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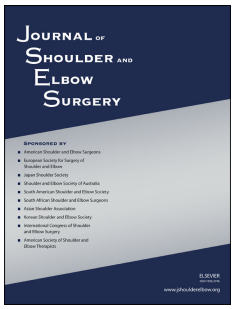

The presence of gastroesophageal reflux disease increases the risk of developing post-operative shoulder stiffness after arthroscopic rotator cuff repair.

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The presence of gastroesophageal reflux disease increases the risk of developing post-operative shoulder stiffness after arthroscopic rotator cuff repair.

Running title: Shoulder stiffness and gastroesophageal reflux disease

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Informed consent

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

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study protocol was approved by the Regional Ethical Committee (authorization number Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico - Milano Area 2, Lombardia, Milan, n°123/2017, Milan, 27-02-2017).

The presence of gastroesophageal reflux disease increases the risk of developing postoperative shoulder stiffness after arthroscopic rotator cuff repair.

Purpose: Postoperative shoulder stiffness (SS) after arthroscopic rotator cuff (RC) repair has been reported with variable incidence and numerous preoperative risk factors have been described. This prospective study aims to document the incidence of postoperative SS and to evaluate the role of preoperative risk factors in the development of this complication, with special focus on the role of gastroesophageal reflux disease (GERD).

Methods: Preoperative risk factors for SS were prospectively evaluated in 237 consecutive patients undergoing single-row arthroscopic RC repair. The presence of GERD was evaluated with the GerdQ diagnostic tool. Postoperative SS was diagnosed according to the criteria described by Brislin and colleagues in 2007.

Results: The incidence of postoperative SS was 8.02%. The presence of GERD was significantly associated with development of postoperative SS (OR: 5.265; 95% CI, 1.657-1.731; p=0.005). Older age (OR: 0.896; 95% CI, 0.847-0.949; p<0.001), male gender (OR: 0.126; 95% CI, 0.0252-0.632; p=0.012) and number of pregnancies (OR: 0.47; 95% CI, 0.228-0.967; p=0.040) emerged as protective factors.

Conclusions: The presence of GERD significantly influences the development of postoperative SS after single-row arthroscopic RC repair. An underlying a specific pro-inflammatory condition, characterized by increased expression of TNF-α and TGF-β, and disorders in retinoid metabolism are hypothesis which could explain this previously unknown association. The documented incidence of postoperative SS falls among previously reported ranges, with females significantly more affected than men.

Level of Evidence: Level II; Prospective Cohort Design; Treatment Study

Keywords: shoulder stiffness; arthroscopy; range of motion; complication; rotator cuff; gastroesophageal reflux disease

Shoulder stiffness (SS) is defined as a painful restriction in active and passive glenohumeral joint range of motion (ROM) and its occurrence after shoulder arthroscopy for rotator cuff (RC) repair has been reported with variable incidence in literature [2,26].

Numerous risk factors for both primary and secondary SS have been described and different possible etiologies have been reported for postoperative SS, which is considered a subgroup of secondary SS [14,24]. However, few studies were specifically designed to investigate how preoperative conditions may affect the incidence of postoperative SS [4]. Furthermore, a recent publication described for the first time a possible role of gastroesophageal diseases in increasing the risk of developing postoperative SS – even though this study had a retrospective design, an unspecific primary goal and subsequently a limited statistical power [15]. This association was never reported in literature before and to confirm or deny it could have relevant clinical implications. The goals of this study are to document the incidence of postoperative SS in a cohort of consecutive patients who underwent shoulder arthroscopy for single-row RC repair and to evaluate the role of preoperative risk factors in the development of postoperative SS, with special focus in evaluating if the presence of gastroesophageal reflux disease (GERD) is associated with the development of postoperative SS.

Materials and Methods

Study design

The primary aim of this study was to test the hypothesis that the presence of GERD was associated with a higher rate of postoperative SS after arthroscopic single-row RC repair.

Secondary goals were to document the incidence of postoperative SS and to evaluate the role of other previously described preoperative conditions as risk factors in the development of postoperative SS after arthroscopic RC repair.

Prior to study begin, a literature review was performed to identify the preoperative risk factors possibly involved in the development of SS. After literature review, the following factors were

selected for investigation: age, body mass index (BMI), sex, dominant side, smoking habits, diabetes mellitus, hypertension, GERD, chronic obstructive pulmonary disease (COPD), anxiety or depressive disorders, hyperthyroidism, hypothyroidism, dislipidemia, hypercholesterolemia. For female patients, specific attention was paid to menarche age, menopausal age, pregnancies, miscarriages and treatment with any hormonal therapy.

Furthermore, previous publications were consulted to select a suitable set of criteria to define the presence of postoperative SS, among the numerous available [2]. The criteria described by Brislin et al were selected for this study, since they refer to a fixed postoperative follow-up time point, provide a rigorous and reproducible definition of each item and do not consider patient's satisfaction as a rule-out criterion, which is expected to reduce the number of false negatives [6].

These criteria are reported in Table 1.

The study protocol was approved by the Regional Ethical Committee (authorization number Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico - Milano Area 2, Lombardia, Milan, n°123/2017, Milan, 27-02-2017).

Enrolment, preoperative evaluation

Patients who referred to our institution to undergo surgery for arthroscopic RC repair for degenerative posterosuperior RC tears were assessed for eligibility. Preoperative exclusion criteria were previous history of trauma, and presence of unequivocally diagnosed concomitant disorders of the shoulder, including glenohumeral arthritis, fracture, osteonecrosis or infection. Intra-operative exclusion criteria were the presence of an isolated subscapularis tear and the use of a double-row repair technique.

The presence of the aforementioned risk factors was evaluated with a detailed and targeted patient's medical history supported by the evaluation of the clinical records. The preoperative presence of GERD was evaluated with a specific diagnostic tool, the "GerdQ" questionnaire [27]. This is a patient-centered, self-assessment questionnaire developed in a large international study performed

in a primary care population presenting with upper gastrointestinal symptoms. The GerdQ has a diagnostic accuracy similar to that of a gastroenterologist supported by endoscopy and esophageal pH monitoring and is therefore recommended to diagnose GERD without initial specialist referral or endoscopy [27].

Operative and perioperative procedures

Surgery was performed under sedation and brachial plexus block with the patient in a lateral decubitus position, with the upper limb kept at about 30° of abduction and 30° of flexion. Diagnostic arthroscopy was performed from standard posterior, midglenoid and lateral portals; the size of the tear was classified according to the Southern California Orthopaedic Institute (SCOI) classification [59]. The tendon was repaired by use of double- or triple-loaded suture anchors (Super Revo® FT and ThRevo® FT Suture Anchors, Conmed, Utica, NY, USA). A standard single-row suture anchor repair was used in all included patients. Acromioplasty was performed with Sampson's cutting block technique in patients with type 2 or 3 acromial morphology according to Bigliani's classification [3]. All the patients were operated by a single surgeon (P.S.R.). Pantoprazol (40 mg) was administered once a day postoperatively for 20 days to all patients, as part of the standardized institution's internal protocols. Patients were discharged the day after the operation wearing a sling (Ultrasling II; Don Joy, Carlsbad, CA, USA) and instructed to wear it day and night for 28 days, allowing to remove it to eat, perform personal hygiene and early self-assisted light passive ROM exercises as well as mobilization of the elbow and scapulothoracic joint. From the 29th day, patients began formal passive rehabilitation assisted by a dedicated physical therapist to recover the full ROM of the shoulder joint and began active training once a satisfactory passive ROM was reached. From the end of the second month the main focus of the physical therapy was to regain full muscle strength.

Postoperative evaluation

As part of the standardized institution's protocols after arthroscopic rotator cuff repair, routine clinical evaluation was scheduled one, three and six months after surgery. Follow-up was extended beyond this time point only for symptomatic patients. Postoperative SS was diagnosed according to the criteria described by Brislin et al, when one of the following was present (Table 1): total passive external rotation with the arm at the side of less than 10°, total passive external rotation with the arm in 90° abduction of less than 30°, or total passive forward flexion of less than 100°. The diagnosis of stiffness was made only when these motion deficits persisted for at least 90 days postoperatively [6].

In patients diagnosed with postoperative SS, recommendations to reduce pain-generating rehabilitation exercises was given, as well as encouragement to perform physiotherapist-assisted mobilization, stretching and exercises for deltoid and rotator cuff activation, always outside the pain range and associated with deep myofascial massage. Furthermore, according to SS severity and patients' comorbidities, cortisone therapy was initiated, either as up to three repeated injections of 40 mg Triamcinolone acetonide or as oral therapy with Methylprednisolone (8 mg each day for 4 days, followed by 4 mg each day for 15 days and then 4 mg every second day for 30 days, associated with the prolongation of pantoprazole coverage for 60 days).

Statistical analysis

A power analysis prior to study begin indicated that a minimal sample size of 236 patients was sufficient to test the hypothesis that the prevalence of GERD is double among the patients who develop SS as compared to that among the patients who do not develop SS, assuming a prevalence of GERD in the overall European population of 15% [51] and an incidence of postoperative SS of 10% [6].

Statistical analysis (A.M.) was performed using GraphPad Prism v 6.0 software (GraphPad Software Inc.). Continuous variables were expressed as the mean ± standard deviation (SD) or medians and first and third quartiles [Q1 - Q3], as appropriate. The Shapiro-Wilk normality test was used to evaluate the normal distribution of the sample and, if the null hypothesis of this test could

not be rejected, the non-parametric Mann-Whitney test (U test) was applied for the analysis of the samples. Variables with a Gaussian distribution were analyzed with Student's t-test.

Categorical variables are expressed in numbers of cases and frequencies; their differences were tested using with the chi-square test or Fisher's exact test.

Variables significant at univariate analysis were inserted in a multivariable logistic regression model to correct for confounding and avoid multiple test correction and to estimate multivariate odds ratios (ORs) for evaluating the association between covariates and postoperative SS.

For all analyses, the significance level was set at p-value lower than 0.05.

Results

Four hundred four patients were considered eligible and 237 patients were included in the final analysis. A flow diagram illustrates the grouping and flow of patients in our clinical study (Figure 1). Patients' demographics are reported in Table 2.

The incidence of postoperative SS in the study population was 8.02% (95% CI:4.90-12.24) and all but two of the patients diagnosed with postoperative SS were women (p=0.0005) (Table 2). Age at surgery was significantly lower in the population with postoperative SS (p=0.0051).

Univariate analysis on the whole study population (Table 3) revealed a significant association between the development of postoperative SS and the presence of GERD (p=0.0026) as well as the presence of anxiety or depression (p=0.0305).

A multivariable logistic regression model could confirm GERD (OR: 5.265; 95% CI, 1.657-1.731; p=0.005) and number of miscarriages (OR: 4.002; 95% CI, 1.154-13.887; p=0.029) as significant risk factors associated with the development of postoperative SS, whereas older age (OR: 0.896; 95% CI, 0.847-0.949; p<0.001, male gender (OR: 0.126; 95% CI, 0.0252-0.632; p=0.012) and number of pregnancies (OR: 0.47; 95% CI, 0.228-0.967; p=0.040) emerged as protective factors (Table 4, Figure 2).

No statistically significant associations were found between the presence of any of the other examined potential risk factors and postoperative SS.

Of the 19 patients who developed postoperative SS, only five (26%) presented complete remission of the symptoms six months post operatively. One year after surgery, all but two of the initially symptomatic patients fully recovered. SS was treated with appropriate modifications of the rehabilitation protocol, combined with oral or intra-articular corticosteroid administration in 79 % of the symptomatic cases.

Discussion

The most relevant finding of this study is that patients affected by GERD are at higher risk of developing postoperative SS after arthroscopic single-row RC repair. Furthermore, the results of this study confirm the data previously published on the incidence of postoperative SS and the association between female sex and the development of this complication. Finally, previously unpublished association between postoperative SS and the presence of anxiety or depression emerged from this prospective cohort.

Codman first used the term “frozen shoulder” to describe “many conditions which cause spasm of the short rotators or adhesions about the joint or bursae” [13]. More recently, the Upper Extremity Committee of ISAKOS discouraged the generic use of the terms “frozen shoulder” and “adhesive capsulitis”, recommending using etiology-based definitions: primary idiopathic SS, or frozen shoulder, which develops without any trauma or specific shoulder disease and secondary SS if a known cause is recognized [26]. Postoperative SS is a subgroup of secondary SS, for which various different definitions have been proposed [2]. Historically, SS was considered one of the most devastating complications of shoulder surgeries, especially after open procedures and after prolonged periods of immobilization [22].

Nowadays, arthroscopic RC repair is accepted as gold standard in surgical treatment of most RC tears [48], having proven to be effective and safe, with a high clinical success rate that is durable over

time [50]; however, numerous possible complications have been described, including postoperative SS. The frequency of postoperative SS varies widely in literature, partly depending on the selected study population and on the rehabilitation protocol, and partly owing to the lack of common criteria used to define postoperative SS [2,61]. SS is a commonly reported complication after arthroscopic RC repair, with rates ranging from 1.5 % to 11.1 % [49]. Huberty et al published the up-to-date largest consecutive series available indicating a rate of postoperative SS of 4.9 % [24]. In the present cohort, the incidence of postoperative SS was higher than in the study by Huberty et al [24]; this could be related to the fact that a stricter definition of SS was used in this study [6], which encompasses both patients dissatisfied and satisfied with a their ROM, as opposed to the less strict "patients' dissatisfaction with their range of motion" chosen by Huberty et al which is likely to rule out stiff but satisfied patients [24].

Numerous risk factors have been related to the occurrence of primary and secondary SS; however, just a small number of publications analyzed the role of preoperative risk factors in the development of postoperative SS after shoulder surgery [4,11,38,56]. A possible role of gastroesophageal diseases in increasing the risk of developing postoperative SS was suggested in a recent study, however biased by its retrospective design and the low statistical power [15]. Therefore, special attention was paid in the present study to address prospectively the presence of GERD in a simple but effective way, using a validated diagnostic tool, the GerdQ. The diagnostic accuracy of this self-assessment questionnaire was tested in a large international study and appeared to be similar to that of a gastroenterologist supported by endoscopy and esophageal pH monitoring: this makes the GerdQ questionnaire recommended to diagnose GERD in a primary care population, without specialist referral or endoscopy [27]. As a consequence, this study could demonstrate that a significant association between the presence of GERD and the development of postoperative SS exists. However, the biological reasons for this association remain unknown. An inflammatory cascade involving synovial cells and capsular fibroblasts and resulting in fibrosis s likely to lie behind the development of SS, with recent studies confirming the presence of several inflammatory mediators

within the joints of patients with SS [9,30,31,34]. This inflammatory-fibrotic cascade is triggered by over-expression of transforming growth factor-beta (TGF-β), tumor necrosis factor-alpha (TNF-α) and other cytokines [36,37], and leads first to a fibroblastic hyperplasia of the synovium, then to a phenotypic shift of fibroblasts to myofibroblasts and an imbalance in matrix metalloproteinases (MMPs) homeostasis; this eventually leads to the alterations of the connective tissue in the glenohumeral capsule typical of the final stage of the disease [36]. In some clinical conditions associated to increased risk of both primary and postoperative SS [4], TGF-β and TNF-α are hyper-expressed: diabetes mellitus is associated with increased TGF-β1 and TNF-α serum concentrations [8,28,47] and subclinical hypothyroidism with high serum levels of TGF-β1, markers of endothelial dysfunction [1] and, in experimental models, with high TNF-α serum concentrations [25]. Furthermore, gene polymorphisms of TGF-β1, interleukin 6 and MMPs have been associated to increased susceptibility to SS and other fibrotic diseases [38,39]. Changes in proteins related to inflammation and tissue homeostasis have been identified also in patients affected by GERD [10,29,46,58]. These evidences support the hypothesis that an underlying a specific pro-inflammatory condition, characterized by increased expression of TNF-α and TGF-β, could represent a "phenotypic pattern" underlying to multiple diseases and represent itself a predisposing risk factor for the development of SS [14,45].

Another possible hypothesis to explain the relation between GERD and SS is related to malabsorption and retinoid metabolism. Hagiwara et al recently demonstrated that processes related to retinoid metabolism and lipid metabolism were downregulated in the inferior glenohumeral ligament of patients affected by primary SS [20]. Since all-*trans*-retinoic acid has the potential to inhibit chondrogenic cell differentiation [42], the authors postulate that a decrease in retinoid metabolism could accelerate chondrogenesis and subsequently development of SS [20]. However, if the presence of GERD is sufficient to negatively affect absorption of Vitamin A in a way that can indirectly affect a metabolic pattern in a specific region of the shoulder joint is currently not proven, so that this remains an intriguing hypothesis which requires further studies to be confirmed.

This newly described association between GERD and postoperative SS has an important clinical relevance and this suggests evaluating the presence of this condition prior to surgery. Considering that the GerdQ is a short and simple questionnaire, with a high diagnostic accuracy, its use in the preoperative evaluation could easily help identifying patients at risk, for whom a closer monitoring of the postoperative rehabilitation would be recommended. Furthermore, stratification of preoperative patient risk could help differentiating physical therapy and pharmacological treatment protocols in a preventive way between patients with high and low risk of developing postoperative SS.

The role of a perioperative prophylaxis with proton-pump inhibitors was not addressed in the present study, since the administration of Pantoprazol (40 mg once a day postoperatively for 20 days) already belonged to the standardized institution's postoperative protocols and the study design did not require changing this. The national recommendation for prescription of this medication has been meanwhile restricted to high risk patients (age > 65, prior ulcers, aspirin use, high dose or combined use of different NSAIDs or NSAIDs and antiplatelet or anticoagulant drug), so that routine administration is not considered necessary after arthroscopic shoulder surgery unless legal reasons guide this choice [54,55].

Furthermore, in the authors' hypothesis it is the presence of GERD itself as a disease (with its underlying pro-inflammatory condition) that affects the development of postoperative SS, rather than the presence of its symptoms: therefore, it is regarded as unlikely that this medication could play a role in preventing postoperative SS, since proton-pump inhibitors act as a symptomatic treatment, blocking the final step of the pathologic events in GERD [57].

Besides to the main study goal, this study also revealed that patients who developed postoperative SS were younger than those who did not, which is in accordance with the data reported by Huberty et al [24], but contrasting with other more recent publications [11,43,56]. In the present series, no significant difference was found between incidence of postoperative SS in patients with and without

diabetes mellitus, thyroid diseases, lipid metabolism disorders, although all these diseases have been reported to associate with primary and secondary SS [4,7,23,35,41,52,62,64,67]. Finally, a female predominance in the SS group, already described by numerous authors, was confirmed in the present study, suggesting that sexual hormones may contribute to SS etiology [21,41,65].

Rehabilitation also plays an important role in regaining ROM and function after arthroscopic RC repair. Ideally, the most efficacious postoperative rehabilitation program is one that protects the repair allowing for optimal tendon-to-bone healing, simultaneously restoring motion and strength. Efforts to avoid stiffness led to two relevant advancements in current rehabilitation protocols: first, postoperative positioning of the arm in a brace in light abduction, which can help to keep the inferior glenohumeral joint capsule stretched out, avoiding early contracture. Second, encouragement of an early passive range of motion protocol, which was believed to reduce the rate of postoperative SS [19]. Nevertheless, too-rapid advancing motion protocols could lead to an inflammatory response, increasing the risk of postoperative adhesions and producing strain on the RC with potential higher risk of retear [43,44,60], and the clinical superiority of strict early passive ROM protocols is debated [12,40,53]. Therefore, current recommendation advise tailoring rehabilitation on intra-operative conditions as well as patients' pain during therapy [33,63]. The protocol used in the current study included the use of an abduction sling and patient-tailored rehabilitation.

This study has some limitations: first of all, it was primarily focused on the evaluation of preoperative risk factors in the development of postoperative SS, therefore, surgery-related variables and the role of rehabilitation in development of postoperative SS were not investigated. Previous reports identified that tears less than 3 cm in diameter, partial articular-sided tears, calcific tendinosis, concomitant labral repair, single tendon repair and open surgery are potential risk factors for the development of SS after RC repair [6,11,24,26,43,56].

Secondly, the diagnosis of SS was based on merely clinical criteria. Although this is widely accepted in literature, the lack of common criteria to define SS makes comparison among outcomes

from different studies difficult; imaging modalities could in the future be used to help to confirm the diagnosis [66].

Conclusions

The presence of GERD is significantly associated with the development of postoperative SS after single-row arthroscopic RC repair. An underlying a specific pro-inflammatory condition, characterized by increased expression of TNF-α and TGF-β and disorders in retinoid metabolism, could explain this previously unknown association. The incidence of postoperative SS encountered in this study falls within previously reported ranges, with females being significantly more affected than men.

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Legends

Figure 1. Flow diagram of the study.

Figure 2. Relevant factors influencing the development of postoperative shoulder stiffness after rotator cuff repair according to the multivariate analysis. Left column: risk factors: female gender (A), GERD (C), number of miscarriages (E). Right column: protective factors: older age (B), number of pregnancies (D). For all analyses, the significance level was set at P values < 0.05: *: P < 0.05; **: P < 0.01; *** P < 0.001.

Table 1: Diagnostic criteria for postoperative shoulder stiffness, adapted from Brislin et al. [6].

Table 2: Patients' demographics.

Table 3: Summary of the main results of the univariate analysis for the study population.

Table 4. Odds Ratios and 95% confidence intervals of significant risk factors for the development of postoperative shoulder stiffness in the study population and in the subgroup of female patients (*) calculated by a multivariable logistic regression model on variables significant at univariate analysis.

Table 1: Diagnostic criteria for post-operative shoulder stiffness, adapted from Brislin et al. [6].

One of the following deficit present for at least 90 days post-operatively:	
Total passive external rotation with the arm at the side	Less than 10°
Total passive external rotation with the arm in 90° abduction	Less than 30°
Total passive forward flexion	Less than 100°

Table 2: Patients' demographics.

Group	Overall	Post-operative SS $^{+}$	Post-operative SS $^{-}$	*p-value*
Age (years)	59.5 [52.9-66.7]	53.3 (± 9.8)	60.0 [53.2-67.2]	***0.0051***
BMI (kg/m^2)	25.7 (± 3.6)	24.3 (± 4.1)	25.7 (± 3.6)	*0.1144 (n.s.)*
Gender (F/M ratio)	0.51/0.49	0.89/0.11	0.48 /0.52	***0.0005***
Dominant side (L/R ratio)	0.04 /0.96	0.05 /0.95	0.04 /0.96	*0.5737 (n.s.)*
Lesion dimension (< 1cm/≥1 cm)	0.48/0.52	0.47/0.53	0.48/0.52	*1.0000 (n.s.)*

Continuous variables were expressed as mean ± standard deviation (SD) or as median and interquartile range (first and third quartiles, Q1-Q3), as appropriate, while the dichotomous variables are expressed in numbers of cases and frequencies. BMI: body mass index; F/M: female/male; L/R: left/right; n.s.: not significant; SS $^{+}$: post-operative shoulder stiffness; SS $^{-}$: no post-operative shoulder stiffness.

Table 3: Summary of the main results of the univariate analysis for the study population.

Group	Overall	Post-operative SS $^{+}$	Post-operative SS $^{-}$	*p-value*
Number of patients per subgroup	237	19	218	
Surgery on dominant side	149 (62.9%)	8 (42.1%)	141 (64.7%)	*0.0804 (n.s.)*
Pre-operative shoulder stiffness	9 (3.8%)	1 (5.3%)	8 (3.7%)	*0.5350 (n.s.)*
Relatives with shoulder stiffness	20 (8.4%)	3 (15.8%)	17 (7.8%)	*0.2071 (n.s.)*
Smoking	112 (47.2%)	5 (26.3%)	107 (49.1%)	*0.0913 (n.s.)*
DM	23 (9.7%)	1 (5.3%)	22 (10.1%)	*0.7032 (n.s.)*
Relatives with DM	78 (32.9%)	5 (26.3%)	73 (33.5%)	*0.6177 (n.s.)*
Hypertension	88 (37.1%)	4 (21.1%)	84 (38.5%)	*0.1463 (n.s.)*
GERD	44 (18.6%)	9 (47.4%)	35 (16.1%)	***0.0026***
COPD	9 (3.8%)	0 (0.0%)	9 (4.1%)	*1.0000 (n.s.)*
Depression or anxiety	24 (10.1%)	5 (26.3%)	19 (8.7%)	***0.0305***
Hyperthyroidism	2 (0.8%)	1 (5.3%)	1 (0.5%)	*0.1542 (n.s.)*
Hypothyroidism	33 (13.9%)	3 (15.8%)	30 (13.8%)	*0.7243 (n.s.)*
Dyslipidaemia	24 (10.1%)	2 (10.5%)	22 (10.1%)	*1.0000 (n.s.)*
Hypercholesterolemia	57 (24.1%)	5 (26.3%)	52 (23.9%)	*0.7835(n.s.)*

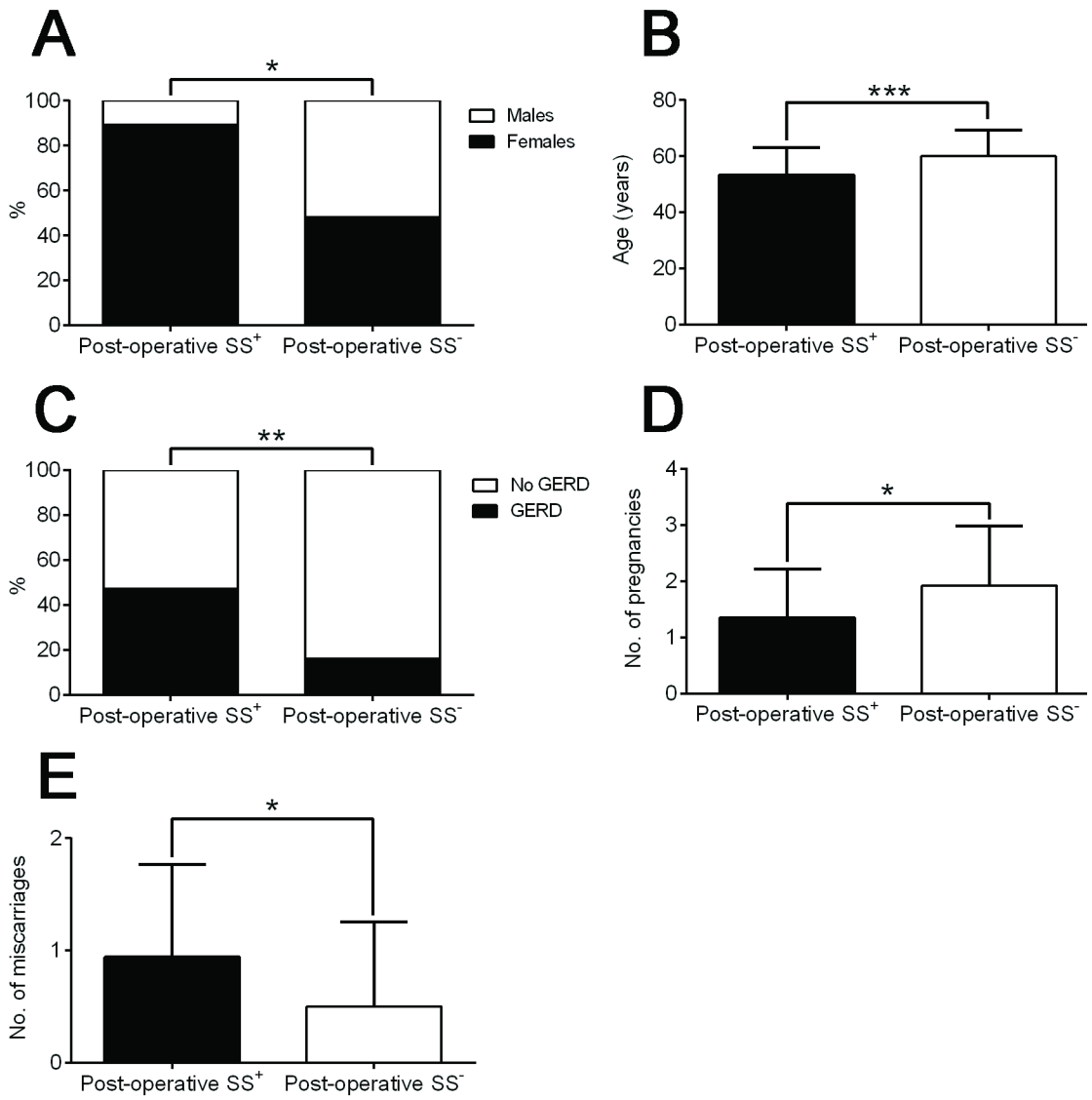
Dichotomous variables are expressed as number of cases with investigated condition (frequency of the investigated condition in the subgroup, %). COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; GERD: gastroesophageal reflux disease; n.s.: not significant; SS $^{+}$: post-operative shoulder stiffness; SS $^{-}$: no post-operative shoulder stiffness; Y/N: yes/no.

Table 4. Odds Ratios and 95% confidence intervals of significant risk factors for the development of post-operative shoulder stiffness in the study population and in the subgroup of female patients (*) calculated by a multivariable logistic regression model on variables significant at univariate analysis.

	Odds Ratio	**[95% CI]**	***p-value***
Male gender	.126	.0252 - .632	***0.012***
Older age	.896	.847 - .949	***< 0.001***
Presence of GERD	5.265	1.657 - 16.731	***0.005***
Depression or anxiety	2.085	.561 - 7.743	*0.272 (n.s)*
Number of pregnancies*	.470	.228 - .967	***0.040***
Number of miscarriages*	4.002	1.154 - 13.887	***0.029***
Menopause*	1.375	.259 - 7.300	*0.708 (n.s.)*

*: multivariate analysis performed only on the subgroup of female patients.

CI: confidence interval; GERD: gastroesophageal reflux disease; n.s.: not significant.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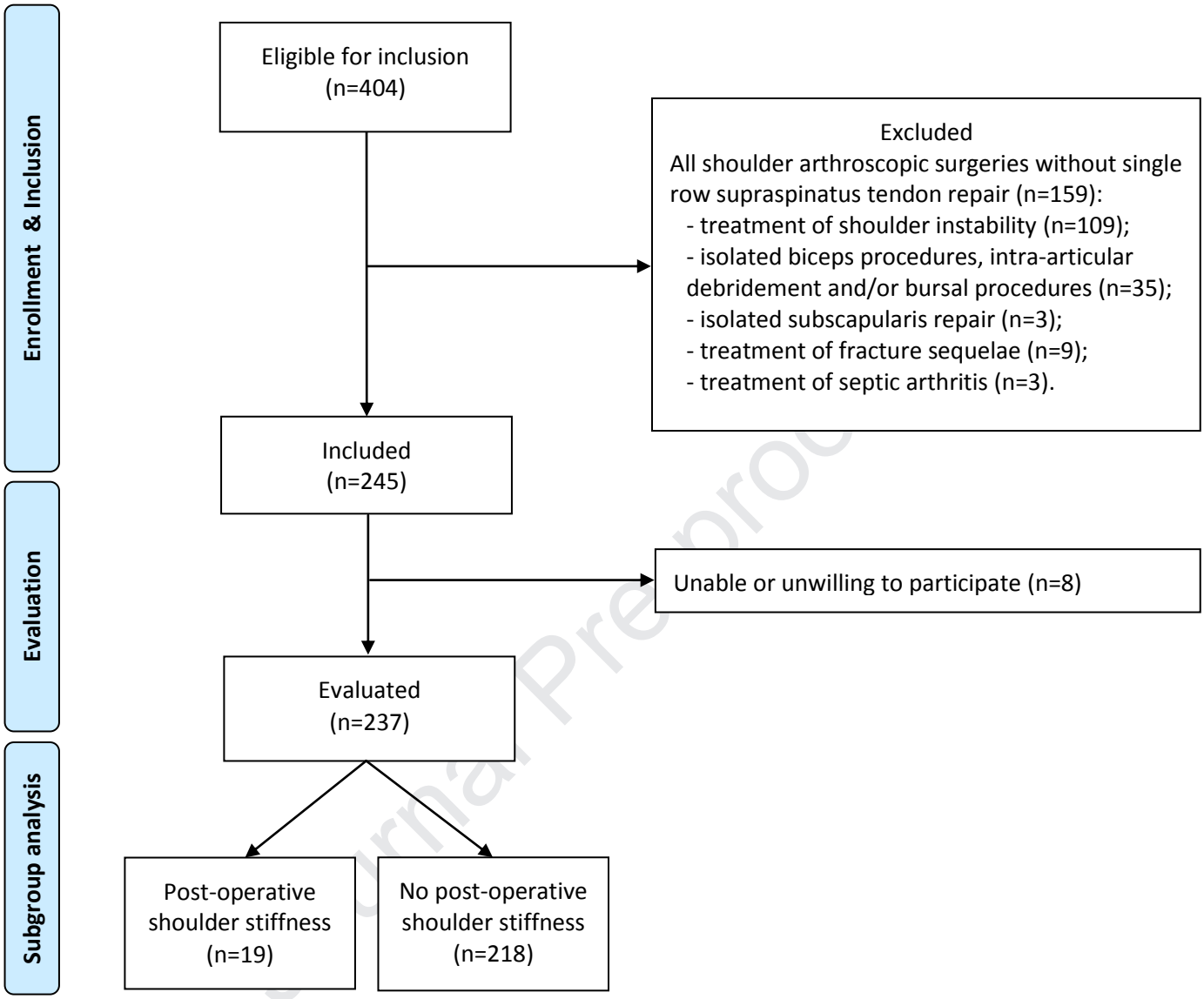
Enrollment & Inclusion
Evaluation
Subgroup analysis
Eligible for inclusion (n=404)
Excluded
All shoulder arthroscopic surgeries without single row supraspinatus tendon repair (n=159):
- treatment of shoulder instability (n=109);
- isolated biceps procedures, intra-articular debridement and/or bursal procedures (n=35);
- isolated subscapularis repair (n=3);
- treatment of fracture sequelae (n=9);
- treatment of septic arthritis (n=3).
Included (n=245)
Unable or unwilling to participate (n=8)
Evaluated (n=237)
Post-operative shoulder stiffness (n=19)
No post-operative shoulder stiffness (n=218)