lesions and surgery. Nevertheless, several limitations of this study need to be addressed. First, the diagnosis of ACTDs and comorbidities were defined using ICD codes from the database; hence, accuracy should be examined. For accurate payment, the Bureau of NHI reviews the medical records regularly. SLE, dermatomyositis, and polymyositis patients in Taiwan can apply for catastrophic illness registration cards, and copayment is free for SLE-related medical problems from the Bureau. Second, laboratory data of the inflammatory status and severity of ACTDs cannot be obtained from the database. The severity and status of ACTDs cannot be categorised in the database, and we cannot identify which status of ACTDs patients were at a high risk of tendon lesions. Third, extrinsic factors affecting RC injuries include repeated impingement and overuse during work and daily living activities. These factors can increase the risk of repair surgery. However, data on work status, daily activities, body weight, alcohol consumption, and smoking are not available in the database. Although a large sample size was obtained from this database, these confounders cannot be excluded completely in this study. Finally, for higher accuracy, we only investigated the risk of RC lesions and the requirement of subsequent repair surgery; therefore, patients with minor tears or those who did not require surgical intervention may have been missed. Despite the limited information available on the types of RC lesions, our population-based study provided crucial information on the high risk of RC surgery among ACTD patients.

Conclusion

The results of this 7-year longitudinal population-based case–control cohort study showed that ACTD patients have a 1.97-fold higher risk of RC repair surgery than do controls. Additional studies on inflammatory severity in ACTDs and the effects of ACTD-related medication on the risk of RC lesions are recommended.

Acknowledgments: None

Contributors: H-SW participated in the study design, conducted the data analysis, drafted the initial manuscript and approved the final manuscript as submitted. L-CL conducted the data analysis, drafted the manuscript and approved the final manuscript as submitted. L-LF contributed to the study design, reviewed and revised the manuscript, and approved the final manuscript as submitted. H-CC reviewed and revised the manuscript, and approved the final manuscript as submitted. L-TH participated in the study design, reviewed and revised the manuscript, and approved the final manuscript as submitted. RE designed and conceptualised the study, and approved the final manuscript as submitted. L-HW participated in the study design, conducted the data analysis, revised manuscript and approved the final manuscript as submitted.

Funding: None

Competing interests: None declared.

Ethics approval: The Institutional Review Board of a Taipei University (N20170724)

Data sharing statement: From HuiWen Lin, linhw@tmu.edu.tw

Provenance and peer review: Not commissioned; externally peer reviewed.

Reference

1. Tsokos GC. Systemic lupus erythematosus. The New England journal of medicine 2011;**365**(22):2110-21 doi: 10.1056/NEJMra1100359[published Online First: Epub Date]|.
2. Rothfield N, Sontheimer RD, Bernstein M. Lupus erythematosus: systemic and cutaneous manifestations. Clinics in dermatology 2006;**24**(5):348-62 doi: 10.1016/j.clindermatol.2006.07.014[published Online First: Epub Date]|.
3. Zoma A. Musculoskeletal involvement in systemic lupus erythematosus. Lupus 2004;**13**(11):851-3 doi: 10.1191/0961203303lu2021oa[published Online First: Epub Date]|.
4. Gutierrez M, Filippucci E, De Angelis R, et al. Subclinical entheseal involvement in patients with psoriasis: an ultrasound study. Seminars in arthritis and rheumatism 2011;**40**(5):407-12 doi: 10.1016/j.semarthrit.2010.05.009[published Online First: Epub Date]|.
5. Grossman JM. Lupus arthritis. Best practice & research. Clinical rheumatology 2009;**23**(4):495-506 doi: 10.1016/j.berh.2009.04.003[published Online First: Epub Date]|.
6. Oliva F, Piccirilli E, Bossa M, et al. I.S.Mu.L.T - Rotator Cuff Tears Guidelines. Muscles, ligaments and tendons journal 2015;**5**(4):227-63 doi: 10.11138/mltj/2015.5.4.227[published Online First: Epub Date]|.
7. Yamamoto A, Takagishi K, Osawa T, et al. Prevalence and risk factors of a rotator cuff tear in the general population. Journal of shoulder and elbow surgery 2010;**19**(1):116-20 doi: 10.1016/j.jse.2009.04.006[published Online First: Epub Date]|.
8. Abdul-Wahab TA, Betancourt JP, Hassan F, et al. Initial treatment of complete rotator cuff tear and transition to surgical treatment: systematic review of the evidence. Muscles, ligaments and tendons journal 2016;**6**(1):35-47 doi: 10.11138/mltj/2016.6.1.035[published Online First: Epub Date]|.
9. Colvin AC, Egorova N, Harrison AK, et al. National trends in rotator cuff repair. The Journal of bone and joint surgery. American volume 2012;**94**(3):227-33 doi: 10.2106/JBJS.J.00739[published Online First: Epub Date]|.
10. Ogura T, Hirata A, Hayashi N, et al. Comparison of ultrasonographic joint and tendon findings in hands between early, treatment-naive patients with systemic lupus erythematosus and rheumatoid arthritis. Lupus 2017;**26**(7):707-14 doi: 10.1177/0961203316676375[published Online First: Epub Date]|.
11. Albayrak I, Kucuk A, Arslan S, et al. Spontaneous patellar tendon rupture in a case followed up for diagnosis of systemic lupus erythematosus. European journal of rheumatology 2014;**1**(4):159-60 doi: 10.5152/eurjrheumatol.2014.140044[published Online First: Epub Date]|.
12. Hosokawa T, Oda R, Toyama S, et al. Spontaneous flexor tendon rupture due to an insufficiency fracture of the hamate hook in a patient with systemic lupus erythematosus: A case report.

International journal of surgery case reports 2016;**27**:63-65 doi: 10.1016/j.ijscr.2016.06.052[published Online First: Epub Date]|.

13. Nakamura S, Nakagawa J. Recurrent extensor tendon rupture in adult-onset dermatomyositis: a case report. Clinical rheumatology 2005;**24**(4):409-10 doi: 10.1007/s10067-004-1050-0[published Online First: Epub Date]|.
14. Cheng TM. Taiwan's new national health insurance program: genesis and experience so far. Health affairs 2003;**22**(3):61-76 doi: 10.1377/hlthaff.22.3.61[published Online First: Epub Date]|.
15. Cheng SH, Chiang TL. The effect of universal health insurance on health care utilization in Taiwan. Results from a natural experiment. Jama 1997;**278**(2):89-93
16. Prabu VN, Agrawal S, Kishore JK, et al. Supraspinatus tendon rupture in lupus: a rarity. Lupus 2009;**18**(11):1026-7 doi: 10.1177/0961203309103099[published Online First: Epub Date]|.
17. Via AG, De Cupis M, Spoliti M, et al. Clinical and biological aspects of rotator cuff tears. Muscles, ligaments and tendons journal 2013;**3**(2):70-9 doi: 10.11138/mltj/2013.3.2.070[published Online First: Epub Date]|.
18. Potasman I, Bassan HM. Multiple tendon rupture in systemic lupus erythematosus: case report and review of the literature. Annals of the rheumatic diseases 1984;**43**(2):347-9
19. Lu M, Johar S, Veenema K, et al. Patellar tendon rupture with underlying systemic lupus erythematosus: a case report. The Journal of emergency medicine 2012;**43**(1):e35-8 doi: 10.1016/j.jemermed.2009.08.054[published Online First: Epub Date]|.
20. Di Matteo A, De Angelis R, Cipolletta E, et al. Systemic lupus erythematosus arthropathy: the sonographic perspective. Lupus 2017:961203317747716 doi: 10.1177/0961203317747716[published Online First: Epub Date]|.
21. Thamer M, Hernan MA, Zhang Y, et al. Prednisone, lupus activity, and permanent organ damage. The Journal of rheumatology 2009;**36**(3):560-4 doi: 10.3899/jrheum.080828[published Online First: Epub Date]|.
22. Halpern AA, Horowitz BG, Nagel DA. Tendon ruptures associated with corticosteroid therapy. The Western journal of medicine 1977;**127**(5):378-82
23. Zayat AS, Md Yusof MY, Wakefield RJ, et al. The role of ultrasound in assessing musculoskeletal symptoms of systemic lupus erythematosus: a systematic literature review. Rheumatology 2016;**55**(3):485-94 doi: 10.1093/rheumatology/kev343[published Online First: Epub Date]|.
24. Alves EM, Macieira JC, Borba E, et al. Spontaneous tendon rupture in systemic lupus erythematosus: association with Jaccoud's arthropathy. Lupus 2010;**19**(3):247-54 doi: 10.1177/0961203309351729[published Online First: Epub Date]|.
25. Furie RA, Chartash EK. Tendon rupture in systemic lupus erythematosus. Seminars in arthritis and rheumatism 1988;**18**(2):127-33

Figure Legends

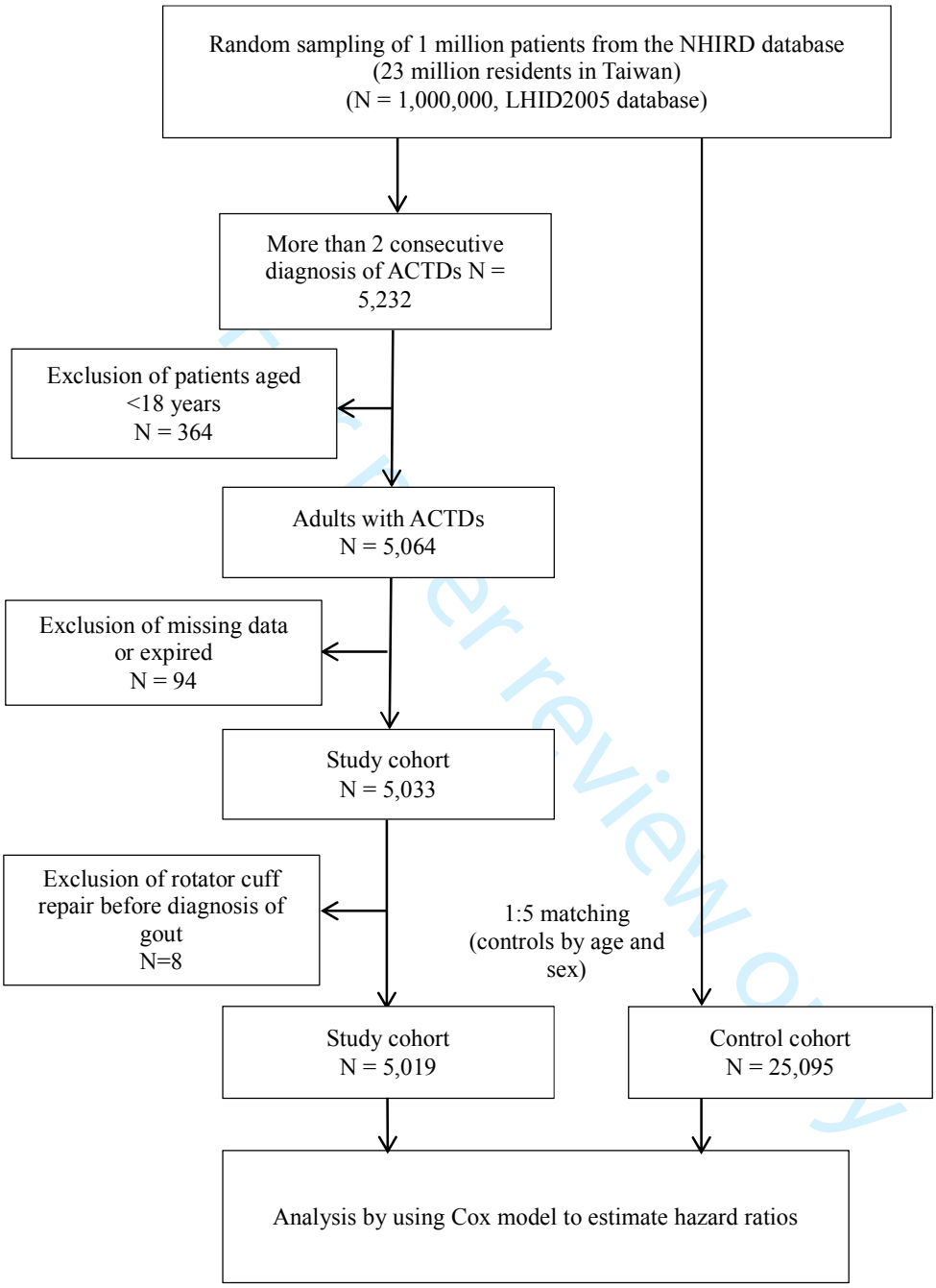
Figure 1 Flowchart showing the study design

Figure 2A Kaplan–Meier hazard curve for rotor cuff tear in autoimmune connective tissue disease patients and controls for an up to 7-year follow-up period.

Figure 2B Kaplan–Meier hazard curve for rotor cuff tear in autoimmune connective tissue disease (ACTD) patients with or without nonsteroidal anti-inflammatory drug use and controls over a 7-year follow-up period.

Figure 2C Kaplan–Meier hazard curve for rotor cuff tear in autoimmune connective tissue diseases (ACTDs) patients with or without steroid use and controls over a 7-year follow-up period.

Figure 1



Autoimmune connective tissue diseases (ACTDs)

Figure 2A.

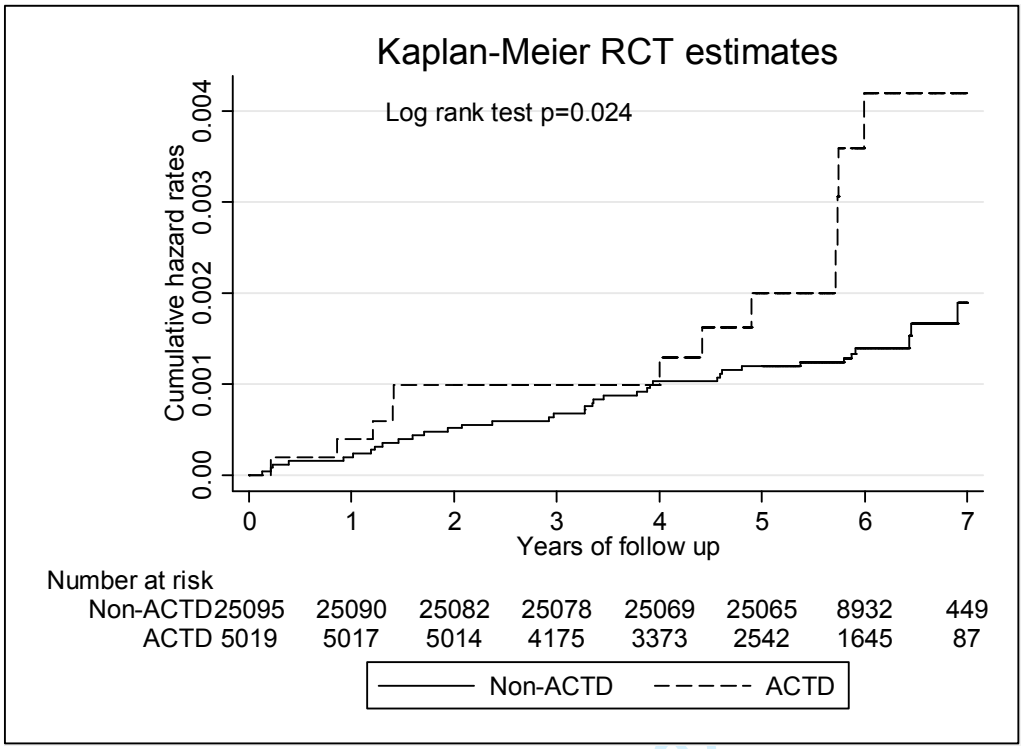


Figure 2B.

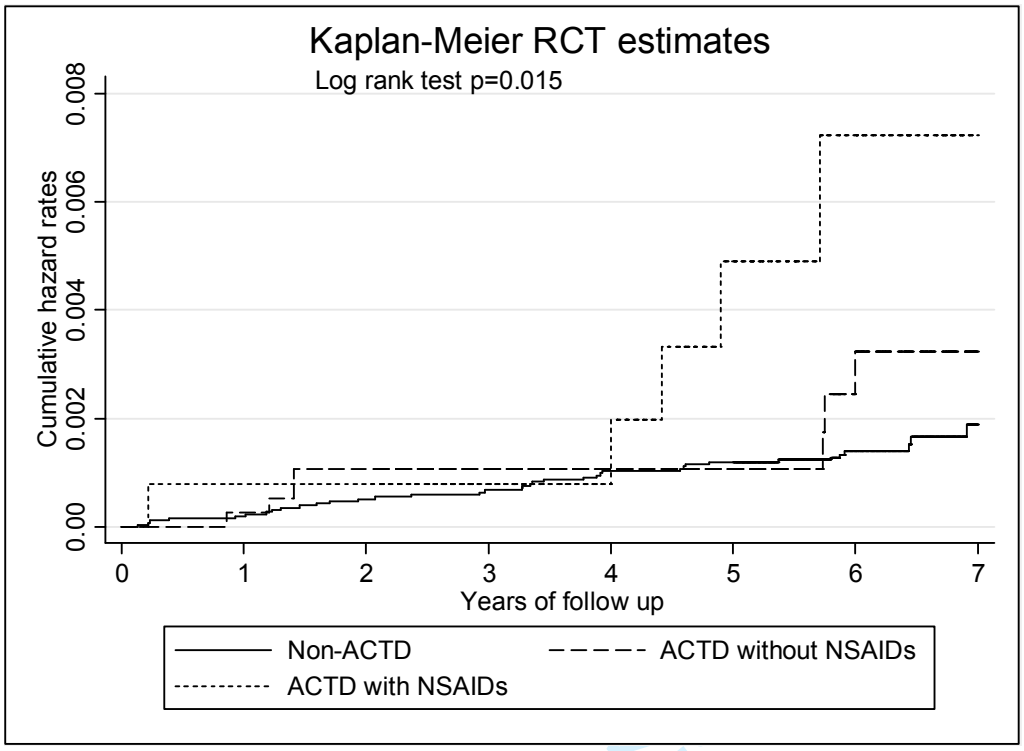
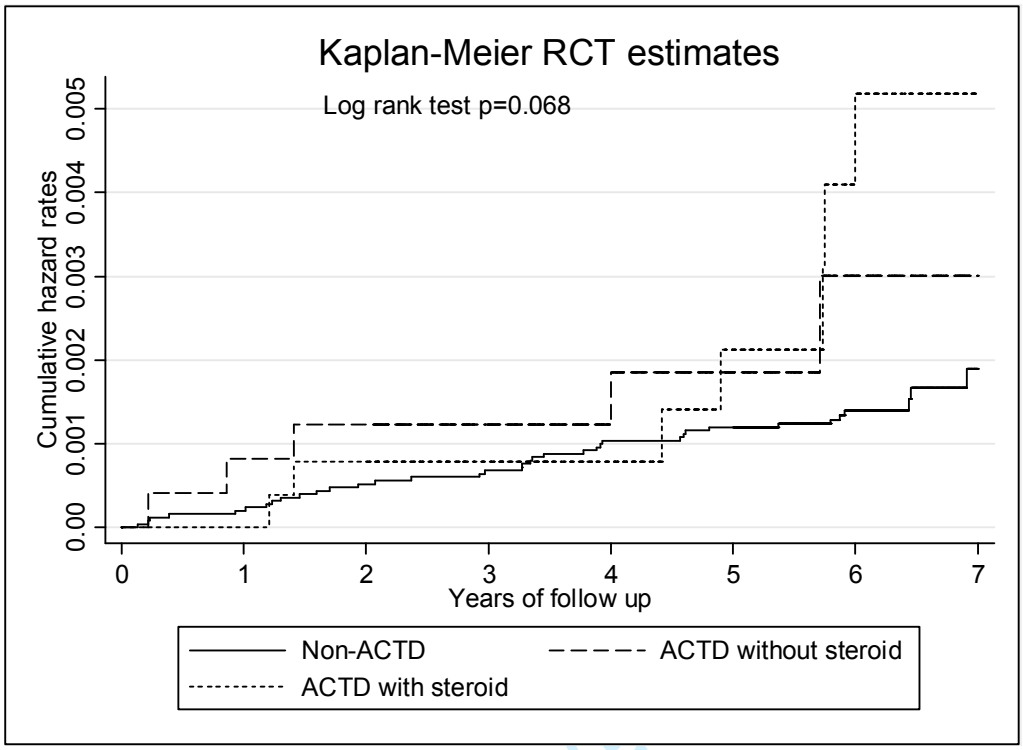


Figure 2C.



STROBE Statement

Checklist of items that should be included in reports of observational studies

Section/Topic	Item No	Recommendation	Reported on Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7-8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-8
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	

Section/Topic	Item No	Recommendation	Reported on Page No
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9-10
		(b) Give reasons for non-participation at each stage	9-10
		(c) Consider use of a flow diagram	9-10
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-10
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	9-10
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-10
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

**Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.*

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Autoimmune Connective Tissue Diseases Increase the Risk of Rotator Cuff Repair Surgery: a Population-Based Retrospective Cohort Study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-023848.R1
Article Type:	Research
Date Submitted by the Author:	11-Sep-2018
Complete List of Authors:	Huang, ShihWei; Shuang Ho Hospital, Physical Medicine and Rehabilitation Lin, CheLi; Taipei Medical University Shuang Ho Hospital, Orthopedics Lin, LiFong; Shuang Ho Hospital, Physical Medicine and Rehabilitation Huang, ChiChang; Graduate Institute of Sports Science, National Taiwan Sport University Liou, Tsan-Hon; Shuang Ho Hospital, Physical Medicine and Rehabilitation Lin, Hui-Wen; Department of Mathematics, Soochow University
Primary Subject Heading:	Rheumatology
Secondary Subject Heading:	Rehabilitation medicine, Sports and exercise medicine
Keywords:	Rheumatology < INTERNAL MEDICINE, Orthopaedic sports trauma < ORTHOPAEDIC & TRAUMA SURGERY, Shoulder < ORTHOPAEDIC & TRAUMA SURGERY

Original Article

Autoimmune Connective Tissue Diseases Increase the Risk of Rotator Cuff Repair Surgery: a Population-Based Retrospective Cohort Study

Shih-Wei Huang[1,2,3] MD, Che-Li Lin[3,4] MD, Li-Fong Lin[1,5] PhD, Chi-Chang Huang[3] PhD, Tsan-Hon Liou[1,2] MD, PhD, Hui-Wen Lin[6,7]* PhD

Running title: ATCD increase the risk of rotator cuff surgery

[1]Department of Physical Medicine and Rehabilitation, Shuang Ho Hospital, Taipei Medical University, Taipei, Taiwan

[2]Department of Physical Medicine and Rehabilitation, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan

[3]Graduate Institute of Sports Science, National Taiwan Sport University, Taoyuan, Taiwan

[4]Department of Orthopedic Surgery, Shuang Ho Hospital, Taipei Medical University, New Taipei City, Taiwan

[5]Institute of Gerontology and Health Management, Taipei Medical University, Taipei, Taiwan

[6]Department of Mathematics, Soochow University, Taipei, Taiwan

[7]Evidence-Based Medicine Center, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan

*Address for reprints:

Hui-Wen Lin, PhD

Department of Mathematics, Soochow University, 70 Linhsi Road, Shihlin, Taipei, Taiwan

Tel: 886-2-2881-9471 ext. 6701

Fax: 886-2-8861-1230

E-mail:linhw@s.tmu.edu.tw

Abstract

Objectives

Autoimmune connective tissue diseases (ACTDs) commonly involve shoulder joint, but clinical epidemiological studies investigating association of tendons are scant. When rotator cuff (RC) tears, it can cause shoulder disability, and surgical intervention is usually required. The aim of this study was to investigate rotator cuff (RC) repair surgery risk in ACTD patients. The secondary aim was to investigate the effect of anti-inflammatory medication for risk of RC repair surgery risk.

Methods

We conducted a retrospective cohort study with a 7-year longitudinal follow-up period. Patients with systemic lupus erythematous, systemic sclerosis, sicca syndrome, dermatomyositis, and polymyositis diagnoses between 2004 and 2008 were enrolled. The control cohort comprised age- and sex-matched controls. The hazard ratio (HR) and adjusted HR (aHR) were estimated for the risk of RC surgery between the ACTD and control cohorts after adjustment for confounders. Effects of steroid and nonsteroidal anti-inflammatory drug (NSAID) use on for HR and aHR of RC surgery risk were also analysed.

Results

We enrolled 5,019 ACTD patients and 25,095 controls in the ACTD and control cohorts, respectively. RC surgery incidence was 49 and 24 per 100,000 person-years in the ACTD and control cohorts, respectively. In the ACTD cohort, the crude HR for RC surgery was 2.08 (95% confidence interval [CI], 1.08–4.02, $P < 0.05$), and the aHR was 1.97 (95% CI, 1.01–3.82, $P < 0.05$). The ACTD patients who used NSAIDs had an aHR of 3.13 (95% CI, 1.21–8.07, $P < 0.05$) compared with controls, but the ACTD patients who used steroids did not have a significantly higher than controls.

Conclusions

ACTD patients had increased risk of RC repair surgery. However, there was no difference of RC surgery risk with comparing control cohort when steroid using. It could indicate that inflammation control may be a strategy for managing subsequent lesions of the RC.

Keywords: Autoimmune connective tissue diseases; rotator cuff surgery; risk factor; population-based study

Strengths and limitations of this study

- First large-scale, population-based study for risk of rotator cuff lesion among autoimmune connective tissue diseases (ACTD) patients.
- The detailed information of ACTD severity cannot be presented in this population based study.
- Although steroid can lower the risk of rotator cuff repair surgery among ACTD patients, our study didn't analysed disease-modifying anti-rheumatic drugs (DMARDs), which could influence the inflammatory status of study cohort.
- For better accuracy of study outcome, we only investigated the risk of RC lesions and the requirement of subsequent repair surgery; therefore, patients with minor tears or those who did not require surgical intervention may have been missed in this study.

Introduction

Autoimmune connective tissue diseases (ACTDs), such as systemic lupus erythematosus (SLE), systemic sclerosis, sicca syndrome, dermatomyositis, and polymyositis, are systemic autoimmune disorders that affect multiple organ systems and exhibit intermittent relapse and remission. Owing to the various organs involved the chronic inflammatory process caused by autoantibody deposition and related inflammatory reactions, ACTD patients, particularly SLE patients, usually present heterogeneous clinical manifestations.[1] The musculoskeletal system is one of the organ systems that is often affected, and initial musculoskeletal symptoms are often similar to those of autoimmune diseases.[2] The severity of clinical musculoskeletal symptoms varies among individuals. SLE patients can present mild arthralgia, without deformity or erosion, nonerosive deforming arthritis, or erosive symmetric polyarthritis. In addition to arthritis and arthralgia, the musculoskeletal symptoms of SLE patients include osteonecrosis, tendonitis, myositis, and tendon rupture.[3] However, few studies have investigated and emphasised the lesions of the enthesis in SLE patients in connection with other ACTDs.[4 5]

Rotator cuff (RC) tear or rupture is one of the most common causes of shoulder dysfunction. RC tears may be asymptomatic, or their clinical presentations can be pain accompanied by a limited range of movement. RC disorders are observed in 30%–70% of patients presenting with shoulder

pain, and the incidence of RC tears is 5%–40%.[6] Because RC tears can be asymptomatic, different studies have reported diverse prevalence rates of RC tears. An ultrasound screening study revealed that the prevalence of RC tears was 20.47% among 1366 shoulders with or without clinical symptoms, and the prevalence increased with age.[7] Initially, RC tears can be treated using conventional methods such as exercise or injections.[8] Patients with extensive RC tears experience limited shoulder function while performing daily activities or working, and surgical repair is recommended to relieve symptoms and restore function. RC repair surgery and subsequent possible complications can increase patients' medical expenditure and the economic burden on the health care system.[9]

A recent cross-sectional study investigating hand tendon findings revealed the predominance of tenosynovitis or tendonitis.[10] Case reports have described rupture of patellar and hand tendons in SLE patients. [11 12] Thus, we hypothesise that SLE patients have a relatively high risk of RC repair surgery due to tendon lesions. In addition, case reports of tendon rupture have mentioned other ACTDs, such as dermatomyositis. [13] When massive tear of RC occurred, it can cause shoulder disability, and surgical intervention is usually required. However, sufficient epidemiological research is not available to prove that SLE and other ACTDs are risk factors for RC tears that require repair surgery. We hypothesized that ACTDs patients had higher risk of RC lesions with requirement of

surgery repair. Therefore, we conducted this longitudinal retrospective cohort study to investigate the risk of RC repair surgery among ACTDs patients. Moreover, we also investigate the effect of anti-inflammatory medication for risk of RC repair surgery risk for ACTDs patients as secondary aim of study.

Methods

Study design

Using a health care database, this longitudinal retrospective cohort study analysed the risk of RC repair surgery for ATCD patients. In the study cohort, we included patients who had been diagnosed with ACTD between 1 January 2004 and 31 December 2008. Their data were obtained from the Taiwan Longitudinal Health Insurance Database 2005 (LHID2005), which was a part of National Health Insurance Research Database (NHIRD) of Taiwan. A control cohort consisting of five age- and sex-matched non-ATCD controls per ATCD patient was obtained using the same database. The follow-up period was 7 years, till the end of 2010. The follow-up period ended when the patients or controls received RC repair surgery. To ensure patient privacy, the names and identity numbers were replaced by numbers and letters from the English alphabet codes, which are used for identifying patient data in the NHIRD. Because the linked identity data were removed, the patient data from the NHIRD could not be identified; hence, the requirement of informed consent

was waived in this study. This study was approved by University of Taipei Institutional Review Board (UT-IRB No.: IRB-2018-07).

A brief background on Taiwan's National Health Insurance, NHIRD, and Longitudinal Health Insurance Database 2005

The National Health Insurance (NHI) system of Taiwan, a form of social insurance, covers more than 96% of the population of Taiwan.[14 15] The NHI programme covers almost all medical services such as outpatient visits, admission service, and emergency hospitalisation. Diagnoses made using International Classification of Diseases Ninth Revision, Clinical Modification (ICD-9-CM) codes, medical prescriptions, procedures, and surgery are recorded in the NHIRD. The data used in this study were obtained from the Taiwan LHID2005. The LHID2005 contains the data of 1,000,000 beneficiaries randomly sampled from the Registry for Beneficiaries of the NHIRD. For research purposes, the National Health Research Institutes of Taiwan collect and maintain registration files and original claims data from the NHI administration and then release them publicly through the NHIRD.

Inclusion and exclusion criteria

The study cohort included ACTD patients diagnosed with SLE (ICD-9-CM code 710.0),

systemic sclerosis (ICD-9-CM code 710.1), sicca syndrome (ICD-9-CM code 710.2), dermatomyositis (ICD-9-CM code 710.3), and polymyositis (ICD-9-CM code 710.4) by using the American College of Rheumatology criteria between 1 January 2004 and 31 December 2008. To ensure the high accuracy of ACTD diagnosis, this study selected only patients who were diagnosed with ACTDs at least twice consistently, according to ICD-9-CM codes, in outpatient clinics or those who had a primary diagnosis of ACTDs during hospitalisation within 1 year and were older than 20 years. ACTD patients who had undergone RC repair surgery before 2004, who had missing data, and who died during the follow-up period were excluded from this study. Finally, 5,019 ACTD patients were enrolled in the study cohort (Figure 1).

Confounders and propensity score adjustment

In addition to the demographic variables of age and sex, economic status and comorbidities, such as diabetes mellitus (ICD-9-CM codes 250 and 251), hypertension (ICD-9-CM codes 401–405), hyperlipidaemia (ICD-9-CM codes 272.0–272.4), coronary heart disease, gout, nonsteroidal anti-inflammatory drugs (NSAIDs), steroid use (defined as 3 months of consecutive using), and fractures, were analysed in this study. With concerning the thyroid diseases and the risk of rotator cuff tear, we also analysed the thyroid disorders as one of the morbidities in this study.[16] To minimise the bias of data selection from the study database, we used propensity scores adjusted for comorbidities and

income, as shown in Table 1.

Outcome identification

We used the first RC repair surgery with the relevant application codes (64121B and 64122B) as the study endpoint from the same database. All participants were followed up from the index date to the endpoint or until 31 December 2010, whichever was earlier, and the final-date observations were censored observations.

Statistical Analysis

Demographic characteristics and comorbidities were analysed using Pearson's chi-square test. We calculated the incidence of ACTDs and compared the risk of RC repair surgery between the two cohorts by using the Cox model after propensity score adjustment. Furthermore, we compared the risk of repair surgery in the ACTDs patients who did or did not receive medication (NSAIDs and steroids) with non-ACTD controls. To clarify the association between medication and RC tears, Kaplan–Meier hazard curves were plotted for RC tears in ACTDs patients who did or did not receive NSAIDs and controls as well as in ACTDs patients who did or did not receive steroids and controls for a 7-year follow-up period. All data analyses were performed using the Stata package (Version 11) and SAS statistical package (Version 9.1.3; SAS Institute, Cary, NC, USA). A value of $P < 0.05$ was

considered statistically significant.

Patient involvement

No patients were involved in developing the hypothesis, the specific aims or the research questions, nor were they involved in developing plans for design or implementation of the study. No patients were involved in the interpretation of study results or write up of the manuscript. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

Results

There were 5,019 ACTD patients in study cohort and 25,095 patients in the control cohort. Women constituted 77.5% in both cohorts, and there was no statistical difference of age and sex. In the study cohort, the prevalence of the comorbidities of hyperlipidaemia (17.8%), coronary heart disease (13.2%), gout (12.1%), and thyroid disorders (8.3%) were higher in the ACTD cohort than in the control cohort (Table 1). The incidence of RC repair surgery was 49.0 and 24.0 per 100,000 person-years in the ACTD and control cohorts, respectively. In the ACTD cohort, the crude hazard ratio (HR) of RC repair surgery was 2.08 (95% CI, 1.08−4.02, $P < 0.05$), and the adjusted HR (aHR) was 1.97 (95% CI, 1.01−3.82, $P < 0.05$) (Table 2). Figure 2 shows the Kaplan–Meier hazard curves for the risk of RC repair surgery in the ACTD and control cohorts during the 7-year follow-up period. A comparison of the ACTD patients who did and did not use NSAIDs (separately) with controls

revealed that the ACTD patients with records of NASID use had a higher risk of RC repair surgery (aHR = 3.13, 95% CI, 1.21–8.07, P < 0.05) than did the ACTD patients without records of NSAID use (Table 3). Figure 3 shows the Kaplan–Meier hazard curves for the risk of RC repair surgery in the ACTD patients who used NSAIDs, the ACTD patients who did not use NSAIDs, and controls during the 7-year follow-up period. Further analysis of the association between steroid use and the risk of RC repair surgery showed that the crude HR was 2.32 (95% CI, 1.03–5.22, P =0.042) among ACTD patients who used steroids. However, there was not significantly higher risk of RC surgery in the ACTD patients than in controls of adjusted HR (aHR= 2.22, 95% CI, 0.98–5.03, P =0.067) when using steroids (Table 4). Figure 4 represents the trend of the risk of RC repair surgery; the risk increased among the ACTD patients who used steroids but was not significant during the 7 year follow-up period.

Discussion

Although case reports have described spontaneous ruptures in the supraspinatus tendon and the patellar tendon and hand flexor tendon,[11-13 17] no relevant epidemiological study has investigated the risk of RC lesions among ACTD patients until now. Our population-based cohort study revealed that the ACTD patients had a higher risk of RC repair surgery than controls. This finding indicates

that in addition to the joints, the periarticular soft tissue is affected in ACTDs. During the 7-year longitudinal follow-up period, the number of events of RC repair surgery increased with ACTD progression. To improve the quality of life and prevent the negative effects of RC injuries among ACTD patients, identifying the possible mechanism of ACTD pathogenesis is crucial for developing an effective prevention strategy.

The factors involved in RC injury pathogenesis can typically be classified into extrinsic and intrinsic factors. [18] For ACTD patients, we suppose that intrinsic pathogenic aetiologies play a crucial role in increasing the risk of RC injuries and the subsequent requirement of repair surgery. ACTD patients exhibit the characteristics of systemic inflammatory processes, and inflammation reactions subsequently affect the RC tendon. Subclinical inflammation persists in ACTD patients even after clinical symptoms are under control. Subclinical chronic inflammation can disrupt the tendon healing and remodelling process. It can lead to weakening of the tendon, thus increasing the risk of subsequent tendon rupture. Previous case reports have also found perivascular mononuclear cell infiltration in the ruptured tendon, which was caused by the ACTD inflammatory process. [19 20] The inflammatory phenomenon can also be detected using ultrasound techniques. A study reported that 49.4% of ultrasound abnormalities were tenosynovitis. [21] In addition to tenosynovitis, ultrasound detected chronic tendinopathy, which led to degeneration of the tendon. The weakened

structure was highly vulnerable to injuries. These intrinsic aetiologies of tendon inflammation and subsequent tendon degeneration can lead a high risk of RC injuries and the subsequent requirement of repair surgery among ACTD patients.

ACTDs represent complicated chronic inflammatory autoimmune diseases that do not have curative treatment. To arrest the progression of autoimmune diseases, systemic steroids are often used and combined with nonsteroidal medication to control flare-up episodes. [22] Corticosteroids can accelerate weakness progression by inhibiting collagen synthesis and impairing blood supply. [23] Corticosteroids inhibit collagen synthesis and may also impair blood supply, thus weakening the tendons. [5] A critical zone near the insertion of the supraspinatus has been described using microangiographic evidence of an area of hypovascularity in the tendon close to its humeral insertion. Relative ischaemia in this zone is reported to mimic tendon degeneration. [6] Previous studies have also mentioned that chronic synovitis, tenosynovitis, and long-term steroid use can lead to degeneration and thus increase the vulnerability of the flexor tendon in ACTD patients. [24 25] However, our study revealed that steroid use in all the patients and controls did not significantly increase the risk of RC repair surgery. Studies have shown that inflammatory changes occur at the site of tendon rupture; these changes have been observed in patients with ACTDs. [19 26] Although steroids can lead to tendon degeneration, inflammatory processes can be arrested by steroid

administration. We hypothesised that the net effect of steroid use can increase the risk of RC repair surgery, but this effect was not significant in ACTD patients. Furthermore, ACTD-induced chronic inflammatory process and related degeneration can accelerate the weakening of the RC with ageing.

Our study revealed that ACTD is a risk factor for RC repair surgery. We hypothesised the possible mechanism underlying this association was chronic inflammation and tendon degeneration, which damage and weaken the RC structure. The strength of this study was its large sample size and data analysis. Moreover, it is the first epidemiological study to investigate the association between ACTDs and the risk of RC lesions and surgery. Nevertheless, several limitations of this study need to be addressed. First, the diagnosis of ACTDs and comorbidities were defined using ICD codes from the database; hence, accuracy should be examined. For accurate payment, the Bureau of NHI reviews the medical records regularly. SLE, dermatomyositis, and polymyositis patients in Taiwan can apply for catastrophic illness registration cards, and copayment is free for SLE-related medical problems from the Bureau. In addition to accuracy of ACTDs diagnosis, the definite onset duration of ACTDs cannot be obtained from the database and diversity of time period of follow up in study cohort are needed to be addressed. Second, laboratory data of the inflammatory status and severity of ACTDs cannot be obtained from the database. The severity and status of ACTDs cannot be categorised in the database, and we cannot identify which status of ACTDs patients were at a high risk of tendon

lesions. Besides the disease-modifying anti-rheumatic drugs (DMARDs), which could influence the severity of ACTDs, were not analysed because of the complexity of using from this database. Further study about DMARDs effect for rotator cuff lesions is needed to investigate separate disease from ACTDs in the future. Third, extrinsic factors affecting RC injuries include repeated impingement and overuse during work and daily living activities. These factors can increase the risk of repair surgery. However, data on work status, daily activities, body weight, alcohol consumption, and smoking are not available in the database. Although a large sample size was obtained from this database, these confounders cannot be excluded completely in this study. Finally, for higher accuracy, we only investigated the risk of RC lesions and the requirement of subsequent repair surgery; therefore, patients with minor tears or those who did not require surgical intervention may have been missed. Despite the limited information available on the types of RC lesions, our population-based study provided crucial information on the high risk of RC surgery among ACTD patients.

Conclusion

The results of this 7-year longitudinal population-based retrospective cohort study showed that ACTD patients have a 1.97-fold higher risk of RC repair surgery than do controls. Additional studies on inflammatory severity in ACTDs and the effects of ACTD-related medication on the risk of RC lesions are recommended.

Acknowledgments: None

Contributors: H-SW participated in the study design, conducted the data analysis, drafted the initial manuscript and approved the final manuscript as submitted. L-CL conducted the data analysis, drafted the manuscript and approved the final manuscript as submitted. L-LF contributed to the study design, reviewed and revised the manuscript, and approved the final manuscript as submitted. H-CC reviewed and revised the manuscript, and approved the final manuscript as submitted. L-TH participated in the study design, reviewed and revised the manuscript, and approved the final manuscript as submitted. RE designed and conceptualised the study, and approved the final manuscript as submitted. L-HW participated in the study design, conducted the data analysis, revised manuscript and approved the final manuscript as submitted.

Funding: None

Competing interests: None declared.

Ethics approval: University of Taipei Institutional Review Board (UT-IRB No.: IRB-2018-07)

Data sharing statement: From HuiWen Lin, linhw@tmu.edu.tw

Provenance and peer review: Not commissioned; externally peer reviewed.

Reference

1. Tsokos GC. Systemic lupus erythematosus. The New England journal of medicine 2011;**365**(22):2110-21 doi: 10.1056/NEJMra1100359[published Online First: Epub Date]|.
2. Rothfield N, Sontheimer RD, Bernstein M. Lupus erythematosus: systemic and cutaneous manifestations. Clinics in dermatology 2006;**24**(5):348-62 doi: 10.1016/j.clindermatol.2006.07.014[published Online First: Epub Date]|.
3. Zoma A. Musculoskeletal involvement in systemic lupus erythematosus. Lupus 2004;**13**(11):851-3 doi: 10.1191/0961203303lu2021oa[published Online First: Epub Date]|.
4. Gutierrez M, Filippucci E, De Angelis R, et al. Subclinical entheseal involvement in patients with psoriasis: an ultrasound study. Seminars in arthritis and rheumatism 2011;**40**(5):407-12 doi: 10.1016/j.semarthrit.2010.05.009[published Online First: Epub Date]|.
5. Grossman JM. Lupus arthritis. Best practice & research. Clinical rheumatology 2009;**23**(4):495-506 doi: 10.1016/j.berh.2009.04.003[published Online First: Epub Date]|.
6. Oliva F, Piccirilli E, Bossa M, et al. I.S.Mu.L.T - Rotator Cuff Tears Guidelines. Muscles, ligaments and tendons journal 2015;**5**(4):227-63 doi: 10.11138/mltj/2015.5.4.227[published Online First: Epub Date]|.
7. Yamamoto A, Takagishi K, Osawa T, et al. Prevalence and risk factors of a rotator cuff tear in the general population. Journal of shoulder and elbow surgery 2010;**19**(1):116-20 doi: 10.1016/j.jse.2009.04.006[published Online First: Epub Date]|.
8. Abdul-Wahab TA, Betancourt JP, Hassan F, et al. Initial treatment of complete rotator cuff tear and transition to surgical treatment: systematic review of the evidence. Muscles, ligaments and tendons journal 2016;**6**(1):35-47 doi: 10.11138/mltj/2016.6.1.035[published Online First: Epub Date]|.
9. Colvin AC, Egorova N, Harrison AK, et al. National trends in rotator cuff repair. The Journal of bone and joint surgery. American volume 2012;**94**(3):227-33 doi: 10.2106/JBJS.J.00739[published Online First: Epub Date]|.
10. Ogura T, Hirata A, Hayashi N, et al. Comparison of ultrasonographic joint and tendon findings in hands between early, treatment-naive patients with systemic lupus erythematosus and rheumatoid arthritis. Lupus 2017;**26**(7):707-14 doi: 10.1177/0961203316676375[published Online First: Epub Date]|.
11. Albayrak I, Kucuk A, Arslan S, et al. Spontaneous patellar tendon rupture in a case followed up for diagnosis of systemic lupus erythematosus. European journal of rheumatology 2014;**1**(4):159-60 doi: 10.5152/eurjrheumatol.2014.140044[published Online First: Epub Date]|.
12. Hosokawa T, Oda R, Toyama S, et al. Spontaneous flexor tendon rupture due to an insufficiency fracture of the hamate hook in a patient with systemic lupus erythematosus: A case report.

International journal of surgery case reports 2016;**27**:63-65 doi: 10.1016/j.ijscr.2016.06.052[published Online First: Epub Date]|.

13. Nakamura S, Nakagawa J. Recurrent extensor tendon rupture in adult-onset dermatomyositis: a case report. Clinical rheumatology 2005;**24**(4):409-10 doi: 10.1007/s10067-004-1050-0[published Online First: Epub Date]|.
14. Cheng TM. Taiwan's new national health insurance program: genesis and experience so far. Health affairs 2003;**22**(3):61-76 doi: 10.1377/hlthaff.22.3.61[published Online First: Epub Date]|.
15. Cheng SH, Chiang TL. The effect of universal health insurance on health care utilization in Taiwan. Results from a natural experiment. Jama 1997;**278**(2):89-93
16. Oliva F, Osti L, Padulo J, et al. Epidemiology of the rotator cuff tears: a new incidence related to thyroid disease. Muscles Ligaments Tendons J 2014;**4**(3):309-14
17. Prabu VN, Agrawal S, Kishore JK, et al. Supraspinatus tendon rupture in lupus: a rarity. Lupus 2009;**18**(11):1026-7 doi: 10.1177/0961203309103099[published Online First: Epub Date]|.
18. Via AG, De Cupis M, Spoliti M, et al. Clinical and biological aspects of rotator cuff tears. Muscles, ligaments and tendons journal 2013;**3**(2):70-9 doi: 10.11138/mltj/2013.3.2.070[published Online First: Epub Date]|.
19. Potasman I, Bassan HM. Multiple tendon rupture in systemic lupus erythematosus: case report and review of the literature. Annals of the rheumatic diseases 1984;**43**(2):347-9
20. Lu M, Johar S, Veenema K, et al. Patellar tendon rupture with underlying systemic lupus erythematosus: a case report. The Journal of emergency medicine 2012;**43**(1):e35-8 doi: 10.1016/j.jemermed.2009.08.054[published Online First: Epub Date]|.
21. Di Matteo A, De Angelis R, Cipolletta E, et al. Systemic lupus erythematosus arthropathy: the sonographic perspective. Lupus 2017:961203317747716 doi: 10.1177/0961203317747716[published Online First: Epub Date]|.
22. Thamer M, Hernan MA, Zhang Y, et al. Prednisone, lupus activity, and permanent organ damage. The Journal of rheumatology 2009;**36**(3):560-4 doi: 10.3899/jrheum.080828[published Online First: Epub Date]|.
23. Halpern AA, Horowitz BG, Nagel DA. Tendon ruptures associated with corticosteroid therapy. The Western journal of medicine 1977;**127**(5):378-82
24. Zayat AS, Md Yusof MY, Wakefield RJ, et al. The role of ultrasound in assessing musculoskeletal symptoms of systemic lupus erythematosus: a systematic literature review. Rheumatology 2016;**55**(3):485-94 doi: 10.1093/rheumatology/kev343[published Online First: Epub Date]|.
25. Alves EM, Macieira JC, Borba E, et al. Spontaneous tendon rupture in systemic lupus erythematosus: association with Jaccoud's arthropathy. Lupus 2010;**19**(3):247-54 doi: 10.1177/0961203309351729[published Online First: Epub Date]|.

26. Furie RA, Chartash EK. Tendon rupture in systemic lupus erythematosus. Seminars in arthritis and rheumatism 1988;**18**(2):127-33

Figure Legends

Figure 1 Flowchart showing the study design

Figure 2 Kaplan–Meier hazard curve for rotor cuff tear in autoimmune connective tissue disease patients and controls for an up to 7-year follow-up period.

Figure 3 Kaplan–Meier hazard curve for rotor cuff tear in autoimmune connective tissue disease (ACTD) patients with or without nonsteroidal anti-inflammatory drug use and controls over a 7-year follow-up period.

Figure 4 Kaplan–Meier hazard curve for rotor cuff tear in autoimmune connective tissue diseases (ACTDs) patients with or without steroid use and controls over a 7-year follow-up period.

Table 1. Demographic characteristics and comorbidities of autoimmune connective tissue disease (ACTD) patients and controls from 2004 to 2008.

Baseline variable	ACTD cohort n = 5019		Control cohort n = 25095		P value	After propensity score adjusted P value
	No	(%)	No	(%)		
Characteristics						
Sex						
Female	3892	77.5	19460	77.5		
Male	1127	22.5	5635	22.5		
Age (years)						
18–30	701	14.0	3505	14.0		
31–40	816	16.3	4080	16.3		
41–50	1042	20.8	5210	20.8		
51–60	1029	20.5	5145	20.5		
61–70	765	15.2	3825	15.2		
>70	666	13.3	3330	13.3		
Income					<0.001	0.478
dependant	1289	25.7	6523	26.0		
1–25000	2217	44.2	12119	48.3		
25001–50000	1095	21.8	4961	19.8		
>50000	418	8.3	1492	5.9		
Comorbid medical disorders						
Fracture						
Yes	62	1.2	284	1.1	0.530	0.944
No	4957	98.8	24811	98.9		
DM						
Yes	562	11.2	2965	11.8	0.214	0.732
No	4457	88.8	22130	88.2		
Hypertension						
Yes	1300	25.9	6287	25.1	0.206	0.808
No	3719	74.1	18808	74.9		
Hyperlipidaemia					<0.001	0.932
Yes	891	17.8	3355	13.4		
No	4128	82.2	21740	86.6		
Coronary heart disease					<0.001	0.899
Yes	660	13.2	2447	9.8		
No	4359	86.8	22648	90.2		
Gout					<0.001	0.901
Yes	608	12.1	2278	9.1		
No	4411	87.9	22817	90.9		
Thyroid					<0.001	0.529
Yes	416	8.3	1158	4.6		
No	4603	91.7	23937	95.4		
Parkinson's disease					0.849	0.956

Yes	74	1.5	379	1.5
No	4945	98.5	24716	98.5

Table 2. Crude and adjusted hazard ratios for RCT between the autoimmune connective tissue disease (ACTD) and non-ACTD cohorts during the 7-year follow-up period, starting from the index date of an ambulatory care visit (n = 30,114).

Presence of RCT	Non-ACTD controls	ACTD patients
7-year follow-up period		
Yes/Total	37/25095	12/5019
Person-years	154275	24536
Incidence per 100,000 person-years	24	49
Crude HR (95% CI)	1.00	2.08* (1.08-4.02)
Adjusted HR [a] (95% CI)	1.00	1.97* (1.01-3.82)

Notes: [a] The propensity score was adjusted according to age, sex, income, diabetes mellitus, hypertension, hyperlipidaemia, coronary heart diseases, fracture, thyroid, gout and Parkinson's disease. *indicates $P < 0.05$

RCT: rotor cuff tear; HR: hazard ratio

Table 3. Crude and adjusted hazard ratios for rotor cuff tear in patients with autoimmune connective tissue diseases (ACTDs) with or without NSAID use and non-ACTD controls during the follow-up period starting from index of ambulatory care.

Presence of **RCT**	Non-ACTD	Patients with ACTDs	
		Without a history of NSAID use	History of NSAIDs use
7-year follow-up period			
Yes/Total	37/25095	7/3745	5/1274
Crude HR (95% CI)	1.00	1.61 (0.71–3.64)	3.53** (1.38–9.01)
Adjusted HR [a] (95% CI)	1.00	1.56 (0.69–3.53)	3.13* (1.21–8.07)

Notes: [a] The propensity score was adjusted according to age, sex, income, diabetes mellitus, hypertension, hyperlipidaemia, coronary heart diseases, fracture, thyroid, gout and Parkinson's disease. *indicates $P < 0.05$, **indicates $P < 0.01$

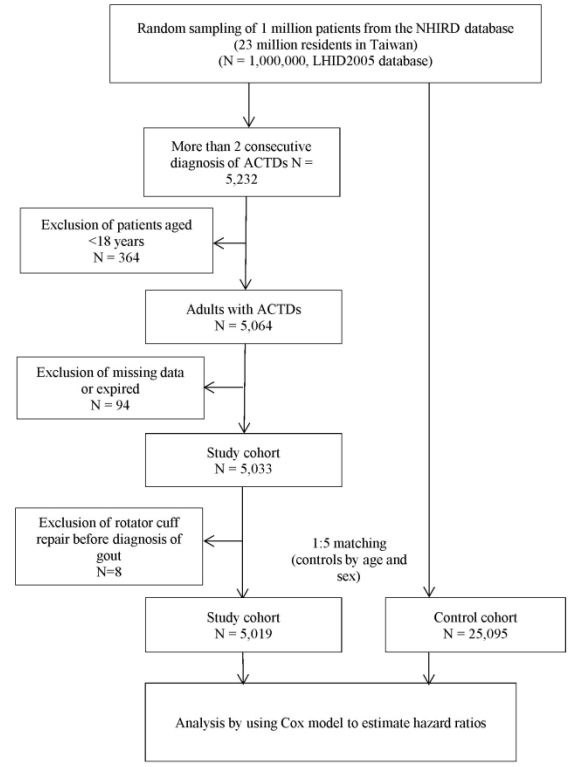
RCT: rotor cuff tear; HR: hazard ratio

Table 4. Crude and adjusted hazard ratios for rotor cuff tear in patients with autoimmune connective tissue diseases (ACTDs) with or without steroid use and non-ACTD controls during the follow-up period starting from index of ambulatory care.

Presence of **RCT**	Non-ACTD	Patients with ACTD	
		Without a history of steroid use	History of steroid use
7-year follow-up period			
Yes/Total	37/25095	5/2452	7/2567
Crude HR (95% CI)	1.00	1.83 (0.71–4.67)	2.32* (1.03–5.22)
Adjusted HR [a] (95% CI)	1.00	1.70 (0.66–4.37)	2.22 (0.98–5.03)

Notes: [a] The propensity score was adjusted according to age, sex, income, diabetes mellitus, hypertension, hyperlipidaemia, coronary heart diseases, fracture, thyroid, gout and Parkinson's disease. *indicates $P < 0.05$.
RCT: rotor cuff tear; HR: hazard ratio

Figure 1



Autoimmune connective tissue diseases (ACTDs)

Figure1/Flowchart showing the study design

209x297mm (300 x 300 DPI)

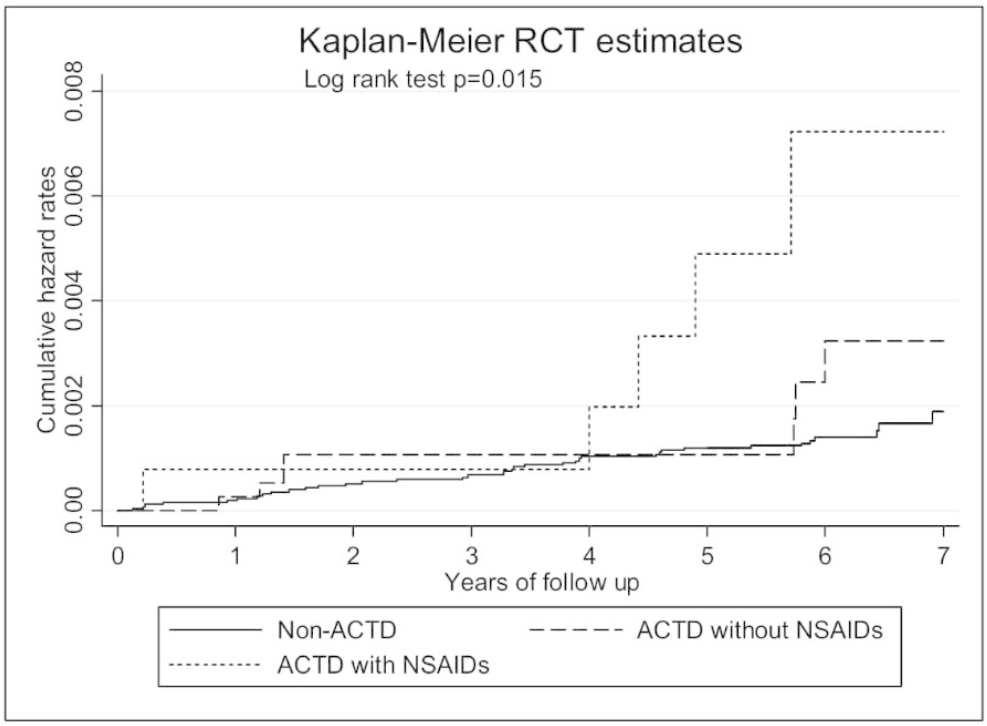


Figure 2/Kaplan–Meier hazard curve for rotor cuff tear in autoimmune connective tissue disease patients and controls for an up to 7-year follow-up period.

318x232mm (72 x 72 DPI)

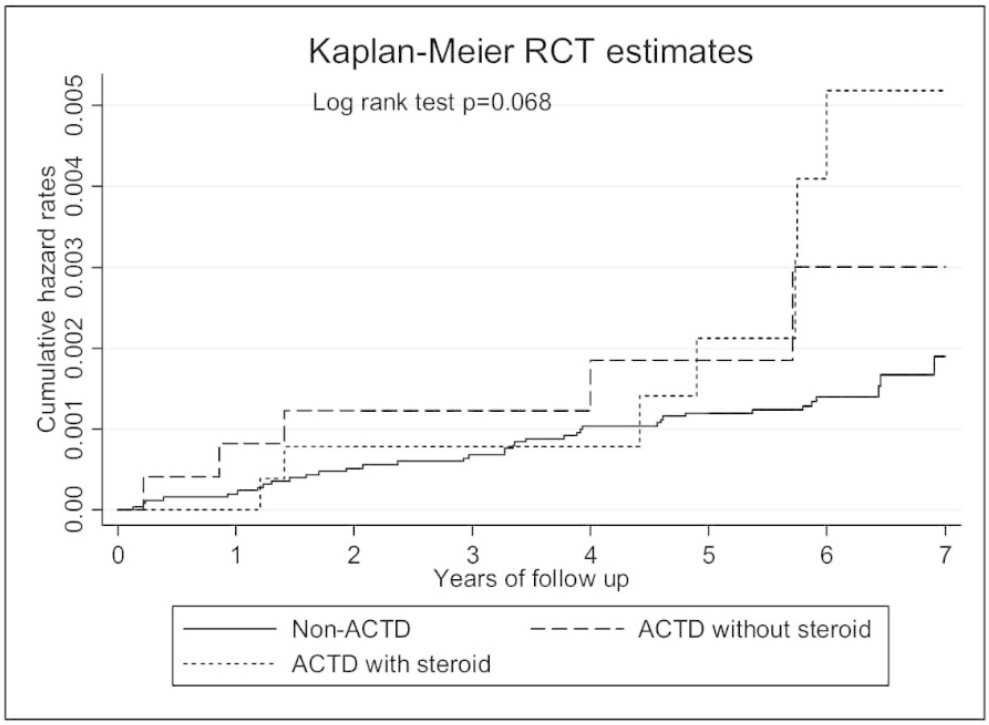


Figure 3/Kaplan–Meier hazard curve for rotor cuff tear in autoimmune connective tissue disease (ACTD) patients with or without nonsteroidal anti-inflammatory drug use and controls over a 7-year follow-up period.

318x233mm (72 x 72 DPI)

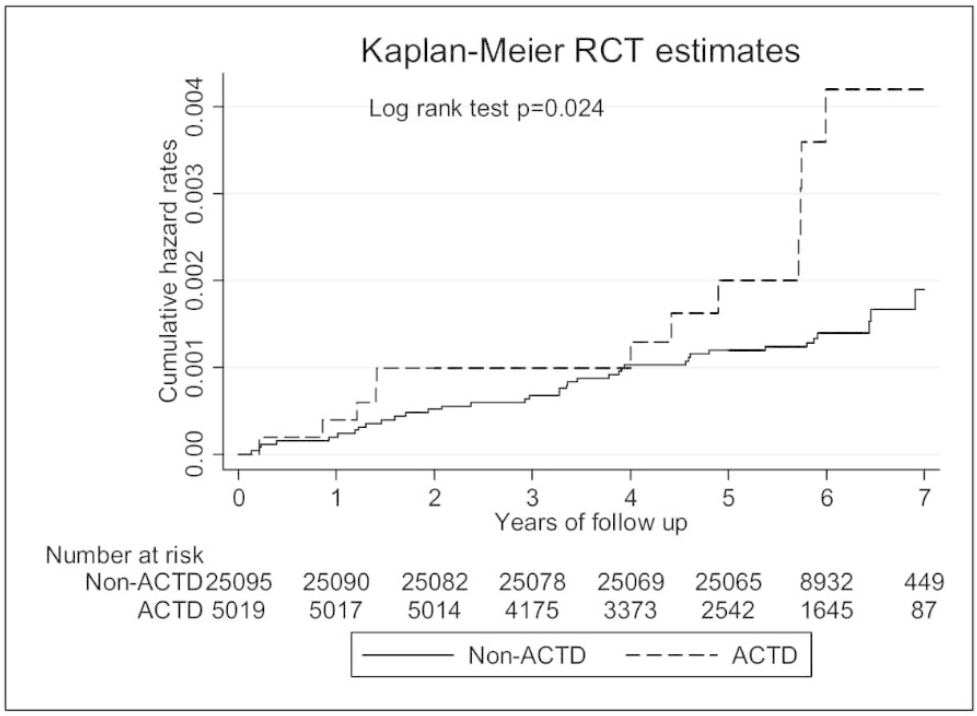


Figure 4/Kaplan–Meier hazard curve for rotor cuff tear in autoimmune connective tissue diseases (ACTDs) patients with or without steroid use and controls over a 7-year follow-up period.

322x235mm (72 x 72 DPI)

STROBE Statement

Checklist of items that should be included in reports of observational studies

Section/Topic	Item No	Recommendation	Reported on Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7-8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-8
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	

Section/Topic	Item No	Recommendation	Reported on Page No
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9-10
		(b) Give reasons for non-participation at each stage	9-10
		(c) Consider use of a flow diagram	9-10
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-10
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	9-10
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-10
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

**Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.*

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Autoimmune Connective Tissue Diseases Increase the Risk of Rotator Cuff Repair Surgery: a Population-Based Retrospective Cohort Study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-023848.R2
Article Type:	Research
Date Submitted by the Author:	20-Nov-2018
Complete List of Authors:	Huang, ShihWei; Shuang Ho Hospital, Physical Medicine and Rehabilitation Lin, CheLi; Taipei Medical University Shuang Ho Hospital, Orthopedics Lin, LiFong; Shuang Ho Hospital, Physical Medicine and Rehabilitation Huang, ChiChang; Graduate Institute of Sports Science, National Taiwan Sport University Liou, Tsan-Hon; Shuang Ho Hospital, Physical Medicine and Rehabilitation Lin, Hui-Wen; Department of Mathematics, Soochow University
Primary Subject Heading:	Rheumatology
Secondary Subject Heading:	Rehabilitation medicine, Sports and exercise medicine
Keywords:	Rheumatology < INTERNAL MEDICINE, Orthopaedic sports trauma < ORTHOPAEDIC & TRAUMA SURGERY, Shoulder < ORTHOPAEDIC & TRAUMA SURGERY

Original Article

Autoimmune Connective Tissue Diseases Increase the Risk of Rotator Cuff Repair Surgery: A Population-Based Retrospective Cohort Study

Shih-Wei Huang[1,2,3] MD, Che-Li Lin[3,4] MD, Li-Fong Lin[1,5] PhD, Chi-Chang Huang[3] PhD, Tsan-Hon Liou[1,2] MD, PhD, Hui-Wen Lin[6,7]* PhD

Running title: ACTDs increase the risk of rotator cuff surgery

[1]Department of Physical Medicine and Rehabilitation, Shuang Ho Hospital, Taipei Medical University, Taipei, Taiwan

[2]Department of Physical Medicine and Rehabilitation, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan

[3]Graduate Institute of Sports Science, National Taiwan Sport University, Taoyuan, Taiwan

[4]Department of Orthopedic Surgery, Shuang Ho Hospital, Taipei Medical University, New Taipei City, Taiwan

[5]Institute of Gerontology and Health Management, Taipei Medical University, Taipei, Taiwan

[6]Department of Mathematics, Soochow University, Taipei, Taiwan

[7]Evidence-Based Medicine Center, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan

*Address for reprints:

Hui-Wen Lin, PhD

Department of Mathematics, Soochow University, 70 Linhsi Road, Shihlin, Taipei, Taiwan

Tel: 886-2-2881-9471 ext. 6701

Fax: 886-2-8861-1230

E-mail:linhw@tmu.edu.tw

Abstract

Objectives

Autoimmune connective tissue diseases (ACTDs) commonly involve the shoulder joint; however, clinical epidemiological studies investigating their association with tendons are scant. Rotator cuff (RC) tears can cause shoulder disability, and surgical intervention is usually required. The study investigated RC repair surgery risk in ACTD patients. The effect of anti-inflammatory medication on RC repair surgery risk was also investigated.

Methods

We conducted a retrospective cohort study with a 7-year longitudinal follow-up period. Patients with systemic lupus erythematous, systemic sclerosis, sicca syndrome, dermatomyositis, and polymyositis diagnoses between 2004 and 2008 were enrolled. The control cohort comprised age- and sex-matched controls. The hazard ratio (HR) and adjusted HR (aHR) were estimated for the risk of RC surgery between ACTD and control cohorts after adjustment for confounders. Furthermore, the effects of steroid and nonsteroidal anti-inflammatory drug (NSAID) use on the HR and aHR of RC surgery risk were analysed.

Results

We enrolled 5,019 ACTD patients and 25,095 controls in the ACTD and control cohorts, respectively. RC surgery incidence was 49 and 24 per 100,000 person-years in the ACTD and control cohorts, respectively. In the ACTD cohort, the crude HR for RC surgery was 2.08 (95% confidence interval [CI], 1.08–4.02, $P < 0.05$), and the aHR was 1.97 (95% CI, 1.01–3.82, $P < 0.05$). The ACTD patients who used NSAIDs had an aHR of 3.13 (95% CI, 1.21–8.07, $P < 0.05$) compared with the controls, but the ACTD patients who used steroids did not have a significantly higher aHR than the controls.

Conclusions

ACTD patients had an increased risk of RC repair surgery. However, no difference was found in RC surgery risk when steroids were used compared with the control cohort. This could indicate that inflammation control may be a strategy for managing subsequent RC lesions.

Keywords: Autoimmune connective tissue diseases; rotator cuff surgery; risk factor; population-based study

Strengths and limitations of this study

- First large-scale, population-based study on the risk of rotator cuff (RC) lesions among patients with autoimmune connective tissue diseases (ACTDs).
- Detailed information of ACTD severity could not be presented.
- Although steroids can lower the risk of RC repair surgery among patients, our study did not analyse disease-modifying anti-rheumatic drugs, which might have influenced the inflammatory status of the study cohort.
- To enhance the accuracy of study outcomes, we only investigated the risk of RC lesions and the requirement of subsequent repair surgery; therefore, patients with minor tears or who did not require surgical intervention might have been missed.

Introduction

Autoimmune connective tissue diseases (ACTDs), such as systemic lupus erythematosus (SLE), systemic sclerosis, sicca syndrome, dermatomyositis, and polymyositis, are systemic autoimmune disorders that affect multiple organ systems and exhibit intermittent relapse and remission. Owing to the various organs involved in the chronic inflammatory process caused by autoantibody deposition and related inflammatory reactions, ACTD patients—particularly SLE patients—usually present heterogeneous clinical manifestations.[1] The musculoskeletal system is one of the organ systems that is often affected, and initial musculoskeletal symptoms are often similar to those of autoimmune diseases.[2] The severity of clinical musculoskeletal symptoms varies among individuals. SLE patients can present mild arthralgia without deformity or erosion, nonerosive deforming arthritis, or erosive symmetric polyarthritis. In addition, the musculoskeletal symptoms of these patients can include osteonecrosis, tendonitis, myositis, and tendon rupture.[3] However, few studies have investigated or emphasised lesions of the enthesis in SLE patients in connection with other ACTDs.[4, 5]

Rotator cuff (RC) tear or rupture is one of the most common causes of shoulder dysfunction. RC tears may be asymptomatic, or their clinical presentations can be pain accompanied by a limited range of movement. RC disorders are observed in 30%–70% of patients presenting with shoulder

pain, and the incidence of RC tears is 5%–40%.[6] Because RC tears can be asymptomatic, studies have reported diverse prevalence rates of RC tears. An ultrasound screening study revealed that the prevalence of RC tears was 20.47% among 1,366 shoulders with or without clinical symptoms, and the prevalence increased with age.[7] Initially, RC tears can be treated using conventional methods such as exercise or injections.[8] Patients with extensive RC tears experience limited shoulder function when performing daily activities or working. Surgical repair is recommended to relieve symptoms and restore function. RC repair surgery and subsequent possible complications can increase patients' medical expenditure and the economic burden on health care systems.[9]

A cross-sectional study investigated hand tendons and revealed the predominance of tenosynovitis or tendonitis.[10] Case reports have described the rupture of patellar and hand tendons in SLE patients.[11, 12] Thus, we hypothesised that SLE patients have a relatively high risk of RC repair surgery because of tendon lesions. In addition, case reports of tendon rupture have mentioned other ACTDs such as dermatomyositis.[13] A massive RC tear can cause shoulder disability and surgical intervention is usually required. However, sufficient epidemiological research has not been conducted to prove that SLE and other ACTDs are risk factors for RC tears requiring repair surgery. Thus, we hypothesised that ACTD patients have a higher risk of RC lesions that require repair surgery and conducted this longitudinal, retrospective cohort study to investigate this risk. In addition,

we investigated the effect of anti-inflammatory medication on the RC repair surgery risk for ACTD patients.

Methods

Study design

Using a health care database, this longitudinal retrospective cohort study analysed the risk of RC repair surgery for ATCD patients. We included patients who had been diagnosed with ACTDs between 1 January 2004 and 31 December 2008. Their data were obtained from the Taiwan Longitudinal Health Insurance Database 2005 (LHID2005), part of Taiwan's National Health Insurance Research Database (NHIRD). A control cohort consisting of five age- and sex-matched non-ACTD controls per ACTD patient was obtained using the same database. We retrieved data from the database since 2004 with a follow-up period of 2–7 years or until the end of 2010. The follow-up period ended when the patients or controls received RC repair surgery. To ensure patient privacy, their names and identity numbers were replaced by numbers and letters from the English alphabet codes that are used for identifying patient data in the NHIRD. Because the linked identity data were removed, patients' data could not be identified, and thus, the requirement for informed consent was waived. This study was approved by the Institutional Review Board of the University of Taipei (UT-IRB No.: IRB-2018-07).

Brief background of Taiwan's National Health Insurance (NHI) system, NHIRD, and LHID2005

Taiwan's NHI system is a form of social insurance that covers more than 96% of the population of Taiwan.[14, 15] The NHI programme covers almost all medical services, such as outpatient visits, admission services, and emergency hospitalisations. Diagnoses made using International Classification of Diseases Ninth Revision, Clinical Modification (ICD-9-CM) codes, medical prescriptions, procedures, and surgeries are recorded in the NHIRD. As previously mentioned, the data used in this study were obtained from the Taiwan LHID2005, which contains the data of 1,000,000 beneficiaries randomly sampled from the Registry for Beneficiaries of the NHIRD. For research purposes, the National Health Research Institutes of Taiwan collects and maintains registration files and original claims data from the NHI administration and then releases them publicly through the NHIRD.

Inclusion and exclusion criteria

The study cohort included ACTD patients diagnosed with SLE (ICD-9-CM code 710.0), systemic sclerosis (ICD-9-CM code 710.1), sicca syndrome (ICD-9-CM code 710.2), dermatomyositis (ICD-9-CM code 710.3), and polymyositis (ICD-9-CM code 710.4) by using the American College of Rheumatology criteria between 1 January 2004 and 31 December 2008. To

ensure high accuracy of the ACTD diagnoses, this study only selected patients diagnosed with ACTDs at least twice consistently, according to ICD-9-CM codes, in outpatient clinics or those who had a primary diagnosis of ACTDs during hospitalisation within 1 year and were older than 20 years. ACTD patients who had undergone RC repair surgery before 2004, had missing data, or had died during the follow-up period were excluded from the study. Finally, 5,019 ACTD patients were enrolled into the study cohort (Figure 1).

Confounders and propensity score adjustment

In addition to the demographic variables of age and sex, economic status and comorbidities such as diabetes mellitus (ICD-9-CM codes 250 and 251), hypertension (ICD-9-CM codes 401–405), hyperlipidaemia (ICD-9-CM codes 272.0–272.4), coronary heart disease, gout, nonsteroidal anti-inflammatory drugs (NSAIDs), steroid use (defined as 3 months of consecutive use), and fractures were analysed in this study. Regarding thyroid diseases and RC tear risk, we also analysed thyroid disorders as a morbidity.[16] Furthermore, comorbidities were determined at the specific time point that the patients were enrolled into the study and not changed during the follow-up period. To minimise bias in data selection from the study database, we used propensity scores adjusted for comorbidities and income, as shown in Table 1.

Outcome identification

We used the first RC repair surgery with the relevant application codes (64121B and 64122B) as the study endpoint from the same database. All participants were followed from the index date to the endpoint or until 31 December 2010, whichever was earlier, and the final-date observations were censored observations.

Statistical analysis

Demographic characteristics and comorbidities were analysed using Pearson's chi-squared test. We calculated the incidence of ACTDs and compared the risk of RC repair surgery between the two cohorts by using the Cox model after propensity score adjustment. Furthermore, we compared the risk of repair surgery in the ACTD patients who did or did not receive medication (NSAIDs and steroids) with that in the non-ACTD controls. To clarify the association between medication and RC tears, Kaplan–Meier hazard curves were plotted for RC tears in the ACTD patients who did or did not receive NSAIDs and the controls as well as in the ACTD patients who did or did not receive steroids and the controls for a 7-year follow-up period. All data analyses were performed using Stata (Version 11) and SAS (Version 9.1.3; SAS Institute, Cary, NC, USA). A value of $P < 0.05$ was considered statistically significant.

Patient involvement

No patients were involved in developing the hypothesis, specific aims, or the research questions, nor were they involved in developing plans for the design or implementation of the study. No patients were involved in the interpretation of the study results or writing of the manuscript. No plans exist to disseminate the research results to the study participants or the relevant patient community.

Results

In total, 5,019 ACTD patients were in the study cohort and 25,095 patients were in the control cohort. Women constituted 77.5% of each cohort and no statistical differences existed in age or sex. The prevalence of the comorbidities hyperlipidaemia (17.8%), coronary heart disease (13.2%), gout (12.1%), and thyroid disorders (8.3%) were higher in the ACTD cohort than in the control cohort (Table 1). The incidence of RC repair surgery was 49.0 and 24.0 per 100,000 person-years in the ACTD and control cohorts, respectively. In the ACTD cohort, the crude hazard ratio (HR) of RC repair surgery was 2.08 (95% confidence interval [CI], 1.08−4.02, $P < 0.05$), and the adjusted HR (aHR) was 1.97 (95% CI, 1.01−3.82, $P < 0.05$) (Table 2). Figure 2 presents the Kaplan–Meier hazard curves for the risk of RC repair surgery in the ACTD and control cohorts during the 7-year follow-up period. A comparison of the patients who did and did not use NSAIDs (separately) with the controls revealed that the ACTD patients with records of NSAID use had a higher risk of RC repair surgery (aHR = 3.13, 95% CI, 1.21–8.07, $P < 0.05$) than did the ACTD patients without records of NSAID use (Table 3). Figure 3 presents the Kaplan–Meier hazard curves for the risk of RC repair surgery in

the ACTD patients who used NSAIDs, the ACTD patients who did not use NSAIDs, and the controls during the 7-year follow-up period. Further analysis of the association between steroid use and the risk of RC repair surgery showed that the crude HR was 2.32 (95% CI, 1.03–5.22, P = 0.042) among the ACTD patients who used steroids. However, the risk of RC surgery in the ACTD patients was not significantly higher than that in the controls in terms of adjusted HR (aHR= 2.22, 95% CI, 0.98–5.03, P = 0.067) when using steroids (Table 4). Figure 4 represents the trend of the risk of RC repair surgery; the risk increased among the ACTD patients who used steroids, but it was not significant during the 7 year follow-up period.

Discussion

Although case reports have described spontaneous ruptures in the supraspinatus tendon, patellar tendon, and hand flexor tendon,[11-13, 17] no relevant epidemiological study has investigated the risk of RC lesions among ACTD patients until now. In our population-based cohort study, the ACTD patients had a higher risk of RC repair surgery than the controls. This finding indicates that in addition to the joints, the periarticular soft tissue is affected in ACTDs. During the 7-year longitudinal follow-up period, the number of RC repair surgery events increased with disease progression. To improve quality of life of ACTD patients, prevent negative effects of RC injuries,

and develop an effective prevention strategy, identifying the possible mechanism of ACTD pathogenesis is crucial.

The factors involved in RC injury pathogenesis can typically be classified into extrinsic and intrinsic factors.[18] For ACTD patients, we supposed that intrinsic pathogenic aetiologies play a crucial role in increasing the risk of RC injuries and the subsequent requirement of repair surgery. ACTD patients exhibit the characteristics of systemic inflammatory processes, and subsequently, inflammation reactions affect the RC tendon. Subclinical inflammation persists in these ACTD patients even after their clinical symptoms are under control. Subclinical chronic inflammation can disrupt the tendon healing and remodelling process, which can lead to weakening of the tendon, thereby increasing the risk of subsequent tendon rupture. Previous case reports have found perivascular mononuclear cell infiltration in the ruptured tendon, which was caused by the ACTD inflammatory process.[19, 20] The inflammatory phenomenon can also be detected using ultrasound techniques. A study reported that 49.4% of ultrasound abnormalities were tenosynovitis.[21] In addition to tenosynovitis, ultrasound detected chronic tendinopathy, which led to degeneration of the tendon; the weakened structure was highly vulnerable to injuries. These intrinsic aetiologies of tendon inflammation and subsequent tendon degeneration can lead to a high risk of RC injuries and the subsequent requirement of repair surgery among ACTD patients.

ACTDs represent complicated chronic inflammatory autoimmune diseases with no curative treatment options. To arrest the progression of autoimmune diseases, systemic steroids are often used and combined with nonsteroidal medication to control flare-up episodes.[22] Corticosteroids can accelerate the progression of weakness by inhibiting collagen synthesis and impairing blood supply.[23] Corticosteroids inhibit collagen synthesis and may also impair blood supply, thereby weakening the tendons.[5] A critical zone near the insertion of the supraspinatus has been described using microangiographic evidence of an area of hypovascularity in the tendon close to its humeral insertion. Relative ischaemia in this zone is reported to mimic tendon degeneration.[6] In addition, studies have mentioned that chronic synovitis, tenosynovitis, and long-term steroid use can lead to degeneration, thereby increasing the vulnerability of the flexor tendon in ACTD patients.[24, 25] However, our study revealed that steroid use in all patients and controls did not significantly increase the risk of RC repair surgery. Relevant studies have shown that inflammatory changes occur at the site of tendon rupture; these changes have been observed in ACTD patients.[19, 26] Although steroids can lead to tendon degeneration, inflammatory processes can be arrested by steroid administration. We hypothesised that the net effect of steroid use can increase the risk of RC repair surgery; however, this effect was not significant in the ACTD patients. Furthermore, the ACTD-induced chronic inflammatory process and related degeneration can accelerate the weakening of RC

with ageing.

Our study revealed that ACTDs are a risk factor for RC repair surgery. We hypothesised that the possible mechanism underlying this association was chronic inflammation and tendon degeneration, which damage and weaken the RC's structure. The strength of this study is its large sample size and data analysis. Moreover, it is the first epidemiological study to investigate the association between ACTDs and the risk of RC lesions and surgery. Nevertheless, this study has several limitations that must be addressed. First, the diagnosis of ACTDs and comorbidities were defined using ICD codes from the database; hence, the accuracy should be examined. For accurate payments, the Bureau of NHI reviews medical records regularly. Patients with SLE, dermatomyositis, and polymyositis in Taiwan can apply for catastrophic illness registration cards, and copayment is free for SLE-related medical problems. In addition to the accuracy of ACTD diagnosis, the definite onset duration of ACTDs could not be obtained from the database, and the diversity of follow-up periods for the study cohort must be addressed. Second, laboratory data of the inflammatory status and severity of ACTDs could not be obtained from the database. Moreover, the severity and status of ACTDs could not be categorised in the database and we could not identify which statuses of ACTD patients were at a high risk of tendon lesions. Furthermore, disease-modifying anti-rheumatic drugs (DMARDs), which could influence the severity of ACTDs, were not analysed because of the complexity of use from this

database. Further studies on DMARDs' effect on RC lesions are required to investigate separate diseases among ACTDs. Third, extrinsic factors affecting RC injuries include repeated impingement and overuse during work and daily living activities. These factors can increase the risk of repair surgery. However, data on work status, daily activities, body weight, alcohol consumption, and smoking are not available in the database; although a large sample size was obtained, these confounders could not be excluded completely from this study. Finally, for higher accuracy, we only investigated the risk of RC lesions and requirement of subsequent repair surgery; therefore, patients with minor tears or those who did not require surgical intervention might have been missed. Despite the limited information available on the types of RC lesion, our population-based study provided crucial information on the high risk of RC surgery among ACTD patients.

Conclusion

The results of this 7-year longitudinal population-based retrospective cohort study showed that ACTD patients had a 1.97-fold higher risk of RC repair surgery than the controls. Additional studies on inflammation severity in ACTDs and the effects of ACTD-related medication on the risk of RC lesions are recommended.

Acknowledgments: None.

Contributors: H-SW participated in the study design, conducted the data analysis, drafted the initial manuscript, and approved the final manuscript as submitted. L-CL conducted the data analysis, drafted the manuscript, and approved the final manuscript as submitted. L-LF contributed to the study design, reviewed and revised the manuscript, and approved the final manuscript as submitted. H-CC reviewed and revised the manuscript and approved the final manuscript as submitted. L-TH participated in the study design, reviewed and revised the manuscript, and approved the final manuscript as submitted. RE designed and conceptualised the study and approved the final manuscript as submitted. L-HW participated in the study design, conducted the data analysis, revised the manuscript, and approved the final manuscript as submitted.

Funding: None.

Competing interests: None to declare.

Ethics approval: Institutional Review Board of the University of Taipei (UT-IRB No.: IRB-2018-07).

Data sharing statement: From Hui-Wen Lin, linhw@tmu.edu.tw

Provenance and peer review: Not commissioned; externally peer reviewed.

Reference

1. Tsokos GC. Systemic lupus erythematosus. The New England journal of medicine 2011;**365**(22):2110-21 doi: 10.1056/NEJMra1100359[published Online First: Epub Date]|.
2. Rothfield N, Sontheimer RD, Bernstein M. Lupus erythematosus: systemic and cutaneous manifestations. Clinics in dermatology 2006;**24**(5):348-62 doi: 10.1016/j.clindermatol.2006.07.014[published Online First: Epub Date]|.
3. Zoma A. Musculoskeletal involvement in systemic lupus erythematosus. Lupus 2004;**13**(11):851-3 doi: 10.1191/0961203303lu2021oa[published Online First: Epub Date]|.
4. Gutierrez M, Filippucci E, De Angelis R, et al. Subclinical entheseal involvement in patients with psoriasis: an ultrasound study. Seminars in arthritis and rheumatism 2011;**40**(5):407-12 doi: 10.1016/j.semarthrit.2010.05.009[published Online First: Epub Date]|.
5. Grossman JM. Lupus arthritis. Best practice & research. Clinical rheumatology 2009;**23**(4):495-506 doi: 10.1016/j.berh.2009.04.003[published Online First: Epub Date]|.
6. Oliva F, Piccirilli E, Bossa M, et al. I.S.Mu.L.T - Rotator Cuff Tears Guidelines. Muscles, ligaments and tendons journal 2015;**5**(4):227-63 doi: 10.11138/mltj/2015.5.4.227[published Online First: Epub Date]|.
7. Yamamoto A, Takagishi K, Osawa T, et al. Prevalence and risk factors of a rotator cuff tear in the general population. Journal of shoulder and elbow surgery 2010;**19**(1):116-20 doi: 10.1016/j.jse.2009.04.006[published Online First: Epub Date]|.
8. Abdul-Wahab TA, Betancourt JP, Hassan F, et al. Initial treatment of complete rotator cuff tear and transition to surgical treatment: systematic review of the evidence. Muscles, ligaments and tendons journal 2016;**6**(1):35-47 doi: 10.11138/mltj/2016.6.1.035[published Online First: Epub Date]|.
9. Colvin AC, Egorova N, Harrison AK, et al. National trends in rotator cuff repair. The Journal of bone and joint surgery. American volume 2012;**94**(3):227-33 doi: 10.2106/JBJS.J.00739[published Online First: Epub Date]|.
10. Ogura T, Hirata A, Hayashi N, et al. Comparison of ultrasonographic joint and tendon findings in hands between early, treatment-naive patients with systemic lupus erythematosus and rheumatoid arthritis. Lupus 2017;**26**(7):707-14 doi: 10.1177/0961203316676375[published Online First: Epub Date]|.
11. Albayrak I, Kucuk A, Arslan S, et al. Spontaneous patellar tendon rupture in a case followed up for diagnosis of systemic lupus erythematosus. European journal of rheumatology 2014;**1**(4):159-60 doi: 10.5152/eurjrheumatol.2014.140044[published Online First: Epub Date]|.
12. Hosokawa T, Oda R, Toyama S, et al. Spontaneous flexor tendon rupture due to an insufficiency fracture of the hamate hook in a patient with systemic lupus erythematosus: A case report.

International journal of surgery case reports 2016;**27**:63-65 doi: 10.1016/j.ijscr.2016.06.052[published Online First: Epub Date]|.

13. Nakamura S, Nakagawa J. Recurrent extensor tendon rupture in adult-onset dermatomyositis: a case report. Clinical rheumatology 2005;**24**(4):409-10 doi: 10.1007/s10067-004-1050-0[published Online First: Epub Date]|.
14. Cheng TM. Taiwan's new national health insurance program: genesis and experience so far. Health affairs 2003;**22**(3):61-76 doi: 10.1377/hlthaff.22.3.61[published Online First: Epub Date]|.
15. Cheng SH, Chiang TL. The effect of universal health insurance on health care utilization in Taiwan. Results from a natural experiment. Jama 1997;**278**(2):89-93
16. Oliva F, Osti L, Padulo J, et al. Epidemiology of the rotator cuff tears: a new incidence related to thyroid disease. Muscles Ligaments Tendons J 2014;**4**(3):309-14
17. Prabu VN, Agrawal S, Kishore JK, et al. Supraspinatus tendon rupture in lupus: a rarity. Lupus 2009;**18**(11):1026-7 doi: 10.1177/0961203309103099[published Online First: Epub Date]|.
18. Via AG, De Cupis M, Spoliti M, et al. Clinical and biological aspects of rotator cuff tears. Muscles, ligaments and tendons journal 2013;**3**(2):70-9 doi: 10.11138/mltj/2013.3.2.070[published Online First: Epub Date]|.
19. Potasman I, Bassan HM. Multiple tendon rupture in systemic lupus erythematosus: case report and review of the literature. Annals of the rheumatic diseases 1984;**43**(2):347-9
20. Lu M, Johar S, Veenema K, et al. Patellar tendon rupture with underlying systemic lupus erythematosus: a case report. The Journal of emergency medicine 2012;**43**(1):e35-8 doi: 10.1016/j.jemermed.2009.08.054[published Online First: Epub Date]|.
21. Di Matteo A, De Angelis R, Cipolletta E, et al. Systemic lupus erythematosus arthropathy: the sonographic perspective. Lupus 2017:961203317747716 doi: 10.1177/0961203317747716[published Online First: Epub Date]|.
22. Thamer M, Hernan MA, Zhang Y, et al. Prednisone, lupus activity, and permanent organ damage. The Journal of rheumatology 2009;**36**(3):560-4 doi: 10.3899/jrheum.080828[published Online First: Epub Date]|.
23. Halpern AA, Horowitz BG, Nagel DA. Tendon ruptures associated with corticosteroid therapy. The Western journal of medicine 1977;**127**(5):378-82
24. Zayat AS, Md Yusof MY, Wakefield RJ, et al. The role of ultrasound in assessing musculoskeletal symptoms of systemic lupus erythematosus: a systematic literature review. Rheumatology 2016;**55**(3):485-94 doi: 10.1093/rheumatology/kev343[published Online First: Epub Date]|.
25. Alves EM, Macieira JC, Borba E, et al. Spontaneous tendon rupture in systemic lupus erythematosus: association with Jaccoud's arthropathy. Lupus 2010;**19**(3):247-54 doi:

10.1177/0961203309351729[published Online First: Epub Date]|.

26. Furie RA, Chartash EK. Tendon rupture in systemic lupus erythematosus. Seminars in arthritis and rheumatism 1988;**18**(2):127-33

Figure Legends

Figure 1. Flowchart showing the study design

Figure 2. Kaplan–Meier hazard curve for rotor cuff tears in patients with autoimmune connective tissue diseases and controls over a 7-year follow-up period

Figure 3. Kaplan–Meier hazard curve for rotor cuff tears in patients with autoimmune connective tissue diseases with or without nonsteroidal anti-inflammatory drug use and controls over a 7-year follow-up period

Figure 4. Kaplan–Meier hazard curve for rotor cuff tears in patients with autoimmune connective tissue diseases with or without steroid use and controls over a 7-year follow-up period

Table 1. Demographic characteristics and comorbidities of autoimmune connective tissue disease (ACTD) patients and controls from 2004 to 2008

Baseline variable	ACTD cohort n = 5019		Control cohort n = 25095		P value	After propensity score adjustment
	No	(%)	No	(%)		P value
Characteristics						
Sex						
Female	3,892	77.5	19,460	77.5		
Male	1,127	22.5	5,635	22.5		
Age (years)						
18–30	701	14.0	3,505	14.0		
31–40	816	16.3	4,080	16.3		
41–50	1,042	20.8	5,210	20.8		
51–60	1,029	20.5	5,145	20.5		
61–70	765	15.2	3,825	15.2		
>70	666	13.3	3,330	13.3		
Income					<0.001	0.478
dependant	1,289	25.7	6,523	26.0		
1–25000	2,217	44.2	12,119	48.3		
25001–50000	1,095	21.8	4,961	19.8		
>50000	418	8.3	1,492	5.9		
Comorbid medical disorders						
Fracture						
Yes	62	1.2	284	1.1	0.530	0.944
No	4,957	98.8	24,811	98.9		
DM						
Yes	562	11.2	2,965	11.8	0.214	0.732
No	4,457	88.8	22,130	88.2		
Hypertension						
Yes	1,300	25.9	6,287	25.1	0.206	0.808
No	3,719	74.1	18,808	74.9		
Hyperlipidaemia					<0.001	0.932
Yes	891	17.8	3,355	13.4		
No	4,128	82.2	21,740	86.6		
Coronary heart disease					<0.001	0.899
Yes	660	13.2	2,447	9.8		
No	4,359	86.8	22,648	90.2		
Gout					<0.001	0.901
Yes	608	12.1	2,278	9.1		
No	4,411	87.9	22,817	90.9		
Thyroid					<0.001	0.529
Yes	416	8.3	1,158	4.6		
No	4,603	91.7	23,937	95.4		
Parkinson's disease					0.849	0.956

Yes	74	1.5	379	1.5
No	4,945	98.5	24,716	98.5

Table 2. Crude and adjusted hazard ratios for rotor cuff tear (RCT) between the autoimmune connective tissue disease (ACTD) and non-ACTD cohorts during the 7-year follow-up period, starting from the index date of an ambulatory care visit (n = 30,114)

Presence of RCT	Non-ACTD controls	Patients with ACTDs
7-year follow-up period		
Yes/Total	37/25,095	12/5,019
Person-years	154,275	24,536
Incidence per 100,000 person-years	24	49
Crude HR (95% CI)	1.00	2.08* (1.08–4.02)
Adjusted HR[a] (95% CI)	1.00	1.97* (1.01–3.82)

Notes: [a]The propensity score was adjusted according to age, sex, income, diabetes mellitus, hypertension, hyperlipidaemia, coronary heart disease, fracture, thyroid, gout, and Parkinson's disease. *indicates $P < 0.05$

RCT: rotor cuff tear; HR: hazard ratio

Table 3. Crude and adjusted hazard ratios for rotor cuff tear (RCT) in patients with autoimmune connective tissue diseases (ACTDs) with or without NSAID use and non-ACTD controls during the follow-up period, starting from the index date of an ambulatory care visit

Presence of **RCT**	Non-ACTD	Patients with ACTDs	
		Without a history of NSAID use	History of NSAID use
7-year follow-up period			
Yes/Total	37/25,095	7/3,745	5/1,274
Crude HR (95% CI)	1.00	1.61 (0.71–3.64)	3.53** (1.38–9.01)
Adjusted HR[a] (95% CI)	1.00	1.56 (0.69–3.53)	3.13* (1.21–8.07)

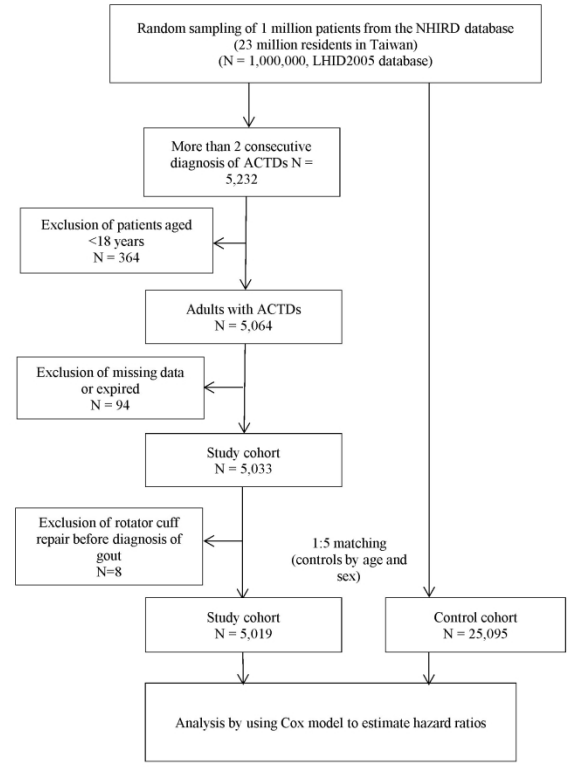
Notes: [a]The propensity score was adjusted according to age, sex, income, diabetes mellitus, hypertension, hyperlipidaemia, coronary heart disease, fracture, thyroid, gout, and Parkinson's disease. *indicates $P < 0.05$, **indicates $P < 0.01$
RCT: rotor cuff tear; HR: hazard ratio

Table 4. Crude and adjusted hazard ratios for rotor cuff tear (RCT) in patients with autoimmune connective tissue diseases (ACTDs) with or without steroid use and non-ACTD controls during the follow-up period, starting from the index date of an ambulatory care visit

Presence of **RCT**	Non-ACTD	Patients with ACTDs	
		Without a history of steroid use	History of steroid use
7-year follow-up period			
Yes/Total	37/25,095	5/2,452	7/2,567
Crude HR (95% CI)	1.00	1.83 (0.71–4.67)	2.32* (1.03–5.22)
Adjusted HR[a] (95% CI)	1.00	1.70 (0.66–4.37)	2.22 (0.98–5.03)

Notes: [a]The propensity score was adjusted according to age, sex, income, diabetes mellitus, hypertension, hyperlipidaemia, coronary heart disease, fracture, thyroid, gout, and Parkinson's disease. *indicates $P < 0.05$.
RCT: rotor cuff tear; HR: hazard ratio

Figure 1



Autoimmune connective tissue diseases (ACTDs)

Figure1/Flowchart showing the study design

209x297mm (300 x 300 DPI)

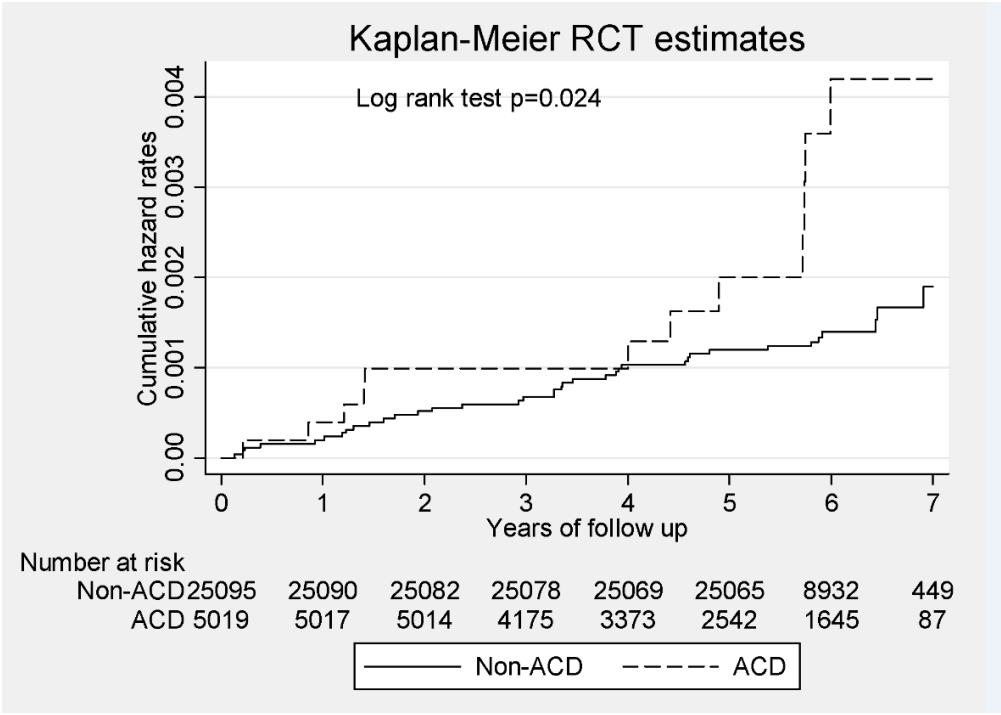


Figure 2/Kaplan–Meier hazard curve for rotor cuff tears in patients with autoimmune connective tissue diseases and controls over a 7-year follow-up period

99x70mm (300 x 300 DPI)

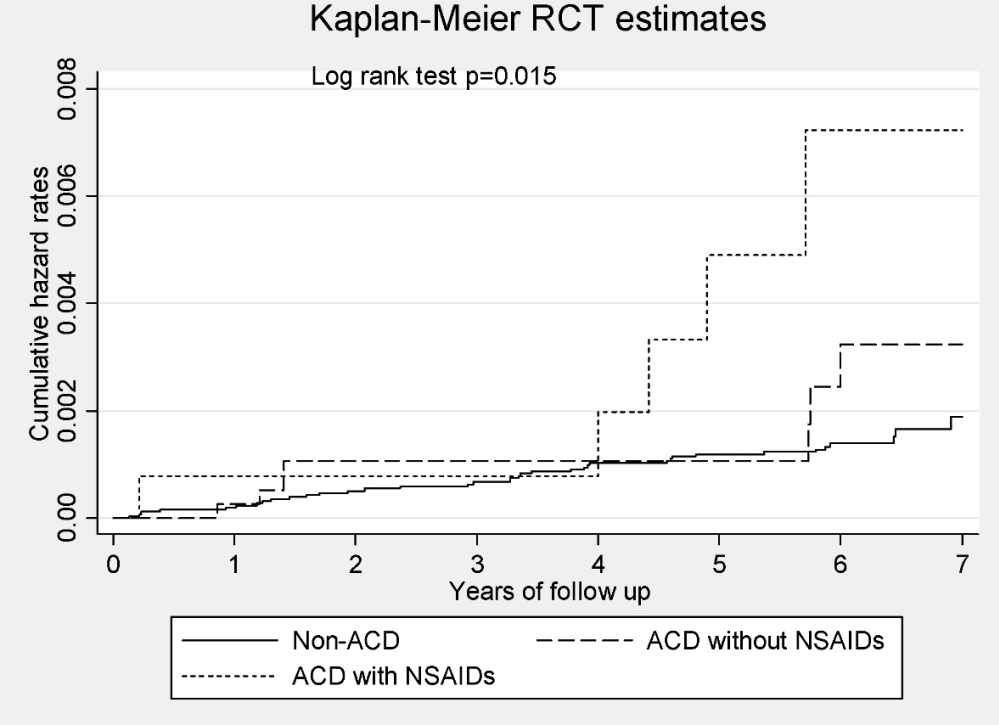


Figure 3/Kaplan–Meier hazard curve for rotor cuff tears in patients with autoimmune connective tissue diseases with or without nonsteroidal anti-inflammatory drug use and controls over a 7-year follow-up period

99x72mm (300 x 300 DPI)

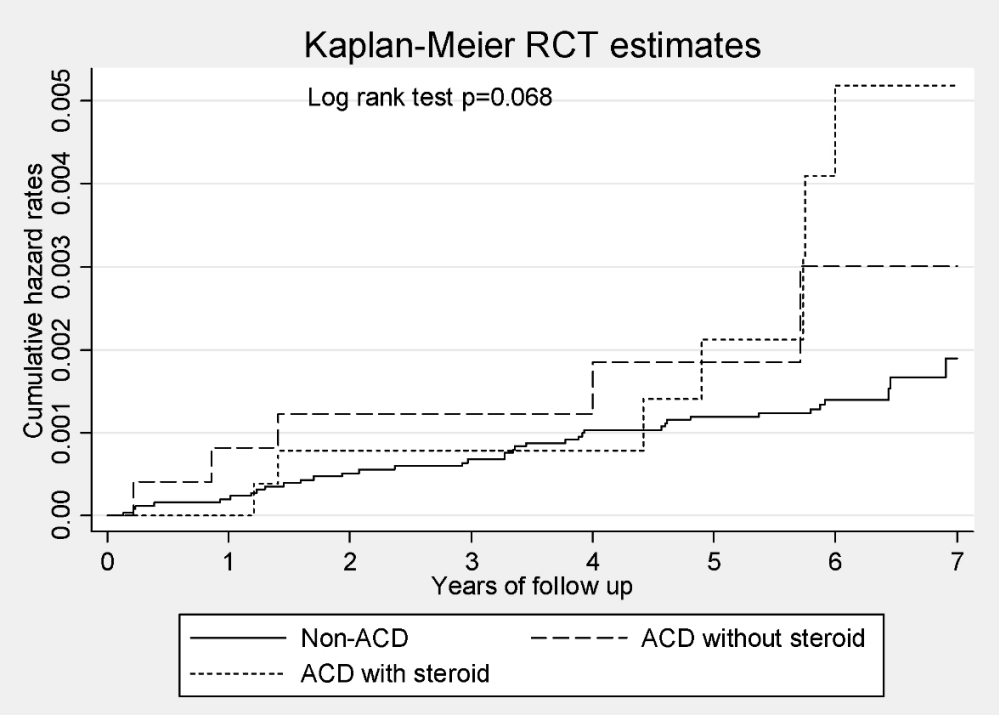


Figure 4/Kaplan–Meier hazard curve for rotor cuff tears in patients with autoimmune connective tissue diseases with or without steroid use and controls over a 7-year follow-up period

99x71mm (300 x 300 DPI)

STROBE Statement

Checklist of items that should be included in reports of observational studies

Section/Topic	Item No	Recommendation	Reported on Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7-8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-8
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	

Section/Topic	Item No	Recommendation	Reported on Page No
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9-10
		(b) Give reasons for non-participation at each stage	9-10
		(c) Consider use of a flow diagram	9-10
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-10
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	9-10
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-10
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

**Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.*

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.