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Original Article

Association between hormone replacement therapy and clinical outcomes in women with rotator cuff tears

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Abstract

Objectives: This study aims to evaluate the association between hormone replacement therapy (HRT) use and clinical outcomes in women with rotator cuff tears (RCTs) over a five-year follow-up period.

Patients and methods: Between February 2011 and June 2015, a total of 77 women aged ≥ 45 years with symptomatic RCTs in a multi-center cohort were retrospectively analyzed. The HRT status was self-reported. Patient-reported outcome measures included the American Shoulder and Elbow Surgeons (ASES) score, Shoulder Pain and Disability Index (SPADI), and Mental Health Inventory (MHI), assessed at multiple time points over 60 months. Magnetic resonance imaging data were used to evaluate tear size, muscle atrophy, and fatty infiltration.

Results: Of a total of 77 women included in the analysis, the HRT group consisted of 13 patients and the non-HRT group consisted of 64 patients. The mean age of women receiving HRT was 58.7 ± 7.0 years, compared to 63.5 ± 8.6 years in those not on HRT ($p = 0.061$). No statistically significant differences in baseline characteristics or clinical outcomes were observed between HRT and non-HRT groups ($p > 0.05$). Patients on HRT showed distinct recovery trends, particularly among those managed non-operatively, with early improvements in ASES and SPADI scores that fluctuated over time. Imaging analysis revealed significantly greater odds of moderate-to-severe muscle atrophy in the HRT group ($p = 0.0187$), although fatty infiltration and tear size did not significantly differ.

Conclusion: Hormone replacement therapy use demonstrated distinct functional recovery trends in women with rotator cuff tears, particularly among non-operatively managed patients, though no statistically significant differences in overall clinical outcomes were observed. These findings suggest that hormonal status may selectively influence musculoskeletal recovery and warrant further investigation to better inform sex-specific management for rotator cuff tears during and following the menopause transition

Keywords: Clinical outcomes, rotator cuff repair, rotator cuff tear, sex hormones, shoulder arthroscopy.

Rotator cuff tears (RCTs) are a prevalent musculoskeletal disorder, with incidence increasing significantly with advancing age.[1,2] The economic burden in the United States is substantial, with estimated direct and indirect costs exceeding $34,000 per patient within the

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first year following surgical repair.[3] Rotator cuff tears can lead to chronic shoulder pain, impaired range of motion, muscle weakness, and difficulty performing activities of daily living, outcomes that may persist irrespective of treatment approach, whether surgical or non-surgical.[4,5]

A hallmark finding in RCTs is the gradual increase in fatty deposits within the rotator cuff muscles, termed fatty infiltration (FI) or more recently myosteatosis. This phenomenon occurs in conjunction with muscle atrophy and is most pronounced in large chronic tears.[6] Fatty infiltration and muscle atrophy is the primary cause of the decrease in function; however, increased concentrations of FI and muscle atrophy are associated with poor clinical outcomes.[7] Fatty infiltration is also one of the most important prognostic factors in the surgical decision-making process.[8-10]

There is growing evidence that female sex is a significant risk factor for FI associated with RCTs, and that FI progresses more rapidly in females than in males.[11-15] The underlying mechanisms driving these sex-based differences remain poorly understood; however, one potential explanation involves the physiological changes occurring during the menopause transition. In a study by Wilson and MacLean,[16] magnetic resonance imaging (MRI) analysis of 52 males and 38 females with a mean age of 51.3 years and an intact supraspinatus tendon revealed that females were significantly more likely to exhibit higher grades of FI. Wilde et al.[17] found that sex hormone deficiencies were prevalent among patients undergoing rotator cuff repairs with 13 of 25 (52%) women with preoperative lab values having low estradiol levels and 63 of 94 (67%) from the entire cohort having either low sex hormones or taking hormone replacement therapy (HRT). Furthermore, Tanaka et al.[18] evaluated the effects of an estrogen-deficient state on rotator cuff healing in an animal model and found that estrogen played an important role in tendon repair healing by way of maturation of granulation and chondroid tissues.

The menopause transition, a unique physiological event in females, marks the end of reproductive function and is characterized by abrupt hormonal changes, including a rapid decline in circulating estradiol and a marked rise in follicle-stimulating hormone (FSH) during the four years surrounding the final menstrual period. More importantly, this transition occurs during the same period in life when the incidence of RCTs begins to increase.[19-21] While age-related FI of cardiac and skeletal muscle occurs in both sexes, studies have shown that this process accelerates in postmenopausal women.[22-27] Therefore, the hormonal changes related to the menopause transition may be an important mechanism leading to the increased risk and progression of rotator cuff FI in females. In the present study, we hypothesized that HRT would be associated with less severe rotator cuff pathology and superior longitudinal recovery. We, therefore, aimed to evaluate the association between HRT use and clinical outcomes in patients with RCTs over a five-year follow-up period, compared to patients not receiving HRT.

PATIENTS AND METHODS

This retrospective study utilized data from the Rotator Cuff Outcomes Workgroup (ROW) cohort, a group of 471 patients recruited between February 2011 and June 2015 from three academic medical centers and one community-based clinic. The cohort comprised individuals aged 45 years and older presenting with symptomatic RCTs. Symptomatic tear was defined as shoulder pain and dysfunction for a period of at least four weeks. Patients were excluded if they had concomitant shoulder injuries (i.e., shoulder fracture), current cervical radiculopathy, or prior shoulder surgery. Patients were included in the study regardless of treatment direction, surgical or non-surgical. The status of HRT was identified by self-reported questionnaire regarding current hormone therapy use, including specific hormonal regimens, at the time of enrollment. The status of HRT was dichotomized such that only those explicitly reporting 'Yes' were placed in the HRT group, while all others, including those reporting 'No' or with missing data, were categorized into the 'No HRT' group for the primary analysis. For the present analysis, we included 77 patients (Figure 1). A written informed consent was

obtained from each participant. The study protocol was approved by the Institutional Review Board (IRB) of the UT Southwestern Medical Center (STU-2020-0572). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Structured patient reported outcome assessments

Patients completed baseline questionnaires at the time of recruitment, which included demographic information, patient characteristics, and questions specific to their shoulder pathology. Patient reported outcome measures included Shoulder Pain and Disability Index (SPADI), American Shoulder and Elbow Surgeons (ASES) Questionnaire, and the Mental Health Inventory (MHI). The inclusion of both SPADI and ASES instruments allowed for the simultaneous evaluation of high-level functional activities of daily living (ADLs) (ASES) and perceived disability (SPADI), ensuring a multidimensional characterization of the recovery trajectory. The SPADI, ASES, and MHI scores were normalized and reported on a 0 to 100% scale, with higher values indicating less pain and greater functional independence. Questionnaires were distributed to patients during routine follow-up visits, through email correspondence, or by mail delivery. The time intervals for follow-up assessment of the questionnaires were three, six, 12-, 18-, 24-, 36-, 48-, and 60 months.

Magnetic resonance imaging assessments

Shoulder MRIs were read by fellowship-trained physicians, who are shoulder experts and found to have good inter- (kappa 0.90 [95% confidence interval [CI]: 0.72-1.00]) and intra-rater (kappa 0.88 [95% CI, 0.72-0.99]) reliability compared to a musculoskeletal radiologist.[28] Imaging characteristics extracted from MRI reviews for this study included muscle atrophy, FI, and tear size. Muscle atrophy was dichotomized into two groups, none/mild and moderate/severe. Fatty infiltration was categorized based on the presence or absence of fat on MRI. Tear size was evaluated in the longitudinal and transverse planes.

Statistical analysis

Descriptive statistics were used to summarize baseline demographic, clinical, and imaging characteristics. Continuous variables were

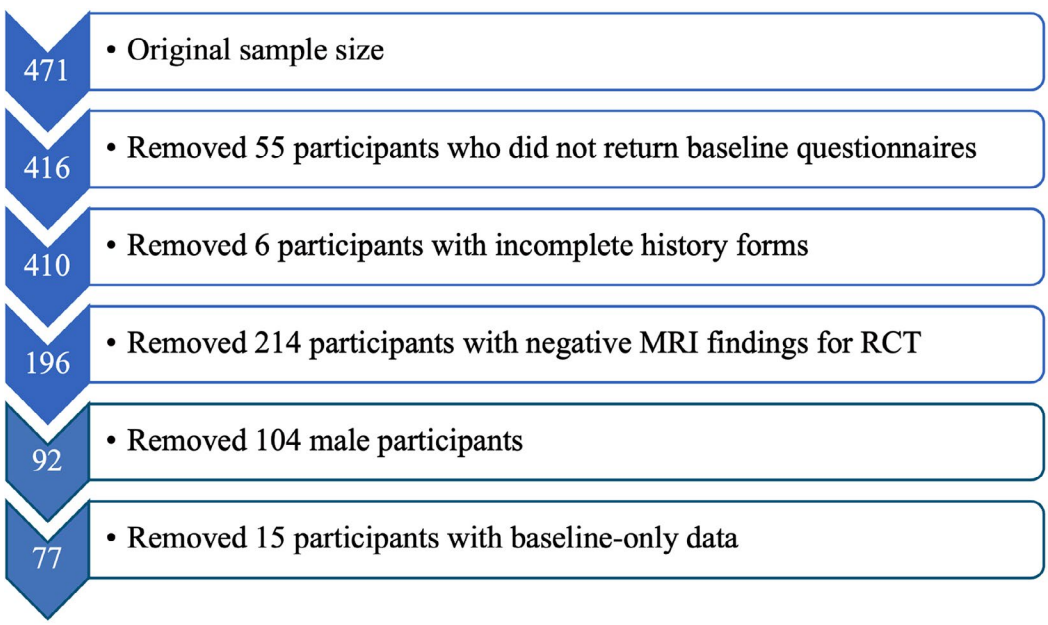

Figure 1. Flow diagram of eligible study sample included in the final analysis.
MRI, magnetic resonance imaging; RCT, rotator cuff tear.

Table 1. Patient demographics and clinical characteristics

	Overall cohort (n = 77)				No HRT (n = 64)				HRT (n = 13)				
	n	%	Median	IQR	n	%	Median	IQR	n	%	Median	IQR	*p*
Group (%)													0.498
Non-operative	45	58.4			39	60.9			6	46.2			
Operative	32	41.6			25	39.1			7	53.8			
Age (year)			64.0	56.2-68.5			64.7	57.8-69.0			60.0	55.0-61.7	0.071
BMI (kg/m²)			27.2	23.4-32.7			28.0	23.7-33.6			24.7	22.5-30.0	0.103
Longitudinal tear			1.00	0.0-2.6			1.0	0.0-2.6			1.9	0.9-2.4	0.244
Transverse tear			0.8	0.0-1.5			0.8	0.0-1.5			1.2	0.8-1.5	0.251
Fatty infiltration (%)													0.274
No	41	53.2			32	50.0			9	69.2			
Yes	17	22.1			14	21.9			3	23.1			
Missing	19	24.7			18	28.1			1	7.7			
Muscle atrophy (%)													0.219
None/mild	50	64.9			40	62.5			10	76.9			
Moderate/severe	7	9.1			5	7.8			2	15.4			
Missing	20	26.0			19	29.7			1	7.7			
ASES questionnaire			50.5	41.1-61.3			50.5	41.6-61.0			50.5	39.9-61.5	0.972
SPADI questionnaire			45.4	33.8-71.1			45.1	34.1-69.0			55.1	33.8-76.0	0.665
MHI questionnaire			80.0	70.0-85.0			82.5	73.8-90.0			80.0	70.0-85.0	0.371
Number of tendons torn (%)													0.533
0 or 1	45	58.4			36	56.2			9	69.2			
2 or 3	18	23.4			15	23.4			3	23.1			
Missing	14	18.2			13	20.3			1	7.7			

IQR, interquartile range; HRT, hormone replacement therapy; BMI, body mass index; ASES, American Shoulder and Elbow Surgeons Questionnaire; SPADI, Shoulder Pain and Disability Index; MHI, Mental Health Index;
* Statistical significance level was set at 0.05.

reported as medians with interquartile ranges (IQR). Categorical variables were summarized using frequencies and column percentages. Group comparisons for continuous variables were conducted using the Kruskal-Walli's test for non-normally distributed variables. For categorical variables, chi-square tests were applied when expected cell counts were ≥ 5; otherwise, Fisher's exact test was used. In addition to p-values, standardized mean differences (SMDs) were reported to quantify the magnitude of between-group differences, with thresholds of 0.2, 0.5, and 0.8 indicating small, medium, and large effects, respectively. Associations between HRT status and imaging characteristics, including rotator cuff tear dimensions, were assessed using logistic regression. To evaluate longitudinal changes in clinical outcomes, including the American Shoulder and Elbow Surgeons (ASES) score, Shoulder Pain and Disability Index (SPADI), and Mental Health Inventory (MHI), generalized linear mixed models (GLMMs) were fitted with a Gamma distribution and a log link to account for the skewed outcome distributions. Each model included fixed effects for HRT status, treatment group (non-operative *vs.* surgery), follow-up time (in months), and relevant baseline covariates (BMI, age, alcohol use, smoking history, work-related shoulder use, comorbidities, and number of tears), with a random intercept for participant ID to account for within-subject correlation. Adjusted mean ratios (AMRs) with 95% CIs were calculated by exponentiating model estimates, allowing interpretation of the relative change in expected outcome scores associated with each covariate. A p-value < 0.05 was considered statistically significant. All analyses were conducted using R version 4.3.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient characteristics

After excluding patients who did not meet the inclusion criteria, a total of 77 women were recruited into the final analysis including HRT (n = 13) and non-HRT group (n = 64). The mean age of women receiving HRT was 58.7 ± 7.0 years, compared to 63.5 ± 8.6 years in those not on HRT (p = 0.061). The mean body

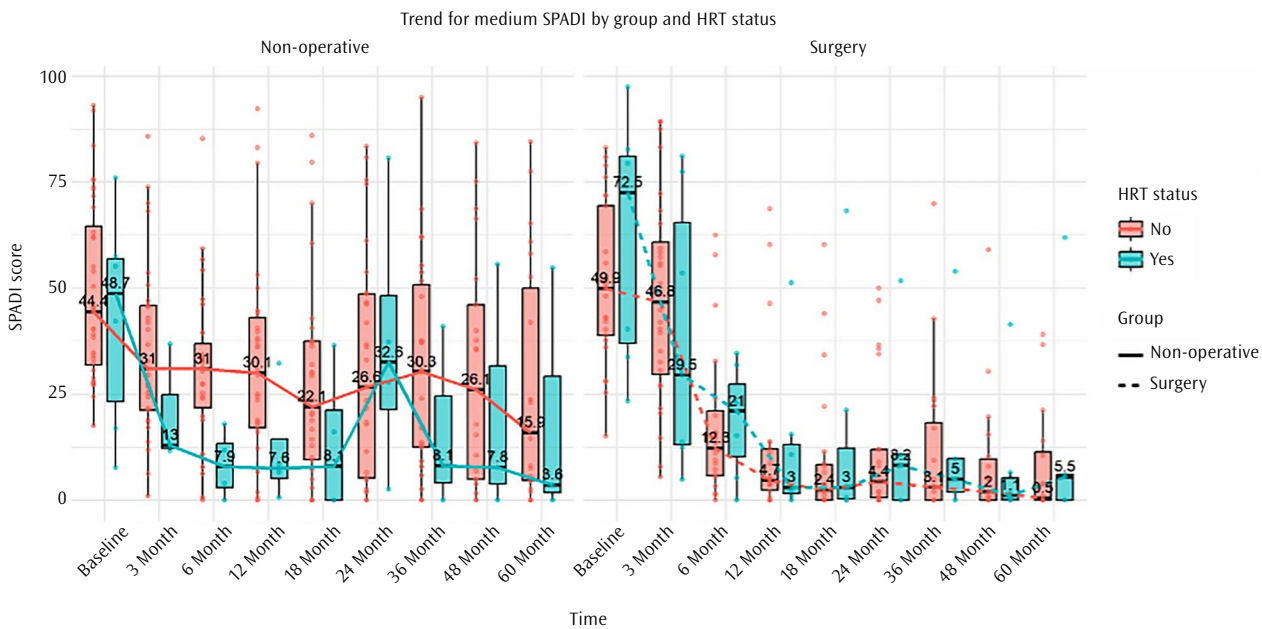

Figure 2. Median SPADI Scores for HRT and Non-HRT Patients Categorized by Intervention over 5-year follow-up.
Recovery trend of normalized SPADI scores between patients on hormone replacement therapy (red) and patients not on hormone replacement therapy (blue) treated non-operatively (solid line) and surgically (dashed line). SPADI scores were normalized to 100% with 0% being pain-free and without functional limitations.
SPADI, Shoulder Pain and Disability Index; HRT, hormone replacement therapy.

mass index (BMI) was 25.8 ± 4.5 kg/m² in the HRT group and 29.3 ± 6.6 kg/m² in the non-HRT group (p = 0.092). Of the total cohort, 45 women (58.4%) were managed non-operatively, while 32 (41.6%) underwent rotator cuff repair surgery (p = 0.498). Among the non-operatively managed group, six women (13.3%) were on HRT, whereas seven women (21.9%) in the operative group received HRT. Baseline outcome measures, including the SPADI, ASES score, and MHI, did not differ significantly between HRT and non-HRT groups (p = 0.663, p = 0.801, and p = 0.361, respectively). A comprehensive summary of baseline characteristics is presented in Table 1.

Hormone replacement therapy and imaging characteristics

Baseline characteristics stratified by HRT status indicated that patients receiving HRT presented with larger RCTs, although differences were not statistically significant. The median tear sizes in the longitudinal dimension were 1.90 cm (range, 0.88 to 2.40 cm) in the HRT group versus 1.00 cm (range, 0.00 to 1.45 cm) in the non-HRT group (p = 0.204), and in the transverse dimension, 1.15 cm (range, 0.83 to 1.50) versus 0.80 cm (range, 0.00 to 1.45), respectively (p = 0.251). No significant interaction was observed between HRT status and treatment group (operative *vs.* non-operative) for tear size (p = 0.1268). There was no significant difference in RCT size between patients on HRT compared to those not on HRT (p = 0.3881). The MRI evidence of FI was present in 23.1% of women on HRT compared to 21.9% in the non-HRT group (p = 0.274), indicating no significant difference.

Hormone replacement therapy and treatment outcomes

Results of the linear mixed model which were fully adjusted for 11 clinical and demographic confounders including HRT status, treatment group (operative *vs.* non-operative), follow-up time (visit), baseline BMI, age, daily shoulder use at work, alcohol use, number of comorbidities, anatomical severity (number of tendons torn), smoking status, and trauma history (see Supplementary Table 1 for model outputs), revealed the main factor influencing ASES scores was time, with a consistent decrease over time. The HRT and treatment group (operative *vs.* non-operative) did not significantly affect ASES

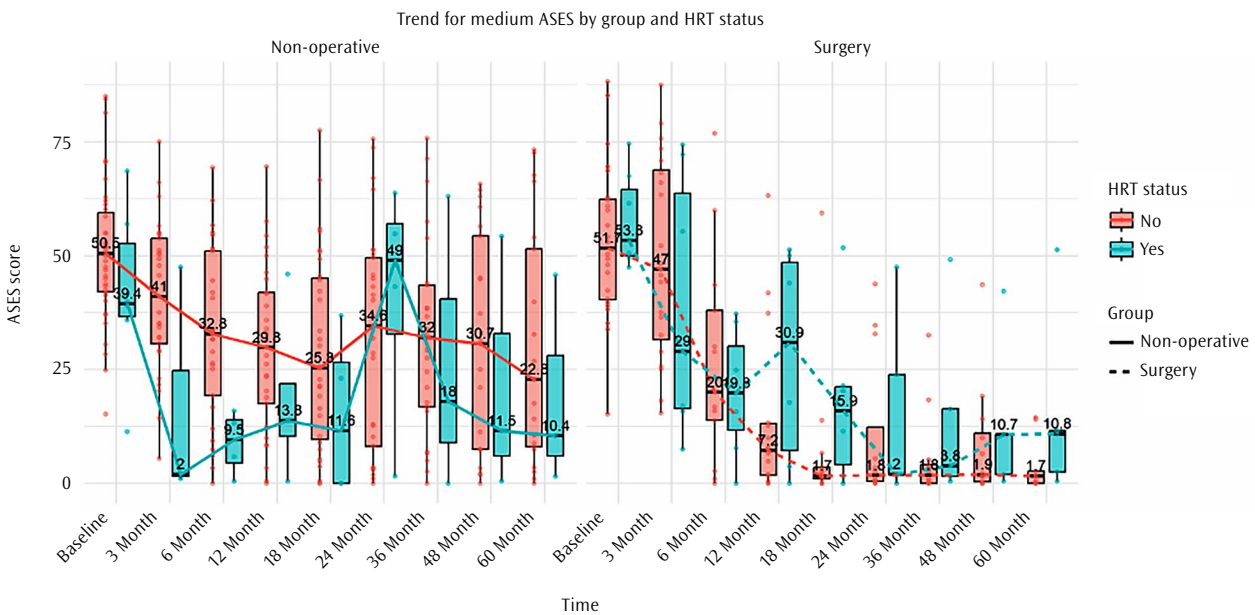

Figure 3. Median ASES Scores for HRT and Non-HRT Patients Categorized by Intervention over 5-year follow-up.
Recovery trend of normalized ASES scores between patients on hormone replacement therapy (red) and patients not on hormone replacement therapy (blue) treated non-operatively (solid line) and surgically (dashed line). ASES scores were normalized to 100% with 0% being pain-free and without functional limitations.
ASES, American Shoulder and Elbow Surgeons Questionnaire; HRT, hormone replacement therapy.

Figure 4. Median MHI scores for HRT and non-HRT patients categorized by intervention over 5-year follow-up. Recovery trend of normalized MHI scores between patients on hormone replacement therapy (red) and patients not on hormone replacement therapy (blue) treated non-operatively (solid line) and surgically (dashed line).
MHI, Mental Health Index; HRT, hormone replacement therapy.

scores (p = 0.1701). Similarly, time was the primary factor influencing SPADI scores, with a consistent decrease over time. The HRT and treatment group did not significantly affect SPADI scores (p = 0.1865). For MHI, time was the primary factor, with a consistent increase in scores over time. Results of the 5-year trend analysis for the SPADI (Figure 2) showed a consistent difference in pain and disability in patients treated non-operatively between groups with the HRT group having a lower median score at each time point except for baseline and two years, although statistical significance was not achieved at any time point. The trend in SPADI scores for those treated with surgical repair is more closely clustered at each time point except for baseline, three months, and six months from surgery with those on HRT reporting greater pain and functional disability; however, statistical significance was not reached. The trend in ASES scores (Figure 3) mirrored that of the SPADI scores in patients treated non-operatively, except at baseline, where the HRT group reported greater pain and functional disability according to the ASES. In patients undergoing rotator cuff repair, the HRT group had a spike in ASES scores whereas the non-HRT group continued the gradual decline in pain and disability over time. The difference in ASES scores at 12 months was not significantly different likely due to the small sample size of the HRT group and the wide interquartile range (IQR). The trend analysis for the MHI in patients treated non-operatively showed consistent scores across the non-HRT group with a drop in MHI scores at four years in the HRT group (Figure 4). The trend in patients treated with surgery reveals a similar recovery between groups with separation beginning at three years; however, this difference did not reach statistical significance.

DISCUSSION

In the present study, we evaluated the association between HRT use and clinical outcomes in patients with RCTs over a five-year follow-up period, compared to patients not receiving HRT. Our study results showed the

increasing prevalence of HRT in the context of RCTs. In patients with RCTs managed with non-surgical interventions, there was a trend for improved pain and function on ASES and SPADI scores for women on HRT within the first 18-months of recovery; however, these differences did not reach statistical significance. These findings suggest that, while a biological effect may exist, our cohort may have been underpowered to detect such an effect. In addition, both groups did achieve the minimally clinically important difference (MCID) on the ASES (13.6 points)[29] and SPADI (10.0 points)[30] at 18-months. A transient crossover was observed at 24-months with the non-HRT group reporting superior ASES and SPADI scores before returning to the original trend at 36-months and continuing through the five-year follow-up, though these differences remained statistically nonsignificant at all time points. For patients treated with surgery, there was less variability in patient reported outcomes on the ASES and SPADI except for the ASES at 12-months where the HRT group reported a spike in pain and functional disability compared to the six-month follow-up. The increase in pain and functional disability was not reflected on SPADI scores for the same follow-up period. The trend for MHI remained compact between groups across both treatment approaches (operative and non-operative) during the first 24-months before the HRT group began reporting a decrease in mental health scores but never reaching statistical significance. The convergence of outcomes observed between 48 and 60 months likely reflects a floor effect. As patients in both the HRT and non-HRT groups achieved high levels of recovery, the statistical 'room' for measurable differentiation between hormone statuses diminished, leading to alignment in the long term.

In the current study, we observed a difference in pain and functional recovery trends for patients currently on HRT with RCTs treated non-operatively compared to patients not on hormone replacement there over a five-year follow-up period; however, statistical significance was not achieved. Sex hormone levels were not measured in this study, limiting our ability to draw definitive conclusions regarding hormonal influences. Participants were asked to report their use of HRT, but no laboratory data were collected to quantify hormone concentrations. There is evidence in the literature highlighting the importance of sex hormones on tendon healing. In a murine model, Tashjian et al.[31] demonstrated the addition of a synthetic estrogen in a non-estrogen-deficient animal resulted in an increase in gene expression of pro-tendon healing factors. In adult male mice, Tashjian et al.[32] supplemented animals undergoing supraspinatus tendon transection and repair with testosterone and estrogen, and observed that hormone-treated groups exhibited improved structural integrity of the repaired tendon enthesis and significant regulation of multiple biological processes compared to the vehicle-treated controls. Although we lack laboratory values to confirm, one potential reason for the more closely linked recoveries in ASES and SPADI scores for patients treated with surgical repair is the role of sex hormones on tendon healing, specifically at the enthesis. The re-tear rate of a rotator cuff repair is estimated to occur in 20 to 60% of cases and, therefore, healing at the enthesis is paramount for long-term healing.[33] The effect of hormone supplementation is not without risk. Testosterone use within six months of shoulder arthroplasty surgery had a significantly higher rate of prosthetic joint infection (odds ratio [OR] = 1.44, 95% CI: 1.10 - 1.44, p = 0.042) compared to those without use.[34] Similarly, in a retrospective study of nearly 1,800 match women who underwent shoulder arthroplasty, estrogen replacement therapy was associated with increased risks of revision procedures and other mechanical complications.[35] Preclinical evidence suggests that sex hormone supplementation may enhance healing and improve structural outcomes; however, clinical studies indicate potential risks, highlighting the need for further investigation, particularly in human populations, to determine the safety and efficacy of such interventions.

The present study has certain strengths and limitations that should be acknowledged. One strength is the long-term follow-up data spanning five years providing visualization of the long-term trend in recovery for women treated surgically and non-surgically for an RCT. Another primary

strength was the implementation of a robust multivariate generalized linear mixed model (GLMM) to mitigate the constraints inherent in our small sample size. Despite a trend toward improved functional recovery, women in the HRT group presented with more severe initial pathology, including larger median longitudinal and transverse tears, a higher prevalence of moderate-to-severe muscle atrophy, and a greater frequency of surgical intervention compared to the non-HRT group. By adjusting for these more severe baseline parameters and clinical indicators such as trauma in our multivariate GLMM, we isolated the independent effect of HRT, which did not reach statistical significance ($p > 0.05$).

On the other hand, the major limitation of this study is the small sample size of women on HRT. The small HRT subgroup size (n = 13) contributes to inherent measurement variability. In particular, the brief inversion of trends at 24 months may be attributed to the high impact of individual participant outliers within the small non-operative (n = 6) and operative (n = 7) HRT cohorts. Another limitation of the study is the lack of details on the HRT and blood serum concentrations of sex hormones.

This study provides preliminary evidence that HRT use may influence recovery trajectories in women with rotator cuff tears, particularly among those managed non-operatively. While no statistically significant differences in overall clinical outcomes were observed between HRT and non-HRT groups, the distinct early improvements in shoulder function and pain scores among HRT users highlight the complexity of hormonal influences on musculoskeletal healing. These findings should be interpreted with caution given the study's retrospective design, self-reported HRT status, and small cohort. Future prospective studies with larger, well-characterized populations are needed to clarify the mechanisms by which HRT modulate muscle integrity and functional recovery in women with rotator cuff tears.

Declaration of Conflicting Interests

The authors declare that there are no conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Author Contributions

A.J.N., N.B.J.: Conceptualization, investigation, visualization; NA.J.N., F.A., W.L., R.P., N.B.J.: Methodology; F.A., W.L., R.P.: Software; A.J.N., F.A., W.L., R.P., N.B.J.: Validation; F.A., W.L., R.P.: Formal analysis; N.B.J.: Resources; A.J.N., F.A., W.L., R.P., M.K., N.B.J.: Data curation; A.J.N., W.L., R.P.: Writing-original draft preparation; A.J.N., W.L., F.A., R.P., M.K., N.B.J.: Writing-review and editing; N.B.J.: Supervision, funding acquisition;M.K., N.B.J.: Project administration. All authors have read and agreed to the published version of the manuscript.

Data Availability

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

AI Disclosure

The authors declare that artificial intelligence (AI) tools were not used, or were used solely for language editing, and had no role in data analysis, interpretation, or the formulation of conclusions. All scientific content, data interpretation, and conclusions are the sole responsibility of the authors. The authors further confirm that AI tools were not used to generate, fabricate, or 'hallucinate' references, and that all references have been carefully verified for accuracy.

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