



Fracture and Polycystic Ovarian Syndrome in Reproductive-Age Women

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Abstract

Background: Polycystic ovarian syndrome (PCOS) is a common endocrine disorder in reproductive-age women and has been associated with alterations in bone metabolism. However, the clinical impact of PCOS on fracture risk remains unclear, particularly in patients with coexisting uterine fibroids.

Methods: We conducted a retrospective cohort study using the Global Collaborative Network database. Women aged 15–45 with both PCOS and uterine fibroids (Cohort 1, n=15,209) were compared to matched controls with fibroids only (Cohort 2, n=15,209). Five fracture sites were analyzed: spine/thoracic/rib, forearm, femur, hip, and humerus. Propensity score matching was performed on baseline characteristics, including BMI, vitamin D deficiency, and tobacco use. Outcomes were assessed through risk analysis, Kaplan-Meier survival, and fracture frequency analysis.

Results: Across all fracture sites, absolute event rates were low (0.1–0.3%) and comparable between groups. No statistically significant differences were found in fracture risk, hazard ratios, or mean number of fracture events. The largest numerical difference was observed in femur fractures, where the control group had a higher mean number of events (12.8 vs. 1.6), but this did not reach statistical significance ($p = 0.072$). All other comparisons showed non-significant differences in both event rates and survival curves.

Conclusion: These findings suggest that PCOS does not confer a higher risk of clinical fractures in women with coexisting fibroids. Despite known hormonal and metabolic changes in PCOS that could theoretically impact bone health, this analysis found no increased incidence, earlier onset, or greater frequency of fractures in patients with PCOS. This supports prior mixed evidence indicating that the skeletal effects of PCOS may not translate into higher fracture risk in this population. Future studies incorporating bone mineral density, hormone profiles, and age- and race-stratified data may further clarify fracture risk among PCOS subtypes.

Keywords: PCOS; Fractures; Reproductive Age; Fracture Risk; Androgen

Introduction

Polycystic ovary syndrome (PCOS) is a complex endocrine disorder affecting reproductive-age women. The 2003 Rotterdam Criteria is most commonly used for the diagnosis of PCOS, with a positive diagnosis indicated by 2 out of the 3 following symptoms: anovulation/irregular cycles, clinical or biochemical signs of hyperandrogenism, and Polycystic ovaries on ultrasound [1]. In addition to its hormonal disturbances, PCOS is commonly associated with a spectrum of metabolic abnormalities, including insulin resistance, obesity, chronic low-grade inflammation, and gut dysbiosis, which can independently influence bone formation and resorption. Though various studies have examined the individual impact of these metabolic factors on bone metabolism, the overall risk of bone fractures in women of reproductive age with PCOS remains inconclusive [2]. This highlights a need for further investigation into the complex interplay between the hormonal and metabolic features of PCOS and their cumulative effect on skeletal health.

Due to its complex pathophysiology, PCOS fosters a wide range of metabolic abnormalities. Studies have examined various mechanisms by which hormonal imbalances including, but not

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limited to, insulin, androgens, and estrogen play a critical role in impacting bone metabolism with increased risk of progression to osteoporosis and bone fractures [3, 4]. Hyperandrogenism, a characteristic feature in PCOS, contributes to excess testosterone, dehydroepiandrosterone sulfate (DHEAS), and dihydrotestosterone (DHT), all of which are typically associated with anabolic effects on bone metabolism. Whereas the associated PCOS features of insulin resistance and reduced estrogen levels interplays with various inflammatory mediators to lower bone mineral density and increase bone resorption [3]. The exact mechanism of these hormonal irregularities is not fully understood, however, one systematic review has noted reduced osteocalcin levels as a bone marker for risk of fractures in women with PCOS and BMI <27 kg/m [2, 5].

The relationship between PCOS and fracture risk has shown conflicting evidence in the literature. Some studies suggest that women with PCOS may have increased cortical bone mineral density (BMD), particularly at weight-bearing sites, which could be protective against fractures. However, a recent meta-analytic data indicate a non-significant trend toward higher fracture prevalence among women with PCOS, suggesting a possible—but inconclusive—elevation in fracture risk [6]. Additional articles suggest vitamin D deficiency as a contributing factor to poor bone health in PCOS, with hypovitaminosis D seen in 67-85% of cases [7]. Given the well-established role of Vitamin D deficiency in poor bone health, prolonged deficiency can lead to skeletal fragility over time. Chronic low-grade inflammation, a common feature of PCOS, has also been associated with reduced bone strength in the hip and radius [8]. Together, these findings highlight the multifactorial and complex nature of bone health in PCOS, particularly in subgroups with coexisting uterine conditions. Our study aims to explore this relationship further by evaluating bone fracture risk in women with PCOS and coexisting uterine fibroids, which is underrepresented in current literature.

Methods

Study Design and Data Source

This was a retrospective cohort study conducted using de-identified electronic health record (EHR) data from the Global Collaborative Network, a federated network encompassing over 140 healthcare organizations. Data were queried through a structured cohort definition and comparative outcomes framework.

Cohort Definition

Two cohorts of women aged 15 to 45 years were defined:

- **Cohort 1 (PCOS + Fibroids):** Included patients with documented diagnoses of polycystic ovarian syndrome (ICD-10: E28.2) and uterine leiomyoma (ICD-10: D25), with exclusions for comorbid endocrine and renal conditions, including hyperlipidemia, acromegaly, Cushing's syndrome, adrenogenital disorders, Turner's syndrome, chronic kidney disease, and premature ovarian failure.
- **Cohort 2 (Controls - Fibroids Only):** Included patients with a diagnosis of uterine leiomyoma (D25) and excluded those with PCOS and the same comorbid conditions as above.

The index event was the first occurrence of the qualifying diagnoses for each cohort, with outcomes assessed starting 1 day after the index event and extending indefinitely unless otherwise specified. Patients with index events occurring more than 20 years ago were excluded.

Propensity Score Matching

To control for baseline confounders, 1:1 propensity score matching was performed using logistic regression based on demographic and clinical characteristics, including age, BMI, vitamin D deficiency, and tobacco use. After matching, both cohorts included 15,209 patients each.

Outcomes and Statistical Analysis

Five fracture outcomes were evaluated:

- Fractures of the **spine, thoracic cage, and ribs** (ICD-10: S22)
- **Forearm** fractures (ICD-10: S52)
- **Femur** fractures (ICD-10: S72)
- **Hip**-related fractures and injuries (ICD-10: S73, M84.359, S32.9XXA)
- **Humerus** fractures (ICD-10: S42)

Three analytical strategies were used:

- **Risk Analysis:** Proportion of patients with each fracture type was compared between cohorts using risk difference, risk ratio, and odds ratio.
- **Kaplan-Meier Survival Analysis:** Time-to-fracture was assessed using survival curves and log-rank tests, with hazard ratios (HRs) calculated.
- **Number of Instances Analysis:** Frequency of fracture episodes was evaluated by visit-based grouping. T-tests were conducted to compare means across cohorts.

All statistical tests were two-sided, and p-values < 0.05 were considered statistically significant.

Results

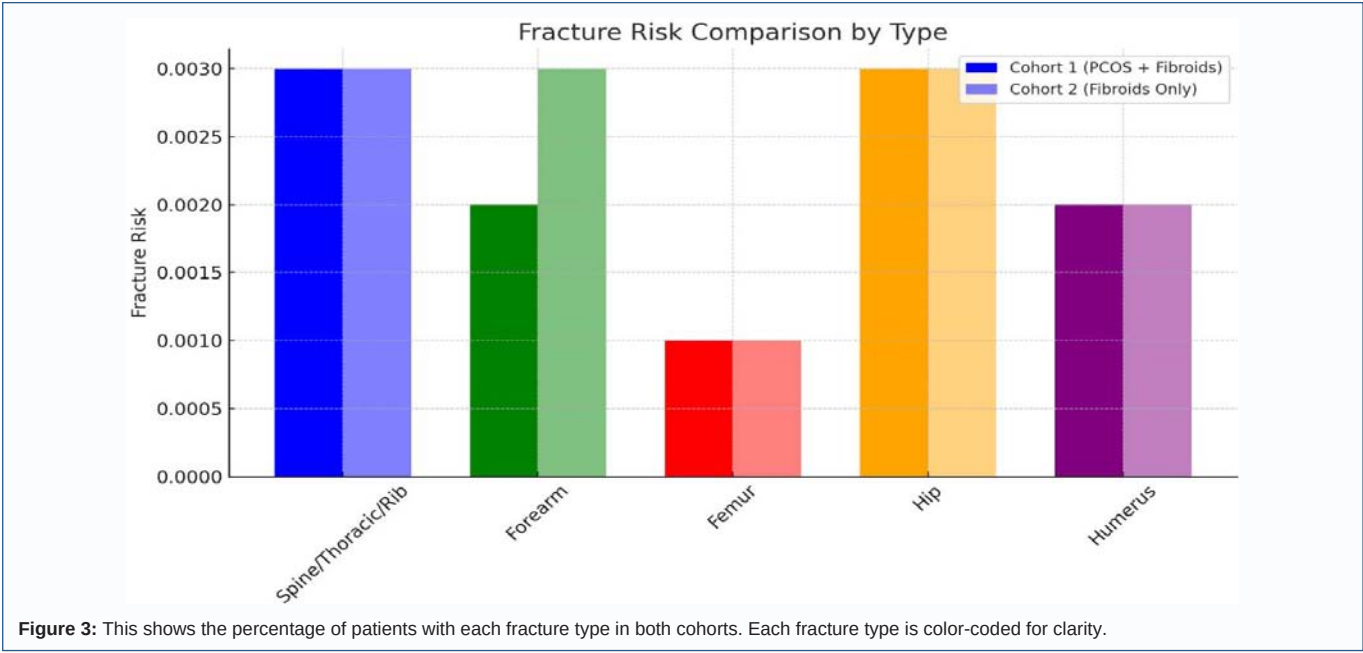
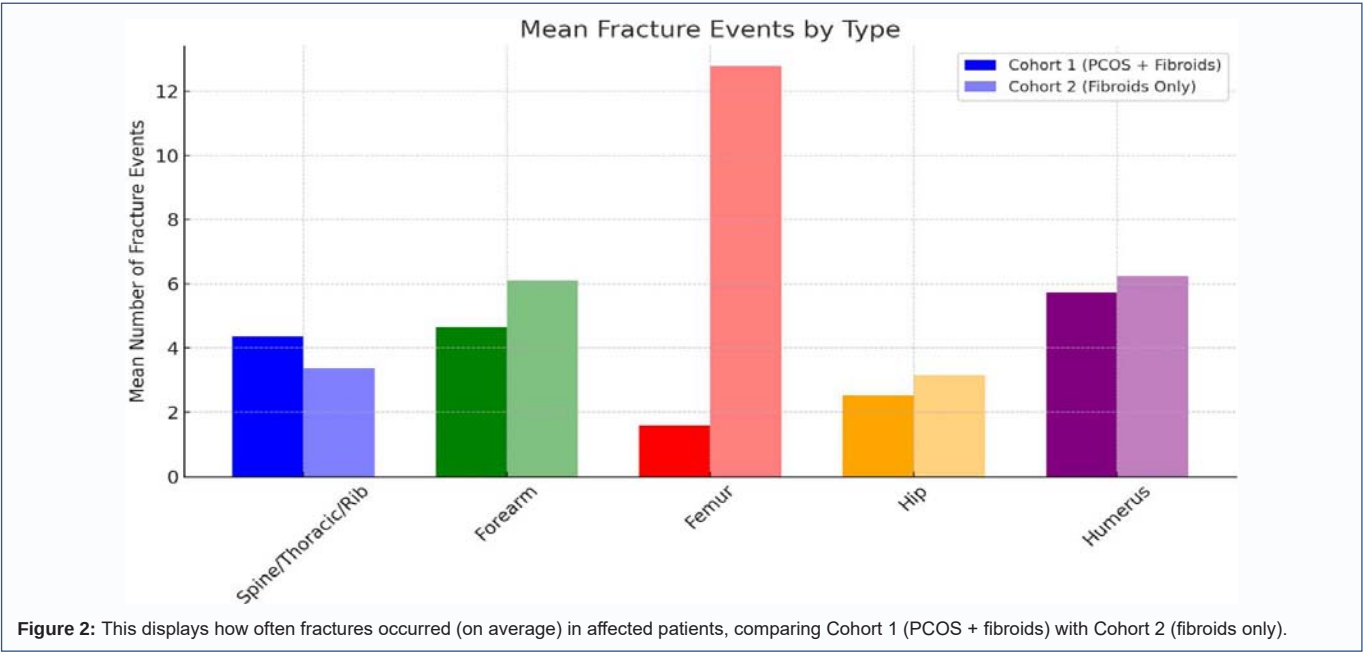
PCOS was not found to have a significant impact on fracture risk in women aged 15-45 years of age. A slight increase was observed in forearm, femur, and humerus fractures among the fibroids-only cohort (Cohort 2), but none of these yielded a p-value that was statistically significant. In the PCOS and fibroid cohort (Cohort 1), it was found that hip fractures were slightly more common (n=53) compared to the fibroids only cohort (n=45), resulting in a risk ratio of 1.18, indicating that the chances of developing a hip fracture in both cohorts were approximately the same. No difference was observed for spine, thoracic, and rib fractures between the two cohorts.

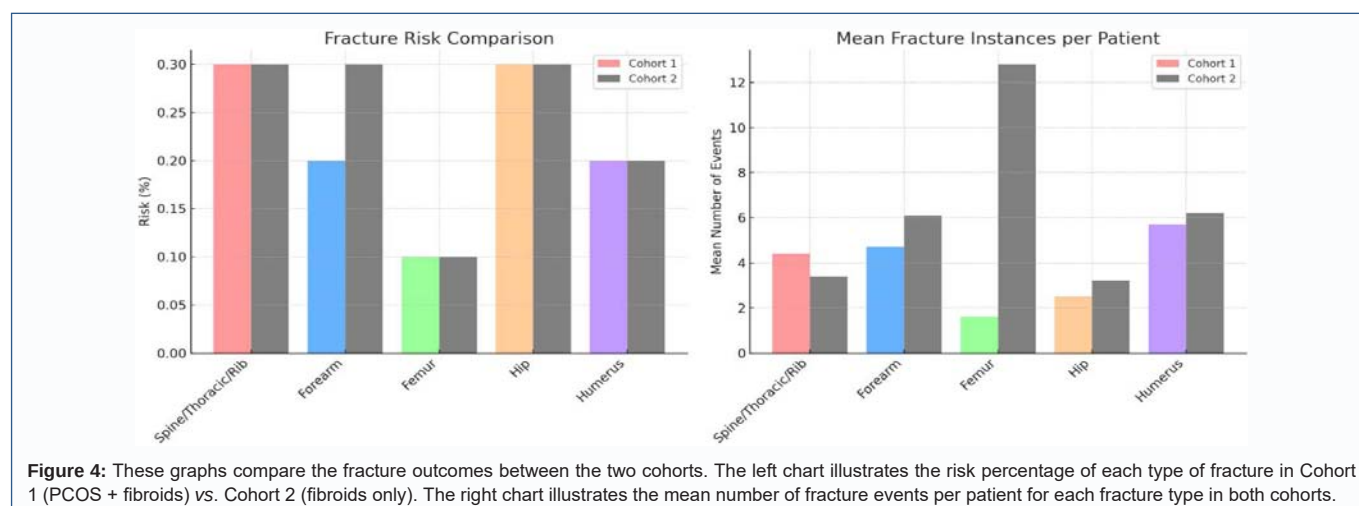
Survival analysis revealed no statistically significant difference in the timing of fractures between cohorts 1 and 2. For all fracture types - except hip fractures - the hazard ratio yielded a number that was less than 1, suggesting a reduced risk of developing spine, forearm, femur, and humerus fractures. With hip fractures, the hazard ratio was slightly greater than 1 with a number of 1.084, revealing a slightly increased risk, but not enough to be declared as significant.

The number of fractures between the two cohorts were greater on average with Cohort 2 being greater than Cohort 1, with the exception of spine, thoracic, and rib fractures (C1 = 4.4; C2 = 3.4; p = 0.442). While femur fractures reached borderline statistical significance with Cohort 2 having 12.8 fractures and Cohort 1 having 1.6 (p=0.072), the number of patients reported was too low to be certain of the correlation (Figures 1-4).

	Fracture Type	Risk Cohort 1 (%)	Risk Cohort 2 (%)	Mean Events Cohort	Mean Events Cohort	Risk Ratio	p-value
1	Spine/Thoracic/Rib	0.3	0.3	4.4	3.4	0.91	0.662
2	Forearm	0.2	0.3	4.7	6.1	0.71	0.138
3	Femur	0.1	0.1	1.6	12.8	1.07	0.853
4	Hip	0.3	0.3	2.5	3.2	1.18	0.418
5	Humerus	0.2	0.2	5.7	6.2	0.9	0.637

Figure 1: Fracture Outcome Summary.





Discussion

This retrospective cohort study investigated whether women with both polycystic ovarian syndrome (PCOS) and uterine fibroids had an increased risk of skeletal fractures compared to women with fibroids alone. Using a large, matched dataset from the Global Collaborative Network, we evaluated fracture outcomes at five key anatomical sites: spine/thoracic cage/ribs, forearm, femur, hip, and humerus. Despite physiological differences associated with PCOS—including hormonal imbalances, insulin resistance, and changes in body composition—our findings revealed no statistically significant increase in fracture risk, time to fracture, or fracture frequency across all sites in patients with PCOS.

This contrasts with a retrospective study done by Yang et al. which supported an increased fracture risk in patients diagnosed with PCOS. They found that women aged older than 15 years demonstrated a higher incidence ratio rate (IRR) of any fractures (IRR:1.26), osteoporotic fractures (IRR: 1.36), spine fractures (IRR: 1.39), and forearm fractures (IRR: 1.41) [9]. Similarly, another meta-analysis reported a 25% increased risk of prevalent fractures, although the values did not reach statistical significance [6]. This variability in the results may be due to the populations evaluated, the inclusion criteria of each study, and the sample sizes.

Also of note is the potentially protective mechanism hyperandrogenism and chronic anovulation may have on bone mineral density (BMD), though the direction of this effect remains debated [10]. Adami et al. found a positive correlation with androstenedione levels and spine BMD (correlation coefficient = 0.23; $p < 0.05$), and a positive correlation with DHEAS ($r = 0.23$; $p < 0.05$) and free testosterone ($r = 0.28$; $p < 0.05$) in reference to neck BMD [10]. These findings suggest improved bone strength with increased androgen levels, opposing an increased fracture risk with PCOS. Similarly, an article reported a stimulatory effect of Dihydrotestosterone on osteoblast cell cultures [11], supporting the potentially protective mechanism of androgens on the bone.

These findings underscore the need for more comprehensive research on the impact of PCOS and fracture risk. Future research should consider variables such as age, BMI, ethnicity, vitamin D status, and hormonal profiles to clarify the correlation between hyperandrogenism and bone health. While some mechanisms,

such as chronic inflammation and obesity with PCOS are thought to cause a decrease in BMD leading to an increased fracture risk, others suggest a protective component. For instance, Sudhakaran et al. have found links between leptin resistance and hyperinsulinemia with the development of osteoporosis in women with PCOS [3]. Additionally, studies have found an inverse relation between vitamin D and PCOS, indicating that with more deficiency, patients have a higher prevalence of the condition [12]. Vitamin D deficiency also accelerates the aging of bone, causing a decreased BMD [13], further supporting a potential pathway behind increased fracture risk among PCOS patients.

Our study's strengths include a large, diverse sample size, comprehensive matching for key confounders, and use of multiple analytical approaches to assess risk, timing, and burden of fractures. However, several limitations merit consideration. We lacked access to direct BMD measurements, detailed medication histories (e.g., corticosteroids or hormonal therapy), and lifestyle data (e.g., physical activity or fall risk), which may influence fracture risk independently. Additionally, race and age-specific subgroup analyses could not be completed due to data constraints, limiting our ability to evaluate differential risk patterns in populations with known disparities in both PCOS prevalence and bone health outcomes.

In conclusion, our findings suggest that women with PCOS and fibroids are not at increased risk for major skeletal fractures compared to matched women with fibroids alone. These results support the growing body of evidence that PCOS-related hormonal changes do not translate into a measurable increase in clinical fracture outcomes among reproductive-age women. Future prospective studies incorporating BMD data, longitudinal hormone profiling, and lifestyle factors will be important to elucidate further fracture risk across PCOS phenotypes and racial/ethnic subgroups.

Conclusion

In this large, matched cohort study of reproductive-age women, the presence of polycystic ovarian syndrome (PCOS) alongside uterine fibroids did not significantly increase the risk, frequency, or timing of fractures across multiple skeletal sites when compared to matched controls with fibroids alone. These findings held across spine, forearm, femur, hip, and humerus fracture types and remained consistent across risk-based, survival, and frequency-based analyses.

Despite the well-documented hormonal and metabolic alterations in PCOS, including insulin resistance and androgen excess, this study found no evidence of increased clinical fracture burden attributable to PCOS.

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