

General

Is Fluoroquinolone Exposure after Primary Tendon Repair Associated with Higher Rates of Reoperations? A Matched Cohort Study

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Background

The association between tendon damage and fluoroquinolone (FQ) antibiotics has been well documented. However, there is limited data evaluating the impact of postoperative FQ use on outcomes of primary tendon repairs. The purpose of this study was to compare rates of reoperation for patients with FQ exposure after primary tendon repair versus controls.

Methods

A retrospective cohort study was conducted using the PearlDiver database. All patients who underwent primary repair of distal biceps ruptures, Achilles tendon ruptures, and rotator cuff tears were identified. For each tendon, patients who were prescribed FQs within 90 days postoperatively were propensity score matched at a 1:3 ratio with controls without postoperative FQ prescriptions across age, sex, and several comorbidities. Rates of reoperation were compared at two years postoperatively with multivariable logistic regression.

Results

A total of 124,322 patients who underwent primary tendon procedures were identified, including 3,982 (3.2%) patients with FQ prescriptions within 90 days postoperatively: 448 with distal biceps repair, 2,538 with rotator cuff repair, and 996 with Achilles tendon repair. These cohorts were matched with 1,344, 7,614, and 2,988 controls, respectively. Patients with postoperative FQ prescriptions exhibited significantly higher rates of revision surgery after primary repair of distal biceps ruptures (3.6% vs. 1.7%; OR 2.13; 95% CI, 1.09–4.04), rotator cuff tears (7.1% vs. 4.1%; OR 1.77; 95% CI, 1.48–2.15), and Achilles tendon ruptures (3.8% vs. 1.8%; OR 2.15; 95% CI, 1.40–3.27).

Conclusion

Patients with FQ prescriptions within 90 days after primary tendon repair demonstrated significantly higher rates of reoperations for distal biceps, rotator cuff, and Achilles tendon repair at two years postoperatively. To achieve optimal outcomes and avoid complications in patients following primary tendon repair procedures, physicians should consider prescribing alternative non-FQ antibiotics and counsel patients on the risk of reoperation associated with postoperative FQ use.

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INTRODUCTION

Fluoroquinolones (FQ) are a class of antibiotics commonly utilized to treat a variety of infections including urinary tract, respiratory tract, gastrointestinal, skin, bone, and joint. With bactericidal coverage extending to multiple organs, the frequency of these prescriptions has more than doubled from 1995 to 2002, and is prescribed by general practitioners, medical specialists, and surgeons.¹ While FQ antibiotics can successfully eradicate several common bacterial infections, they also place patients at risk for complications including tendinopathy,^{2,3} peripheral neuropathy,⁴ alteration in blood glucose,^{6,7} QT prolongation,⁸ as well as aortic aneurysm and dissection.⁹

Abundant evidence has documented an increased risk of tendinopathy and tendon ruptures in patients who are prescribed FQ antibiotics. Van der Linden et al. found that 2% to 6% of Achilles tendon ruptures in people older than 60 years can be attributed to FQ use,¹⁰ and a case-control study by Corrao et al. reported the use of FQs significantly increases the risk of tendon ruptures (OR 1.3; 95% CI, 1.0–1.8) including rupture of the Achilles tendon (OR 4.1; 95% CI, 1.8–9.6).¹¹ Furthermore, a systematic review by Stephenson et al. reported that individuals exposed to FQ antibiotics were at an increased risk of Achilles tendon rupture with odds ratios ranging from 1.1 to 7.1.³ Although the Achilles tendon is most affected tendon in FQ-induced tendinopathy, other tendons may be affected including those of the biceps brachii, supraspinatus, extensor pollicis longus, patellar tendon, quadriceps muscle, and rotator cuff (RTC).^{12–14}

There is a lack of consensus regarding which FQ is associated with the highest risk of tendinopathy and tendon rupture; however, ciprofloxacin has been reported in many case series.^{2,12,15,16} Among the other FQ antibiotics, Khaliq et al. documented pefloxacin to be responsible for 37% of FQ-induced tendinopathy cases followed by ciprofloxacin being responsible for 25.5% of cases.¹² Levofloxacin has been reported to be the safest and most tolerable FQ regarding tendon health^{17,18}; however, several other case reports demonstrate Achilles tendon ruptures with Levofloxacin utilization.^{18–20}

While a substantial body of literature supports a strong association between FQs and tendinopathy, the effect of FQ antibiotics on outcomes of primary tendon repairs has not been elucidated. The aim of this study was to determine if FQ prescriptions within 90 days of primary tendon repair is associated with higher rates of reoperation compared to patients with no preoperative or postoperative FQ exposure. It was hypothesized that patients with FQ prescriptions after primary tendon repair would exhibit significantly higher rates of reoperation within two years postoperatively.

METHODS AND MATERIALS

DATA SOURCE

The PearlDiver Mariner Patient database (PearlDiver Technologies, Colorado Springs, CO, USA), a large commercially available administrative claims database, was used to retro-

spectively review deidentified patient records. This dataset utilized (“M91Ortho”) contains records of orthopaedic procedures and diagnoses in the inpatient and outpatient setting for 91 million patients in the United States (U.S.) from 2010 through Q3 of 2020. All health insurance payors are represented. Patient records were identified using Current Procedural Technology (CPT), International Classification of Diseases (ICD) Ninth Revision and Tenth Revision (ICD-9/ICD 10), Uniform System of Classification (USC) drug codes, and generic drug codes. Institutional review board exemption was granted from our institution as the provided data was de-identified and compliant with the Health Insurance Portability and Accountability Act. IRB exemption was granted for this study (reference #2022-637)

PATIENT SELECTION

Patients who underwent primary repair of distal biceps ruptures, RTC tears, and Achilles tendon ruptures were identified. In order to limit potential transfer bias resulting from patients leaving or joining the database during the study period, only patients with continuous database enrollment for at least three months before and two years after the index tendon repair procedure were included. All patients with FQ prescriptions (identified with the USC code for all FQ medications, USC-15180) within three months before primary tendon repair were excluded.

Unlike datasets limited to single insurance carriers used in previous studies, the PearlDiver dataset used in this study does not include CPT modifiers for laterality. Therefore, a different methodological approach was implemented for defining each tendon repair cohort based on (1) the presence or absence of a unique CPT code for revision tendon repair, (2) the prevalence of bilateral tendon ruptures and incidence of subsequent contralateral tendon injuries, and (3) consequential likelihood of coding bias with respect to counting contralateral primary tendon repairs as ipsilateral revisions during the two-year follow-up ([Table 1](#)).

Bilateral RTC disease is common, and thus the primary RTC repair cohort was defined with the CPT code for arthroscopic repair (CPT-29827) paired with ICD-10 diagnosis codes for right or left RTC tears. Complete, incomplete, and unspecified RTC tears were included. Additionally, to reduce selection bias with respect to patients with larger or more complex tear patterns, patients with prior or concomitant open RTC repair procedures were excluded.

Patients who underwent primary Achilles tendon repair were identified with CPT-27650 and CPT-27652, and revision Achilles tendon repair was defined with the unique code CPT-27654. Subsequent contralateral Achilles tendon ruptures are not insignificant.^{27,28} Thus, ipsilaterality of the primary and secondary repairs were ensured simply by excluding additional primary tendon repairs (i.e., CPT-27650 or CPT-27652) during the two-year follow-up.

Patients who underwent primary repair of ruptured distal biceps tendons were identified with CPT-24342. Bilateral biceps tendon ruptures were excluded. There is no unique CPT code for revision biceps tendon repair, and the minimal existing data on the incidence of contralateral biceps tendon ruptures after primary repair report rates at

Table 1. CPT codes for primary and revision tendon repair procedures and prevalence of bilateral or subsequent contralateral tendon injuries/procedures.

Tendon	CPT Code(s) for Primary Repair	Unique CPT Code(s) for Secondary Repair	Prevalence of Bilateral / Subsequent Contralateral Pathology	Risk of Coding Bias	ICD-10 Codes Used for Laterality
Distal Biceps	24342	N/A	<u>Subsequent Contralateral Rupture:</u> 7.8% (25/321) – 13.0% (3/23), both at >4-year follow-up ^{21,22} <u>Bilateral Ruptures:</u> 1.2 per 100,000 ²³	Low-to-Medium ^a	No
Rotator Cuff	29827	N/A	<u>Subsequent Contralateral Repair:</u> 56.6% within 2 years of first surgery in patients with bilateral tears ²⁴ <u>Bilateral Tears:</u> 25.9% (38/147) – 38.3% (69/180) ^{25,26}	High	Yes
Achilles	27650, 27652	27654	<u>Subsequent Contralateral Rupture:</u> 1.8% (4/226) – 6.5% (10/154) ^{27,28} <u>Bilateral Ruptures:</u> < 1% of all ruptures ²⁹	Low ^b	No

^aBilateral ruptures were excluded, and since reported rates of subsequent contralateral ruptures in small samples were at follow-ups >4 years (vs. 2 years in this study), we deemed risk of coding bias as low-to-medium and did not use ICD-10 diagnosis codes to ensure laterality. ^bThough rates of subsequent contralateral Achilles ruptures are not insignificant, the existence of a unique CPT code for secondary Achilles tendon repair mitigates possible associated coding bias. Therefore, ICD 10 diagnosis codes were not used to ensure laterality.

>4-year follow-up in small cohorts.^{21–23} As this study evaluated a two-year follow-up, we assumed that the risk of capturing such instances was low, and therefore ICD-10 diagnosis codes were not used in conjunction with CPT-24342 to define the cohort.

Subsequently, for each cohort of patients undergoing primary tendon repair, patients with postoperative FQ exposure were identified by at least one prescription claim for a FQ medication (USC-15180) within 90 days of the index procedure. For subgroup analyses, generic drug codes were used to identify patients with isolated exposure to two commonly prescribed FQ antibiotics: ciprofloxacin and levofloxacin.³⁰ Conversely, controls were defined as patients with no prescription claims for a FQ medication at any time during the two-year follow-up. A comprehensive list of all codes used to define the study cohorts can be found in **Appendix 1**.

DEMOGRAPHIC DATA AND OUTCOMES

Demographic data including age, sex, and several comorbidities identified as risk factors for impaired tendon healing were queried for each cohort.^{10,31,32} Additionally, rates of at least one FQ prescription within 90 days following eight common elective non-tendon-repair orthopedic procedures (composite index) were compared to queried rates after distal biceps, RTC, and Achilles tendon repairs.³³ The composite index included arthroscopic anterior cruciate ligament (ACL) repair, arthroscopic meniscus repair, arthroscopic partial meniscectomy, carpal tunnel decom-

pression, lumbar spine decompression, lumbar spine fusion, total hip replacement, and total knee replacement.

Rates of reoperation within two years of primary tendon repair were queried for patients with and without postoperative FQ exposure. RTC reoperations were identified using CPT codes for arthroscopic RTC repair (CPT-24342), open RTC repair (CPT-23410, CPT-23412, or CPT-23420), and total shoulder arthroplasty (CPT-23472) paired with ICD-10 diagnosis codes for rotator cuff tears that were ipsilateral to the primary repair procedure. Revision Achilles tendon repair was defined with CPT-27654. Patients who underwent revision distal biceps tendon repair were identified by the second instance of a claim containing CPT-24342.

STATISTICAL ANALYSIS

Statistical analysis was performed using R statistical software (Version 4.1.0; R Project for Statistical Computing, Vienna, Austria) integrated within the PearlDiver software with an α level set to 0.05. In order to generate comparable patient cohorts, for each individual primary tendon repair procedure, propensity score matching was used to match patients with FQ prescriptions within 90 days of the index procedure with controls without FQ prescriptions within 2 years of index procedure. Matching was performed at a 1:3 ratio across age, sex, renal failure, diabetes mellitus, rheumatoid arthritis, and tobacco use at a caliper of 0.20.³⁴ An *a priori* power analysis was performed based on the results from Cancienne et al. to determine the minimum number of patients with FQ exposure required.³⁵ To detect

a 2.1% difference in rates of revision tendon repair, assuming a 1:3 ratio of FQ patients to controls, a minimum of 421 patients with postoperative FQ prescriptions were needed for each tendon repair cohort to achieve 80% power.

Demographic data for the two cohorts were compared with chi-square test for categorical variables and Welch's *t* test for continuous variables. Rates of at least one FQ prescription after within 90 days of primary tendon repairs were compared against the rate after the composite index of common non-tendon-repair orthopaedic procedures using chi-square analysis. Multivariable logistic regression analyses controlling for patient age and sex were performed to compare rates of reoperations within two years after primary repair for patients with FQ exposure within 90 days after primary tendon repair versus controls. Subgroup analyses were also performed to compare reoperation rates for controls versus patients with (A) prescriptions for only Ciprofloxacin or (B) only Levofloxacin, and (C) only one FQ prescription claim or (D) more than one FQ prescription claim during the 90-day postoperative global period. Odds ratios (OR) with corresponding 95% confidence intervals (CI) were reported for each outcome.

RESULTS

STUDY POPULATION

A total of 124,322 patients with procedures for primary tendon tears met inclusion criteria, including 3,982 (3.20%) patients with at least one prescription for a FQ medication within 90 days after the index surgery and 105,792 (85.10%) patients with no FQ prescription claims within 2 years after the index procedure. For each tendon, patients who were prescribed FQs within 90 days postoperatively were propensity score matched at a 1:3 ratio with controls without postoperative FQ prescriptions across age, sex, and several comorbidities (Table 2). Within the FQ cohort, the mean time between the index procedure and the first FQ claim was 44.3 ± 26.7 days.

QUINOLONE RX RATES FOR TENDON REPAIR VS. OTHER COMMON ELECTIVE ORTHOPAEDIC PROCEDURES

Rates of at least one FQ prescription within 90 days after the index surgery were compared for the included tendon repair procedures versus a composite index of eight common elective orthopaedic procedures unrelated to tendon repairs (Rx rate: 5.02%) (Table 3). Patients who underwent primary repair of distal biceps tears (2.39%), RTC tears (3.08%), and Achilles tendon tears (3.53%) exhibited significantly lower rates of FQ prescriptions than patients in the composite index of common elective orthopaedic procedures (all $p < 0.001$).

RATES OF REOPERATIONS, ANY FQ MEDICATION VS. CONTROLS

Compared to controls, patients with FQ prescriptions within 90 days of primary repair of distal biceps tendon rupture exhibited a significantly higher rate of reoperation

(3.6% vs. 1.7%; OR 2.13; 95% CI, 1.09–4.04) (Table 4). Stratifying by FQ prescription claim count, patients with multiple FQ claims exhibited a significantly higher rate of reoperation compared to controls (9.1% vs. 1.7%; OR 6.77; 95% CI, 2.17–17.74) while patients with only one FQ claim exhibited comparable rates ($p > 0.05$).

The rate of reoperation for RTC repair was significantly higher for patients with FQ prescriptions (7.1% vs. 4.1%; OR 1.77; 95% CI, 1.48–2.15). In subgroup analyses, patients who only filed one FQ claim also exhibited a significantly higher rate of reoperation (7.2%) than controls (OR 1.81; 95% CI, 1.49–2.19) while reoperation rates were comparable for patients who filed more than one FQ claim ($p > 0.05$).

Following primary Achilles tendon repair, patients with FQ prescriptions exhibited significantly higher rates of reoperation relative to controls (3.8% vs. 1.8%; OR 2.15; 95% CI, 1.40–3.27). This result was also observed in subgroup analyses of patients with only one FQ prescription (3.6% vs. 1.8%; OR 2.05; 95% CI, 1.28–3.22) and multiple FQ prescriptions (2.6% vs. 1.8%; OR 2.55; 95% CI, 1.16–5.01).

RATES OF REOPERATIONS, CIPROFLOXACIN VS. CONTROLS

Within the FQ cohort, 2,363 (59.3%) patients only filed prescriptions for Ciprofloxacin within 90 days after the index tendon repair procedure (Table 5). Following primary repair of ruptured distal biceps tendons, patients with Ciprofloxacin exposure and controls exhibited statistically comparable rates of reoperation (OR 1.89; 95% CI, 0.79–4.12). However, in subgroup analyses based on the number of Ciprofloxacin prescription claims, patients with more than one claim exhibited a significantly higher rate of reoperation than controls (OR 6.61; 95% CI, 1.50–20.58).

The rate of reoperation for RTC repair was significantly higher for patients with postoperative Ciprofloxacin exposure (6.8% vs. 4.1%; OR 1.70; 95% CI, 1.34–2.14). Patients who filed only one Ciprofloxacin claim also exhibited a significantly reoperation rate (6.9%) than controls (OR 1.73; 95% CI, 1.36–2.18) while patients who filed more than one claim exhibited a comparable rate ($p > 0.05$).

Patients with any Ciprofloxacin exposure within 90 days after primary Achilles tendon repair exhibited a significantly higher reoperation rate than controls (3.4% vs. 1.8%; OR 1.86; 95% CI, 1.09–3.05). This result was also found in a subgroup analysis of patients with only one Ciprofloxacin prescription (3.3% vs. 1.8%; OR 1.84; 95% CI, 1.03–3.14), though patients who filled multiple prescriptions exhibited a comparable reoperation rate ($p > 0.05$).

RATES OF REOPERATIONS, LEVOFLOXACIN VS. CONTROLS

In the FQ cohort, 1,455 (36.5%) patients only filed prescriptions for Levofloxacin within 90 days postoperatively (Table 6). Patients with Levofloxacin exposure within 90 days after primary distal biceps tendon repair exhibited a higher but statistically comparable rate of reoperation relative to controls (OR 2.43; 95% CI, 0.95–5.49).

Table 2. Demographic data of FQ and control cohorts.

	Distal Biceps			Rotator Cuff			Achilles		
	No FQ (n = 1,344)	FQ (n = 448)	P value	No FQ (n = 7,614)	FQ (n = 2,538)	P value	No FQ (n = 2,988)	FQ (n = 996)	P value
Age (years) Mean, $\pm$ SD	55.53 $\pm$ 11.10	55.43 $\pm$ 11.38	0.87	61.58 $\pm$ 9.59	61.52 $\pm$ 9.66	0.77	54.05 $\pm$ 12.46	53.94 $\pm$ 12.40	0.82
Females, n (%)	138 (10.27)	52 (8.62)	0.48	4,205 (55.23)	1,411 (55.59)	0.76	1,728 (57.83)	571 (57.33)	0.81
Comorbidities, n (%)									
Tobacco Use	292 (21.73)	93 (20.76)	0.71	2,428 (31.89)	795 (31.32)	0.61	525 (17.57)	193 (19.38)	0.22
Diabetes Mellitus	355 (26.41)	116 (25.89)	0.88	3,663 (48.11)	1,220 (37.62)	1.00	1,124 (33.20)	364 (36.55)	0.57
Hyperlipidemia	672 (50.00)	220 (49.11)	0.79	5,776 (75.86)	1,923 (75.76)	0.95	1,380 (46.18)	447 (44.88)	0.50
Renal Failure	79 (5.88)	26 (5.80)	1.00	608 (7.99)	201 (7.92)	0.95	190 (6.36)	58 (5.82)	0.60
Obesity	263 (19.57)	85 (18.97)	0.84	2,628 (34.52)	860 (33.88)	0.58	834 (27.91)	286 (28.71)	0.65
Rheumatoid Arthritis	14 (1.04)	7 (1.56)	0.53	401 (5.27)	131 (5.16)	0.76	100 (3.35)	41 (4.12)	0.30

Table 3. Rates of at least one fluoroquinolone prescription within three months following eight common elective orthopedic procedures (composite index) versus tendon repairs.

Procedure	FQ Prescription within 90 days after Surgery			
	Total	Rx ³⁶	Rx Rate ³⁶	p value
Composite Index	2,480,772	124,613	5.02%	-
Distal Biceps Tendon Repair	18,770	449	2.39%	< 0.001
Rotator Cuff Repair	82,532	2,539	3.08%	< 0.001
Achilles Tendon Repair	28,233	997	3.53%	< 0.001

Rates of at least one FQ prescription after within 3 months of initial procedure; all patients with no history of FQ prescription before within 3 months of initial procedure. All FQ prescription rates were compared against the rate for the composite index of eight common non-tendon repair elective orthopaedic procedures. ³⁶Composite index included arthroscopic ACL repair, arthroscopic meniscus repair, arthroscopic partial meniscectomy, carpal tunnel decompression, lumbar spine decompression, lumbar spine fusion, total hip replacement, and total knee replacement. Bolded p-values indicate statistically significant results.

Table 4. Rates of reoperation within two years for patients with FQ exposure within 90 days after primary tendon repair versus controls with no FQ exposure.

	No FQ	FQ Exposure (Any Claim Count)		1 FQ Prescription		>1 FQ Prescriptions	
Tendon Repair Procedure	n (%)	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)
Distal Biceps	23 (1.7)	16 (3.6)	2.13 (1.09-4.04)	11 (2.8)	1.64 (0.76-3.33)	5 ^a (9.1)	6.77 (2.17-17.74)
Rotator Cuff	312 (4.1)	180 (7.1)	1.77 (1.48-2.15)	165 (7.2)	1.81 (1.49-2.19)	15 (6.2)	1.59 (0.90-2.63)
Achilles	54 (1.8)	38 (3.8)	2.15 (1.40-3.27)	29 (3.6)	2.05 (1.28-3.22)	5 ^a (4.5)	2.55 (1.16-5.01)

Bolded OR (95% CI) indicate statistically significant results. The reference group for each OR (95% CI) was the respective fluoroquinolone cohort. ^aFor the sake of protecting patient identities, the PearlDiver software only reports exact patient counts when defined groups have at least 11 patients, though actual values are used when calculating ORs. When such instances arose in the present study, a value of 5 (median between 1 and 10) was assigned for the patient count.

Table 5. Rates of reoperation within two years for patients with ciprofloxacin exposure within 90 days after primary tendon repairs versus controls with no postoperative FQ exposure.

	No FQ	Ciprofloxacin (Any Claim Count)		1 Ciprofloxacin Prescription		>1 Ciprofloxacin Prescriptions	
Tendon Repair Procedure	n (%)	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)
Distal Biceps	23 (1.7)	5 ^a (3.2)	1.89 (0.79-4.12)	5 ^a (2.2)	1.36 (0.45-3.33)	5 ^a (10.3)	6.61 (1.50-20.58)
Rotator Cuff	312 (4.1)	101 (6.8)	1.70 (1.34-2.14)	95 (6.9)	1.73 (1.36-2.18)	5 ^a (5.5)	1.40 (0.54-2.94)
Achilles	54 (1.8)	21 (3.4)	1.86 (1.09-3.05)	17 (3.3)	1.84 (1.03-3.14)	5 ^a (3.4)	1.95 (0.58-4.89)

Bolded OR (95% CI) indicate statistically significant results. The reference group for each OR (95% CI) was the respective ciprofloxacin cohort. ^aFor the sake of protecting patient identities, the PearlDiver software only reports exact patient counts when defined groups have at least 11 patients, though actual values are used when calculating ORs. When such instances arose in the present study, a value of 5 (median between 1 and 10) was assigned for the patient count.

Table 6. Rates of reoperation within two years for patients with levofloxacin exposure within 90 days after primary tendon repairs versus controls with no postoperative FQ exposure.

	No FQ	Levofloxacin (Any Claim Count)		1 Levofloxacin Prescription		>1 Levofloxacin Prescriptions	
Tendon Repair Procedure	n (%)	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)
Distal Biceps	23 (1.7)	5 ^a (4.1)	2.43 (0.95-5.49)	5 ^a (3.9)	2.29 (0.83-5.38)	5 ^a (6.3)	3.90 (0.21-20.65)
Rotator Cuff	312 (4.1)	72 (7.5)	1.89 (1.44-2.46)	67 (7.6)	1.92 (1.45-2.51)	5 ^a (6.2)	1.59 (0.55-3.58)
Achilles	54 (1.8)	16 (5.0)	2.92 (1.60-5.05)	12 (4.5)	2.65 (1.34-4.87)	5 ^a (7.1)	4.19 (1.23-10.80)

Bolded OR (95% CI) indicate statistically significant results. The reference group for each OR (95% CI) was the respective levofloxacin cohort. ^aFor the sake of protecting patient identities, the PearlDiver software only reports exact patient counts when defined groups have at least 11 patients, though actual values are used when calculating ORs. When such instances arose in the present study, a value of 5 (median between 1 and 10) was assigned for the patient count.

Patients with Levofloxacin exposure exhibited a significantly higher rate of reoperation for RTC repair relative to controls (7.5% vs. 4.1%; OR 1.89; 95% CI, 1.44–2.46). The reoperation rate for patients with only one Levofloxacin prescriptions (7.6%) was also significantly higher than controls (OR 1.92; 95% CI, 1.45–2.51) while patients with multiple prescriptions exhibited a statistically comparable rate ($p > 0.05$).

Levofloxacin exposure within 90 days of primary Achilles tendon repair was associated with significantly higher rates of reoperation (5.0% vs. 1.8%; OR 2.92; 95% CI, 1.60–5.05). This result was also found in subgroup analyses of patients with only one Levofloxacin prescription (4.5% vs. 1.8%; OR 2.65; 95% CI, 1.34–4.87) and multiple prescriptions (OR 4.19; 95% CI, 1.23–10.80).

DISCUSSION

In this analysis of a large patient database, rates of FQ prescriptions within 90 days after tendon repair procedures were significantly lower than rates among patients who underwent other common non-tendon-repair elective orthopaedic surgeries. Patients who were prescribed FQ antibiotics within 90 days after primary distal biceps, RTC, and Achilles tendon repair exhibited significantly higher rates of reoperation at two-year follow-up compared to matched controls who did not receive FQ antibiotics postoperatively. Furthermore, significantly higher reoperation rates were observed for patients with only one postoperative FQ prescription suggesting that even minimal FQ exposure during the acute postoperative period increases risk of re-rupture. The present study also demonstrated that isolated exposure to two commonly prescribed FQs, ciprofloxacin and levofloxacin, were both associated with increased rates of reoperation in the short-term.

Our study builds upon the results in a recent study by Cancienne et al. which demonstrated that FQ use after within 2 months after arthroscopic RTC repair is associated with higher rates of re-rupture and reoperation compared to matched controls without FQ exposure (OR 1.8; 95% CI, 1.3–2.5); however, this relationship did not achieve statistical significance for patients with FQ prescriptions in the 2–4-month postoperative period (OR 1.0; 95% CI, 0.7–1.6).³⁵ This pattern viewed in concert with our findings that FQ exposure within 3 months after RTC repair was associated with increased rates of retear and reoperation (OR 1.77; 95% CI, 1.48–2.15) suggests that FQ antibiotics may be most detrimental during the acute postoperative period. Local trauma is naturally inflicted upon a tendon during surgical repair, and FQ-induced tendinopathy may significantly retard the healing process and increase risk of re-rupture.

The present study also demonstrated that isolated levofloxacin and ciprofloxacin use in the postoperative period are both associated with increased risk of RTC re-rupture and reoperation, and levofloxacin may inflict tendinopathy more severely (OR 1.89; 95% CI, 1.44–2.51) than ciprofloxacin (OR 1.70; 95% CI, 1.34–2.14). A similar result was found for Achilles tendon re-rupture and reoperation.

While both Levofloxacin and Ciprofloxacin exposure after primary Achilles tendon repair were associated with significantly higher reoperation rates, Levofloxacin exposure yielded an odds ratio of 2.92 (95% CI, 1.60–5.05) versus an odds ratio of 1.86 (95% CI, 1.09–3.05) for Ciprofloxacin. This result appears to contradict prior reports citing Levofloxacin as the safest FQ medication with respect to tendon damage,^{17,18} though other factors may have also contributed to revision rates.

Several mechanisms have been proposed to explain the deleterious effects of FQ-induced tendinopathy. Childs et al evaluated the pathogenesis of tendon rupture secondary to FQ utilization, reporting microscopically visible apoptotic changes within tendon cells, tendon ischemia, reduced proliferation and activity of tenocytes, and reduction of type 1 collagen influenced by FQs.³⁷ Additionally, Sendzik et al demonstrated the expression of matrix metalloproteinases, enzymes of matrix degradation, is increased in fibroblasts treated with FQs by 5- to 18- fold depending on time and concentration.³⁸ The same study also reported a concentration- and dose-dependent increase in the amount of the apoptosis marker, caspase-3, in tenocytes after treatment with FQs.^{38,39} Importantly, findings of the present study suggest that even minimal postoperative FQ exposure increases risk of tendon re-rupture given the significantly increased rates of reoperation for RTC (OR 1.81; 95% CI, 1.49–2.19) and Achilles (OR 2.05; 95% CI, 1.28–3.22) among patients with only one FQ prescription. Also, our results support a dose-dependent relationship as described by Sendzik.³⁸ Patients with only one FQ claim within 90 days after primary distal biceps repair demonstrated comparable rates of re-rupture and reoperation versus controls, but patients with two or more FQ claims exhibited significantly higher rates (OR 6.77; 95% CI, 2.17–17.74). Similarly, for Achilles tendon repair, we found an odds ratio of 2.15 (95% CI, 1.40–3.27) for reoperations for patients with only one FQ prescription compared to 2.55 (95% CI, 1.16–5.01) for patients with multiple prescriptions.

Despite the well-documented risk of Achilles tendon rupture and tendinopathy in the setting of FQ exposure,^{3,11} this study also demonstrated FQ prescription rates within 90 days of primary tendon repair of 2.39% for distal biceps tendon repair, 3.08% for RTC repair, and 3.53% for Achilles tendon repair. For patients with primary Achilles tendon repairs in our study, rates of reoperation within two years were significantly higher for patients with FQ prescriptions than matched controls without FQ exposure (3.8% vs. 1.8%; OR 2.44, 95% CI 1.57–3.75). This data highlights the importance of astute clinical judgement when patients require antibiotics after primary tendon repair procedures. Of note, a review of drug-induced musculoskeletal disorders by Banerth did not identify any other antimicrobials that cause tendinopathy besides FQs.⁴⁰ Thus, with heightened awareness of a patient's surgical history, a clinician may mitigate the risk of tendon re-rupture and reoperation by prescribing non-FQ antibiotic alternatives. Given the significant association between FQ exposure and short-term rates of tendon re-rupture warranting reoperation, orthopaedic surgeons may improve outcomes by contacting patients'

primary care providers to ensure FQs are avoided to the greatest extent possible during the postoperative period after primary tendon repair.

LIMITATIONS

Several limitations must be acknowledged. First, as the PearlDiver database only includes data on a particular group of patients during a specific time period, sampling bias is present. Given the complex nature of medical billing, there is a possibility of coding bias through manual entry of diagnosis/procedural codes. Coding errors are inherent with any analysis of administrative claims data, though such instances are rare and made up only 0.7% of Medicare and Medicaid payments in both 2020 and 2021.³⁶ With respect to laterality, the PearlDiver Mariner database does not contain CPT code modifiers for laterality. ICD-10 diagnosis codes, which include laterality information, were only used for analyzing primary and secondary RTC repairs given the notably high rates of bilateral RTC tears and staged bilateral RTC repair. Though it is possible that some primary contralateral procedures were counted as revisions for patients with primary Achilles and biceps tendon repair, this possibility is minimal and affects both FQ patients and controls equally ([Table 1](#)). Additionally, because the primary outcome evaluated was reoperations, it is possible that more patients had recurrent tendon injuries within two years postoperatively but did not receive a reoperation in that timeframe.

Another important limitation concerns the difficulty of establishing a causal relationship between FQ exposure and risk of tendon retears given the retrospective nature of the study. Additionally, although researchers can identify instances in which patients filled prescriptions for FQ medications, it is not possible to determine how much of the prescription was consumed by patients. Duration of FQ therapy was also unable to be quantified, though this limitation was mitigated through subgroup analyses of FQ claim counts with the hypothesis that patients with more FQ claims had greater FQ exposure and potentially higher risk of tendon re-rupture. Though some data in this study provided evidence to support this hypothesis, it is possible that some subgroup analyses were underpowered to detect significant differences in reoperation rates, namely for the comparison of rates for patients with more than one FQ prescription versus controls. Given the inability to quantify the amount of FQ consumed by patients and identify the etiology of retears (e.g., related to FQ exposure, traumatic injury, etc.) with complete certainty, we cannot assert there is a definitive causal relationship between FQ exposure and rates of reoperations for retears, though the data does suggest a significant association. Lastly, although propensity

score matching and multivariable regression were used, other confounders could have influenced the results. For example, while the matched cohorts were created based on known risk factors for primary tendon repair failure, there are several other risk factors that cannot be identified or controlled for in the database. Such risk factors include the size and chronicity of the tear, fatty infiltration of the muscle, repair technique, postoperative rehabilitation protocol, and concomitant biological treatment such as platelet-rich plasma.⁴¹⁻⁴⁵

CONCLUSION

Patients with FQ prescriptions within 90 days after primary tendon repair exhibited significantly higher rates of reoperations for distal biceps, Achilles, and rotator cuff tendon re-ruptures at two years postoperatively. Although a dose effect of FQ was observed with higher reoperation rates among patients with multiple prescriptions, only one FQ prescription was also associated with significantly higher reoperation rates suggesting that even minimal FQ exposure during the acute postoperative period increases the risk of tendon re-rupture. To achieve optimal outcomes and avoid complications in patients following primary tendon repair procedures, physicians should consider prescribing alternative non-FQ antibiotics and counsel patients on the risk of reoperation associated with postoperative FQ use.

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AUTHOR CONTRIBUTIONS

- (I) Conception and design: William F. Sherman
- (II) Administrative support: William F. Sherman
- (III) Provision of study materials or patients: William F. Sherman
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- (V) Data analysis and interpretation: Timothy L. Waters, Bailey J. Ross, William F. Sherman
- (VI) Manuscript writing: All authors
- (VII) Final approval of manuscript: All authors

CONFLICTS OF INTEREST

All authors report no disclosures or conflicts of interest.

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